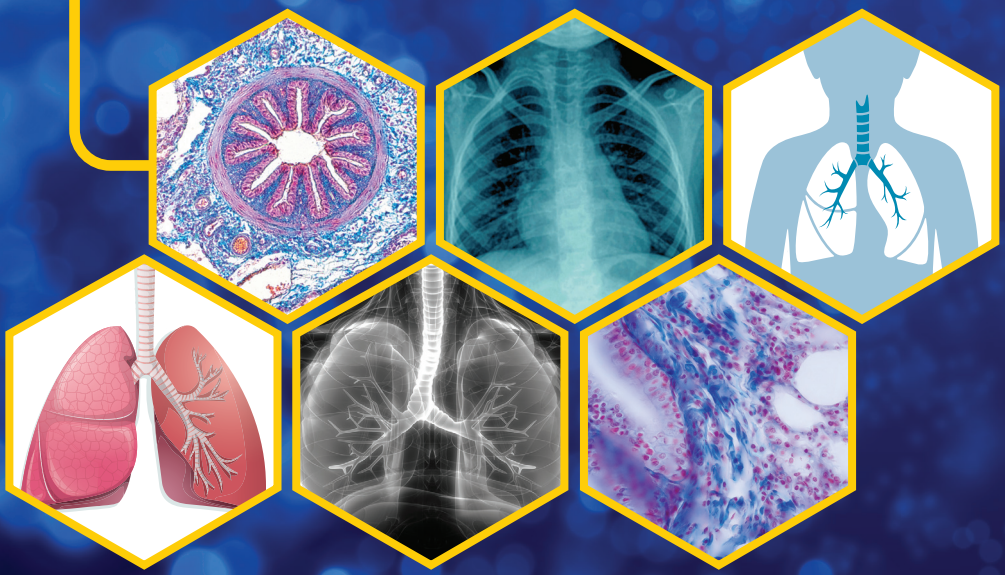
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Dennis C. Stokes, MD, MPH, FAAP

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Contributors

Editors in Chief

Michael J. Light, MD, FAAP
Orlando Pediatric Pulmonary and Sleep Associates
Orlando, FL

Kristin Van Hook, MD, MPH, FAAP
Ochsner Hospital for Children
New Orleans, LA

Associate Editors

Lee J. Brooks, MD, FAAP
Professor of Pediatrics
Rowan University
School of Osteopathic Medicine
Stratford, NJ

Mary Bono Cataletto, MD, FAAP
Clinical Professor of Pediatrics
Division of Pediatric Pulmonology
NYU–Long Island School of Medicine
Mineola, NY

Allen J. Dozor, MD, FAAP
President, Boston Children's Health Physicians
Associate Physician-in-Chief
Maria Fareri Children's Hospital at WMCHealth
Professor of Pediatrics and Clinical Public Health
New York Medical College
Valhalla, NY

Thomas G. Keens, MD, FAAP
Professor Emeritus of Pediatrics, Physiology, and Neuroscience
Keck School of Medicine of USC
Children's Hospital Los Angeles
Los Angeles, CA

Richard M. Kravitz, MD, FAAP
Professor of Pediatrics
Division Chief, Division of Pediatric Respiratory Medicine
University of Virginia School of Medicine
Charlottesville, VA

Shruti M. Paranjape, MD, FAAP
Eudowood Division of Pediatric Respiratory Sciences
Johns Hopkins University
Baltimore, MD

Michael S. Schechter, MD, MPH, FAAP
Professor and Chief
Division of Pulmonary Medicine
Department of Pediatrics
Virginia Commonwealth University
Children's Hospital of Richmond at VCU
Richmond, VA

Girish D. Sharma, MD, FAAP, FCCP
Professor of Pediatrics
Rush University
Chief, Division of Pediatric Pulmonology
Director, Rush Cystic Fibrosis Center
Rush University Medical Center
Chicago, IL

Dennis C. Stokes, MD, MPH, FAAP
Professor of Pediatrics
Vanderbilt University School of Medicine
Division of Allergy, Immunology, and Pulmonary Medicine
Department of Pediatrics
Monroe Carell Jr Children's Hospital at Vanderbilt
Nashville, TN

Chapter Authors

Mutasim Abu-Hasan, MD
Senior Attending Physician
Pediatric Pulmonology
Sidra Medicine
Doha, Qatar

Jennifer Accardo, MD, MSCE
Associate Professor of Pediatrics and Neurology
Virginia Commonwealth University School of Medicine
Richmond, VA

Suzanne E. Beck, MD
Professor of Clinical Pediatrics
Perelman School of Medicine at the University of Pennsylvania
Division of Pulmonary and Sleep Medicine
Children's Hospital of Philadelphia
Philadelphia, PA

Ariel Berlinski, MD, FAAP, FAARC
Professor of Pediatrics
Division of Pediatric Pulmonology and Sleep Medicine
University of Arkansas for Medical Sciences
Pediatric Aerosol Research Laboratory
Arkansas Children's Research Institute
Little Rock, AR

Shyall Bhela, MD
Division of Pediatric Pulmonology
Boston Children's Health Physicians
Maria Fareri Children's Hospital
Westchester Medical Center
Westchester, NY

Ellen K. Bowser, MS, RDN, LDN, RN, FAND
Associate in Pediatrics
Codirector and Nutrition Faculty
Pediatric Pulmonary Center Leadership Training Program
Pediatric Pulmonary Division
University of Florida
Gainesville, FL

John S. Bradley, MD, FAAP
Distinguished Professor
Division of Infectious Diseases
Department of Pediatrics
UCSD School of Medicine
Rady Children's Hospital San Diego
San Diego, CA

Deborah M. Brooks, MD
Assistant Professor of Child and Adolescent Psychiatry
University of Maryland School of Medicine
Baltimore, MD

Pi Chun Cheng, MD, MS
Assistant Professor of Pediatrics
Division of Pediatric Pulmonology, Allergy, and Sleep Medicine
Riley Hospital for Children
Indiana University School of Medicine
Indianapolis, IN

Christopher M. Cielo, DO, MS
Assistant Professor of Pediatrics
University of Pennsylvania
Division of Pulmonary & Sleep Medicine
Children's Hospital of Philadelphia
Philadelphia, PA

Robyn T. Cohen, MD, MPH
Division of Pediatric Pulmonary and Allergy
Boston Medical Center
Associate Professor of Pediatrics
Chobanian and Avedisian Boston University School of Medicine
Boston, MA

Carol Conrad, MD
Associate Professor of Pediatrics
Director, Pediatric Lung Transplant Program
Stanford University
Palo Alto, CA

Zarmina Ehsan, MD, FAAP
Associate Professor of Pediatrics
University of Missouri–Kansas City
Division of Pulmonary and Sleep Medicine Children's Mercy–Kansas City
Kansas City, MO

Laurie C. Eldredge, MD, PhD
Assistant Professor of Pediatrics
Division of Pulmonary and Sleep Medicine
University of Washington School of Medicine
Seattle Children's Hospital
Seattle, WA

Harold J. Farber, MD, MSPH, FAAP
Professor of Pediatrics, Pulmonary Division
Baylor College of Medicine
Texas Children's Hospital
Houston, TX

David Fedele, PhD, ABPP
Associate Professor
Department of Clinical and Health Psychology
University of Florida
Gainesville, FL

Thomas W. Ferkol, MD
Professor of Pediatrics
Department of Pediatrics
Division of Pulmonology
University of North Carolina at Chapel Hill
Chapel Hill, NC

Julie L. Fierro, MD, MPH
Assistant Professor
Division of Pulmonary and Sleep Medicine
Children's Hospital of Philadelphia
Philadelphia, PA

Edward W. Fong, MD
Assistant Clinical Professor of Pediatrics
University of Hawaii
Kapiolani Medical Center for Women and Children
Honolulu, HI

Emily S. Gillett, MD, PhD, FAAP
Assistant Professor of Clinical Pediatrics
Division of Pediatric Pulmonology and Sleep Medicine
Keck School of Medicine of USC
Children's Hospital Los Angeles
Los Angeles, CA

Samuel B. Goldfarb, MD
Professor of Pediatrics
Codirector, Pediatric Cystic Fibrosis Program
Codirector, University of Minnesota Cystic Fibrosis Center
Division of Pediatric Pulmonary and Sleep Medicine
University of Minnesota
Minneapolis, MN

Madeleine Grigg-Damberger, MD
Professor of Neurology
University of New Mexico School of Medicine
Medical Director, Pediatric Sleep Medicine Services
Associate Director, University of New Mexico Neurodiagnostic Laboratory
Associate Director, Clinical Neurophysiology Fellowship Program
University of New Mexico
Albuquerque, NM

Pallav Halani, MD, FAAP
Fellow, Division of Pediatric Pulmonology
University of North Carolina
Chapel Hill, NC

Karen Ann Hardy, MD, FATS
Clinical Professor
Division of Pediatric Pulmonary, Asthma, and Sleep Medicine
Stanford University
Palo Alto, CA

Christopher E. Harris, MD, FAAP
Medical Director
Enanta Pharmaceuticals
Watertown, MA

Leslie Hendeles, PharmD
Professor Emeritus, College of Pharmacy
Courtesy Professor of Pediatrics (Pulmonary)
University of Florida
Gainesville, FL

Jordana E. Hoppe, MD, MSCS
Associate Professor of Pediatrics
University of Colorado School of Medicine
Aurora, CO

Paul Houin, MD
Senior Instructor
Department of Pediatric Pulmonology and Sleep Medicine
University of Colorado School of Medicine Anschutz Medical Campus
Pediatric Pulmonologist
Children's Hospital Colorado
Aurora, CO

Caitlin Hurley, MD
Assistant Member
Division of Critical Care Medicine and Department of Bone Marrow Transplantation and Cellular Therapy
Medical Director, Continuing Medical Education
St. Jude Children's Research Hospital
Memphis, TN

Manju S. Hurvitz, MD, FAAP
Fellow, Pediatric Pulmonology
Division of Respiratory Medicine
Department of Pediatrics
University of California San Diego
San Diego, CA

Maki Ishizuka, MD
Division of Pulmonary and Sleep Medicine
Children's Hospital of Philadelphia
Philadelphia, PA

Jay Jin, MD, PhD
Assistant Professor of Clinical Pediatrics
Section of Allergy and Immunology
Division of Pediatric Pulmonology, Allergy, and Sleep Medicine
Riley Hospital for Children at Indiana University Health
Indianapolis, IN

Katharine Kevill, MD, MHCDS, FAAP
Assistant Professor of Pediatrics
Division of Pediatric Pulmonology
Stony Brook Children's Hospital
Stony Brook, NY

T. Bernard Kinane, MD
Associate Professor of Pediatrics
Division of Pediatric Pulmonology
Massachusetts General Hospital for Children
Harvard Medical School
Boston, MA

Sankaran Krishnan, MD, MPH
Associate Professor of Pediatrics and Public Health
Division Chief, Pediatric Pulmonology, Allergy, Immunology, and Sleep Medicine
Maria Fareri Children's Hospital at Westchester Medical Center
Boston Children's Health Physicians
New York Medical College
Valhalla, NY

Patricia Lenhart-Pendergrass, MD, PhD
Assistant Professor of Pediatrics
Division of Respiratory Medicine
University of California San Diego
San Diego, CA

Evans M. Machogu, MBChB, MS, FAAP
Assistant Professor of Pediatrics
Section of Pediatric Pulmonology, Allergy, and Sleep Medicine
Indiana University School of Medicine
Riley Hospital for Children
Indianapolis, IN

Stacey L. Martiniano, MD
Associate Professor of Pediatrics
Section of Pediatric Pulmonology and Sleep Medicine
University of Colorado Denver
Aurora, CO

Oscar Henry Mayer, MD
Medical Director, Pulmonary Function Testing Laboratory
Division of Pulmonology
Children's Hospital of Philadelphia
Professor of Clinical Pediatrics
The Perelman School of Medicine at the University of Pennsylvania
Philadelphia, PA

Susanna A. McColley, MD, FAAP
Associate Director for Child Health
Northwestern University Clinical and Translational Sciences Institute
Scientific Director, Interdisciplinary Research Partnerships
Stanley Manne Children's Research Institute
Ann & Robert H. Lurie Children's Hospital of Chicago
Professor of Pediatrics in Pulmonary and Sleep Medicine
Northwestern University Feinberg School of Medicine
Chicago, IL

Peter H. Michelson, MD, MS
Medical Director, Clinical Development
Vertex Pharmaceuticals, Inc
Boston, MA

Kenneth N. Olivier, MD, MPH
Michael E. Hatcher Distinguished Professor
Department of Medicine
Division of Pulmonary Diseases and Critical Care Medicine
University of North Carolina at Chapel Hill
Chapel Hill, NC

Brian P. O'Sullivan, MD
Professor of Pediatrics
Pediatric Pulmonology
Geisel School of Medicine at Dartmouth
Hanover, NH

Howard B. Panitch, MD
Director, Technology Dependence Center
Division of Pulmonary Medicine
Children's Hospital of Philadelphia
Professor of Pediatrics
The Perelman School of Medicine at the University of Pennsylvania
Philadelphia, PA

Madhuri Penugonda, MD
Pediatric Pulmonology
Assistant Professor of Pediatrics
University of Florida College of Medicine
Pensacola, FL

Iris A. Perez, MD, FAAP
Associate Professor of Clinical Pediatrics
Keck School of Medicine of USC
Division of Pediatric Pulmonology and Sleep Medicine
Children's Hospital Los Angeles
Los Angeles, CA

Yehudit Pollack, MD
Assistant Professor of Pediatrics
New York Medical College
Division of Pediatric Pulmonology, Allergy, Immunology, and Sleep Medicine
Boston Children's Health Physicians
Maria Fareri Children's Hospital at Westchester Medical Center
Valhalla, NY

Priya Prashad, MD, MSCE, DABSM
Assistant Professor of Pediatrics
New York Medical College
Division of Pediatric Pulmonology, Allergy, Immunology, and Sleep Medicine
Boston Children's Health Physicians
Maria Fareri Children's Hospital at Westchester Medical Center
Valhalla, NY

Courtney M. Quinlan, DO, MS
Assistant Professor of Pediatrics
University of South Florida College of Medicine
Division of Pulmonary and Sleep Medicine
Lehigh Valley Reilly Children's Hospital
Allentown, PA

Nanda Ramchandar, MD, MPH, FAAP
Associate Professor of Pediatrics
Uniformed Services University
Voluntary Assistant Clinical Professor of Pediatrics
University of California San Diego
San Diego, CA

Clement L. Ren, MD, MBA
Professor of Pediatrics and Richard B. Johnston Jr Chair in Pediatrics
University of Pennsylvania Perelman School of Medicine
Cystic Fibrosis Center Director
Children's Hospital of Philadelphia
Philadelphia, PA

Bruce K. Rubin, MEngr, MD, MBA, FRCPC, FAAP
Jessie Ball duPont Distinguished Professor, Department of Pediatrics
Professor and Chair Emeritus of Pediatrics
Professor of Biomedical Engineering
Virginia Commonwealth University School of Medicine
Richmond, VA

Danieli B. Salinas, MD, MS
Associate Professor of Pediatrics and Preventive Medicine
Keck School of Medicine of USC
Associate Director, Cystic Fibrosis Center
Department of Pediatrics
Division of Pulmonology
Children's Hospital Los Angeles
Los Angeles, CA

Adrienne P. Savant, MD, MS
Service Line Chief, Pediatric Pulmonology
Children's Hospital of New Orleans
Professor of Pediatrics
Chief, Pediatric Pulmonology
Tulane University School of Medicine
New Orleans, LA

Mark H. Sawyer, MD
Professor of Clinical Pediatrics
Department of Pediatrics
University of California San Diego
Rady Children's Hospital San Diego
San Diego, CA

James W. Schroeder Jr, MD, MBA, FACS, FAAP
Vice Chair of Education–Department of Surgery
Ann & Robert H. Lurie Children's Hospital of Chicago
Professor
Departments of Otolaryngology Head and Neck Surgery and Medical Education
Northwestern University Feinberg School of Medicine
Chicago, IL

Marianna Martin Sockrider, MD, DrPH, FAAP
Professor of Pediatrics, Pulmonary Division
Baylor College of Medicine
Chief of Pulmonary Clinics
Texas Children's Hospital
Houston, TX

Paul C. Stillwell, MD, FAAP
Senior Instructor, Department of Pediatrics
University of Colorado School of Medicine Anschutz Medical Campus
Pediatric Pulmonologist
Children's Hospital Colorado
Aurora, CO

Jade B. Tam-Williams, MD, FAAP
Assistant Professor of Pediatric Pulmonology
Division of Pulmonary and Sleep Medicine
Children's Mercy–Kansas City
Kansas City, MO

Danna Tauber, MD, MPH
Associate Professor of Pediatrics
University of Pennsylvania School of Medicine
Division of Pulmonary and Sleep Medicine
Children's Hospital of Philadelphia
Philadelphia, PA

Nadav Traeger, MD, DABSM, FCCP, FAAP
Associate Professor of Clinical Pediatrics
Division of Pediatric Pulmonology, Allergy, and Sleep Medicine
Boston Children's Health Physicians
Maria Fareri Children's Hospital at Westchester Medical Center
New York Medical College
Valhalla, NY

Timothy J. Vece, MD
Director, Rare and Genetic Lung Disease Program
Associate Professor of Pediatrics
Division of Pediatric Pulmonology
University of North Carolina–Chapel Hill
Chapel Hill, NC

Nico W. Vehse, MD
Associate Professor, UMass Chan Medical School–Baystate
Chief, Pediatric Pulmonology
Medical Director, CF Center
Medical Director, Pediatric Respiratory Care
Baystate Children's Hospital
Springfield, MA

Karen Z. Voter, MD, FAAP
Professor of Pediatrics
Division of Pediatric Pulmonology
University of Rochester School of Medicine
Rochester, NY

Mary H. Wagner, MD
Professor of Pediatrics
Division of Pediatric Pulmonary and Sleep Medicine
University of Florida
Gainesville, FL

Miles Weinberger, MD, FAAP
Professor Emeritus
University of Iowa
Visiting Clinical Professor of Pediatrics
University of California San Diego
Rady Children's Hospital
San Diego, CA

Pnina Weiss, MD, MHPE, FAAP
Professor of Pediatrics
Vice Chair for Education
Section on Pulmonology, Allergy, Immunology, and Sleep Medicine
Yale School of Medicine
New Haven, CT

John Welter, MD
Assistant Professor of Pediatrics
Division of Pediatric Pulmonology, Allergy, and Sleep Medicine
Boston Children's Health Physicians
Maria Fareri Children's Hospital at Westchester Medical Center
New York Medical College

Valhalla, NY

Amy S. Whigham, MD, MS-HPEd
Associate Professor
Department of Otolaryngology–Head and Neck Surgery
Division of Pediatric Otolaryngology
Vanderbilt University School of Medicine
Nashville, TN

Eric D. Zee, MD
Clinical Associate Professor of Pediatrics
Department of Pediatrics
Division of Pulmonary Medicine
Stanford University School of Medicine
Palo Alto, CA

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Preface

We are pleased to present the second edition of *Pediatric Pulmonology.* While the first edition was intended for primary care physicians, many pediatric pulmonologists have come to rely on "the blue book" as an excellent reference. In the second edition, we attempted to provide a broad-based reference that would be useful to subspecialists while still being a most useful reference for primary care physicians, residents, and students. Recognizing that an ever-growing number of pulmonology sections and practices include sleep medicine specialists, this edition dedicates a full section to pediatric sleep medicine—expanding beyond apparent life-threatening events (now termed *brief*, *resolved*, *unexplained events*) and sleep-disordered breathing to include information on normal sleep, sleep-related movement disorders, sleep-wake disorders, and disorders of excessive somnolence.

As with the first, this edition begins by covering the fundamental topics of lung anatomy, pulmonary physiology, and the basics of eliciting a thorough pulmonary history and physical examination. Among the many updates throughout the book, the chapters on cystic fibrosis and cystic fibrosis transmembrane conductance regulator (CFTR)-related metabolic syndrome are significantly different, as they reflect the many developments and advances in the treatment of these disorders since the first edition was published in 2011. In addition, the section on lower airway infections was updated and expanded with more in-depth coverage of pneumonia and the complications of pneumonia, including pneumonia caused by COVID-19.

Dr Light, editor in chief of the first edition, returns to lend his experience and expertise to this revision, collaborating this time with Dr Van Hook, past chair of the American Academy of Pediatrics (AAP) Section on Pediatric Pulmonology and Sleep Medicine, as well as an esteemed team of associate editors. This update would not have been possible without the tireless efforts of Chris Wiberg, our liaison with American Academy of Pediatrics Publishing; we are indebted to him for his assistance. We would also like to thank the authors of the individual chapters, who spent countless hours researching and revising their individual contributions to make this book possible.

Michael J. Light, MD

Kristin Van Hook, MD, MPH, FAAP

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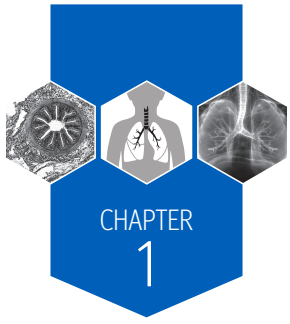
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Anatomy of the Lung

Michael J. Light, MD

Introduction

Knowledge of the development of the lungs helps us to understand congenital pulmonary anomalies. The lungs develop after 22 to 24 weeks with the ultimate purpose of sustaining life after delivery of the newborn. This occurs by oxygen from the atmosphere being inhaled into the lungs and carbon dioxide being exhaled. Oxygen provides the fuel to allow the human body to function. In this chapter, the gross anatomy of the lung, rather than microscopic anatomy, is described.

Embryology of the Lungs

The 3 laws of development of the lungs according to Hislop and Reid[1] are as follows:

1. The bronchial tree is developed by the 16th week of intrauterine life.
2. Alveoli develop at 28 weeks, increasing in number until 5 to 8 years of age, and increasing in size until growth of the chest wall finishes with adulthood.
3. The pre-acinar vessels (arteries and veins) follow the development of the airways; development of the intra-acinar vessels follows that of the alveoli. Muscularization of the intra-acinar arteries does not keep pace with the appearance of new arteries.

There are 5 phases or periods of lung development (**Figure 1-1**). Before 3 weeks of gestation, a pouch arises from the primitive foregut, at which time the embryo is 3 mm long. This period constitutes the embryonic phase. The lung bud divides into right and left, which will become the right and left lungs. By the end of the embryonic period, there will be 5 additional branches, which are the major bronchi, and the lung buds will have elongated into primary lung sacs. Developmental anomalies at this stage will result in anomalies of the major airways, including atresia (closed or undeveloped) and tracheoesophageal fistula.

The glandular period (also called *pseudoglandular*) starts at the end of the fifth week of gestation and continues to the 16th week as the conducting airways are formed by dichotomous branching. This period is called *pseudoglandular* because the airways are blind tubes lined by columnar or cuboidal epithelium. The terminal bronchioles are formed, and primitive acinar (terminal airway) structures are developing. If there is a diaphragmatic hernia, there is the potential for a reduction in the number of branches formed on the side of the hernia with a resultant hypoplastic lung.

The canalicular period is from the 16th week until the 24th week. During this period, the terminal bronchioles will have divided to produce a number of respiratory bronchioles, and the capillary bed is forming so that toward the end of this stage gas exchange can occur and potentially life can be sustained, even though the alveoli have not yet formed.

The airways from the trachea to the 19th generation are the conducting airways, and the gas-exchanging units are from the 20th to 27th generation and are the terminal respiratory units. From the major bronchi at the eighth generation to the 20th are the nonrespiratory bronchioles, and the respiratory bronchioles are from 20th to 23rd generation (**Figure 1-1**).

The saccular period extends from the end of the canalicular phase until birth and overlaps with the alveolar period, which extends to 5 to 8 years of age. The terminal respiratory unit comprises the respiratory bronchiole and the alveolar ducts, including the alveoli, and the unit is also known as the *acinus*. Alveoli

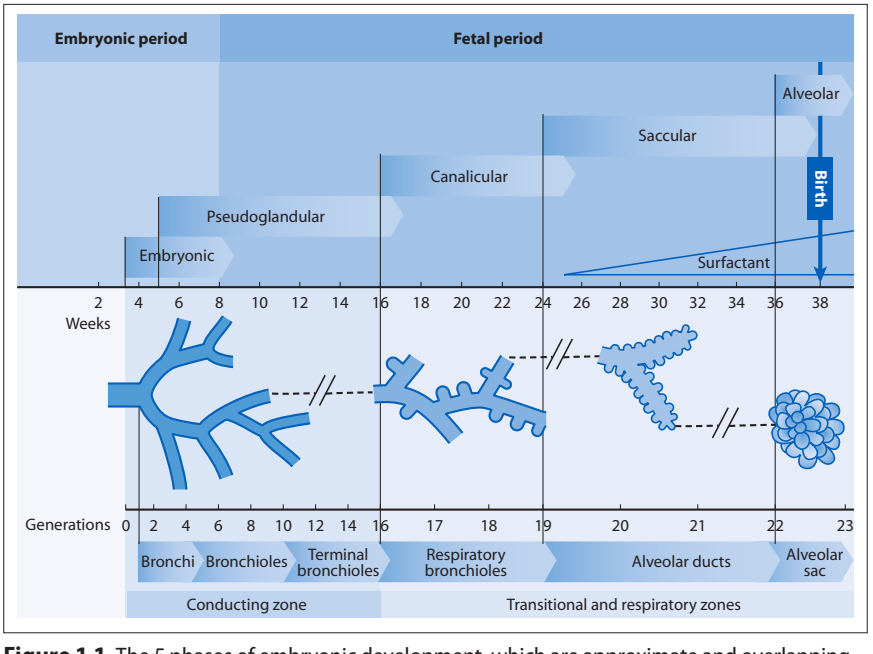


Figure 1-1. The 5 phases of embryonic development, which are approximate and overlapping.

are lined by both type 1 and type 2 pneumocytes. Type 2 pneumocytes are cuboidal and synthesize surfactant. They are able to divide and undergo repair. Eventually, most of them flatten out to form type 1 pneumocytes, which are supportive in function. Type 1 pneumocytes cover most of the alveolar surface and compose 95% of alveolar cells. They are not able to divide or be repaired. If damaged, they are replaced by transformation of the type 2 cells into type 1 cells. The primitive airways, before birth, contain lung fluid, which drains into the amniotic fluid.

In the postnatal period, alveoli continue to develop until 5 to 8 years of age and enlarge through adolescence. The term infant has between 20 million and 50 million alveoli at birth, and this number increases to about 300 million at age 8 years. The alveolar surface area is approximately 2.8 m^2 at birth, 32 m^2 at 8 years of age, and 75 m^2 at adulthood. This last number is often equated to the size of a tennis court.

The Bony Thorax

The bony thorax provides protection to the heart and lungs (**Figure 1-2**). The components are the 12 paired ribs, the sternum, and the bodies of the thoracic vertebrae.

The ribs 1 through 7 are true ribs connecting to the sternum by costal cartilage. Ribs 8 through 10 are false ribs connecting to the seventh rib by costal cartilage. Ribs 11 and 12 are floating because they are unattached. The sternum is in 3 parts: the manubrium is where the clavicles and first rib attach. The sternal body articulates directly with ribs 2 through 7 and indirectly with ribs 8 through 10. The xiphoid process is an attachment site for part of the rectus abdominis muscle. The ribs have a groove on the inferior surface, which is the site of the neurovascular bundle. Between the ribs and attached to them are the intercostal muscles, internal and external. The thoracic vertebrae are numbered T1 through T12, and the corresponding pairs of ribs to which they are attached are numbered 1 through 12.

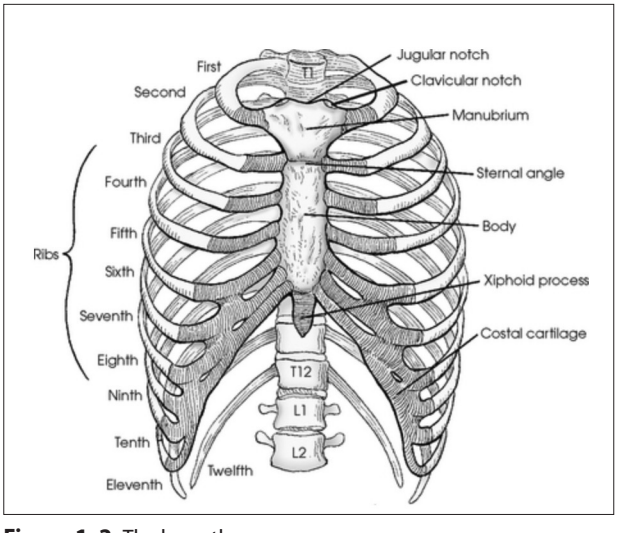


Figure 1–2. The bony thorax.

Blood Supply

During the embryonic and glandular periods, the development of the pulmonary arteries parallels that of the branching airways. During this same period, the bronchial vessels are close to the pulmonary vessels. The bronchial arteries supply blood for the nutrition of the lung; they are derived from the thoracic aorta or from the upper aortic intercostal arteries. The conducting airways receive their blood supply from the bronchial vessels, and the terminal respiratory units receive their blood from the pulmonary vessels. The pulmonary veins form from the capillary network and join together to form the 4 main pulmonary veins, which drain oxygenated blood into the left atrium. The pulmonary artery pressures are high at birth and decrease in response to higher oxygen levels over the next days and weeks. The bronchial arterial circulation is at systemic pressures.

Pulmonary Lymphatics

The lymphatics draining from the lung comprise lymph ducts, lymph nodes, and the thoracic duct. At birth, the pulmonary lymphatics are vital for the removal of amnionic fluid. There are 2 lymphatic networks: the pleural and parenchymal networks. Most drainage is toward the hilum, and, because of the valves in the lymph channels, the flow moves in one direction. Fully formed lymph nodes are not seen until birth and further develop in infancy. The main right lymphatic ducts follow the right side of the trachea, joining the venous system at the junction of the right jugular and subclavian veins. On the left side, the veins follow the trachea and empty into the thoracic duct, which drains into

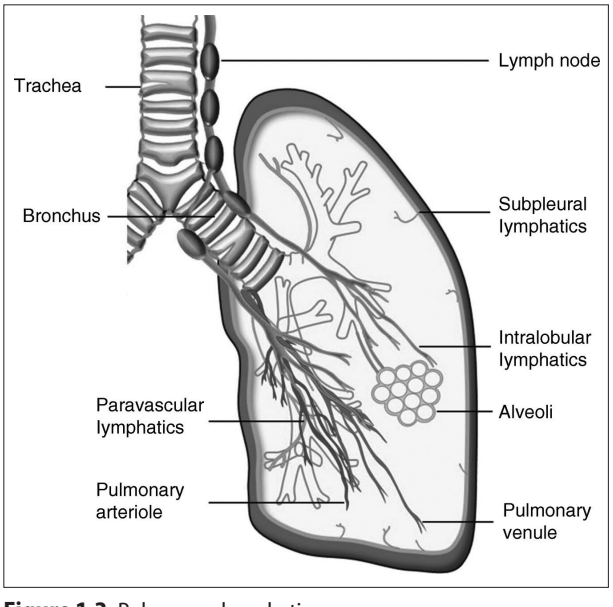


Figure 1-3. Pulmonary lymphatics.

Reprinted with permission of the American Thoracic Society. Copyright © 2022 American Thoracic Society. All rights reserved. Stump B, Cui Y, Kidambi P, Lamattina AM, El-Chemaly S. Lymphatic changes in respiratory diseases: more than just remodeling of the lung? *Am J Respir Cell Mol Biol.* 2017;57(3):272–279. *The American Journal of Respiratory Cell and Molecular Biology* is an official journal of the American Thoracic Society.

the veins on the left side of the neck. Pulmonary lymphatic drainage is complex and highly variable from individual to individual (**Figure 1-3**).

Nerve Supply

The nerve supply of the lungs is from branches of the thoracic sympathetic ganglia and the vagus nerve. The upper 3 to 5 branches of the sympathetic ganglia supply the lungs, and the lower branches supply the intercostal nerves. Almost all of the afferent (sensory) pathways are through the vagus nerve. **Figure 1-4** shows the efferent (motor) component. The efferent fibers control the caliber of the conducting airways, the activity of bronchial glands, and the caliber (constricted or dilated) of the pulmonary vessels. The parietal pleura is richly innervated with pain fibers. The visceral pleura has no pain fibers. The phrenic nerves supply the diaphragm, originating from the third to fifth cervical roots (C3–C5) (**Figure 1-4**).

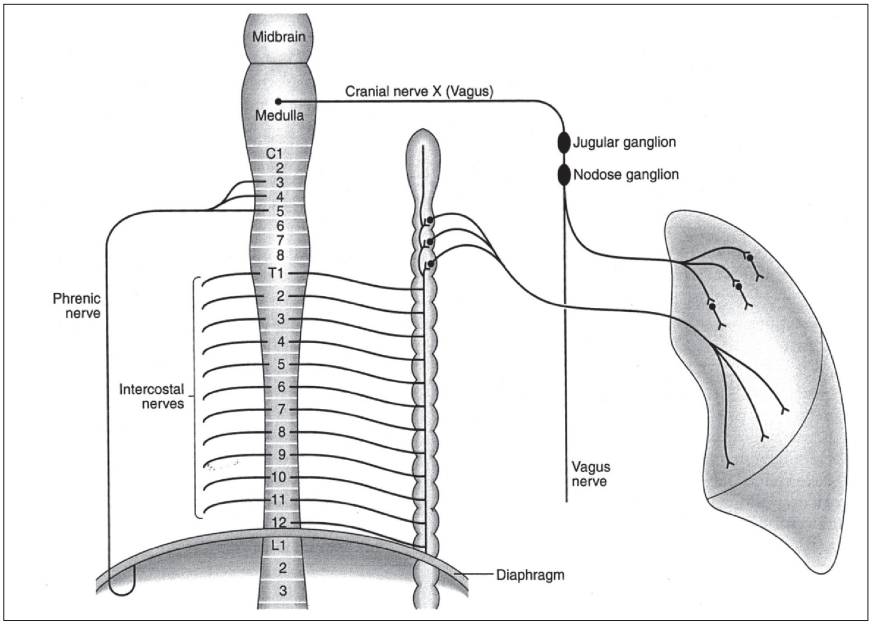


Figure 1-4. Efferent nervous system of the lungs and innervation of the diaphragm, intercostal muscles, and lungs. The efferent (motor) systems are shown. The afferent (sensory) system is mainly in the vagus nerve.

Gross Anatomy of the Lung

The lungs are within the thoracic cavity, separated by the heart and mediastinum (**Figure 1-5**). The airways terminate in the acinus where gas exchange occurs. The whole lung is spongelike and pink in the early years, gradually becoming grayer with age. The apex extends into the root of the neck, and the base is concave, resting on the convexity of the diaphragm. The right lung has 3 lobes and 2 fissures (the minor or *horizontal* fissure between the right upper and middle lobes and the major or *oblique* fissure between the right middle and lower lobes), and the left lung has 2 lobes and 1 fissure (the major or *oblique* fissure). The lobes of the lung are further divided into segments, and these are shown diagrammatically in **Figures 1-6** and **1-7**.

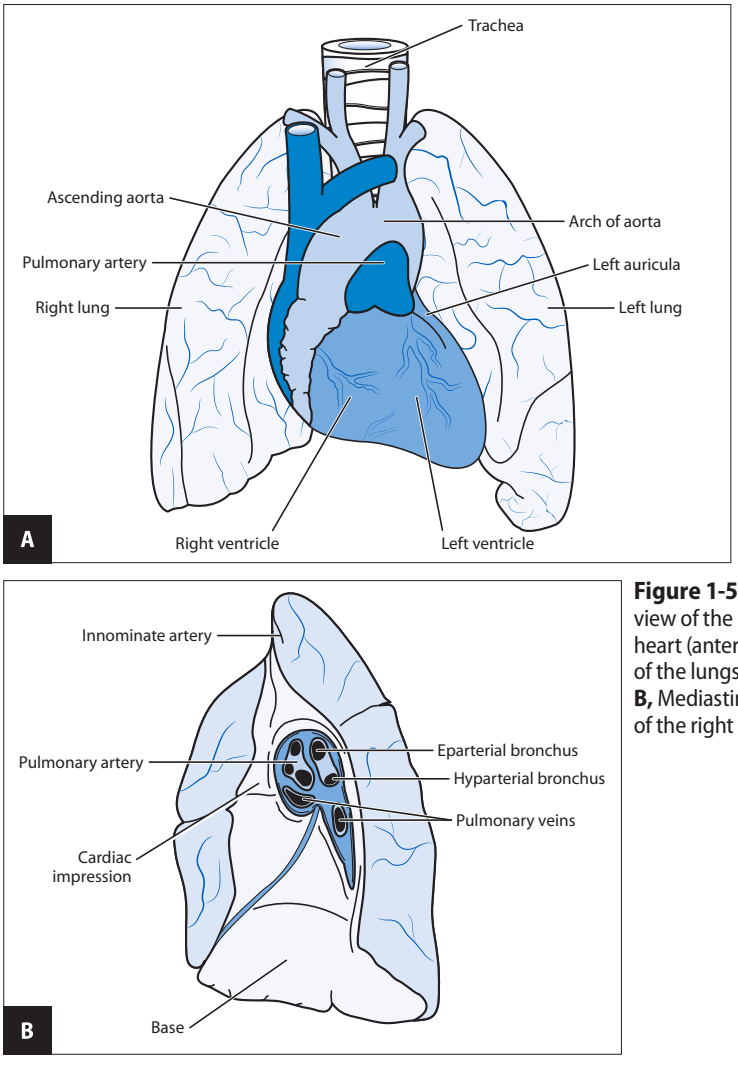


Figure 1-5. A, Front view of the lungs and heart (anterior borders of the lungs retracted). **B,** Mediastinal surface of the right lung.

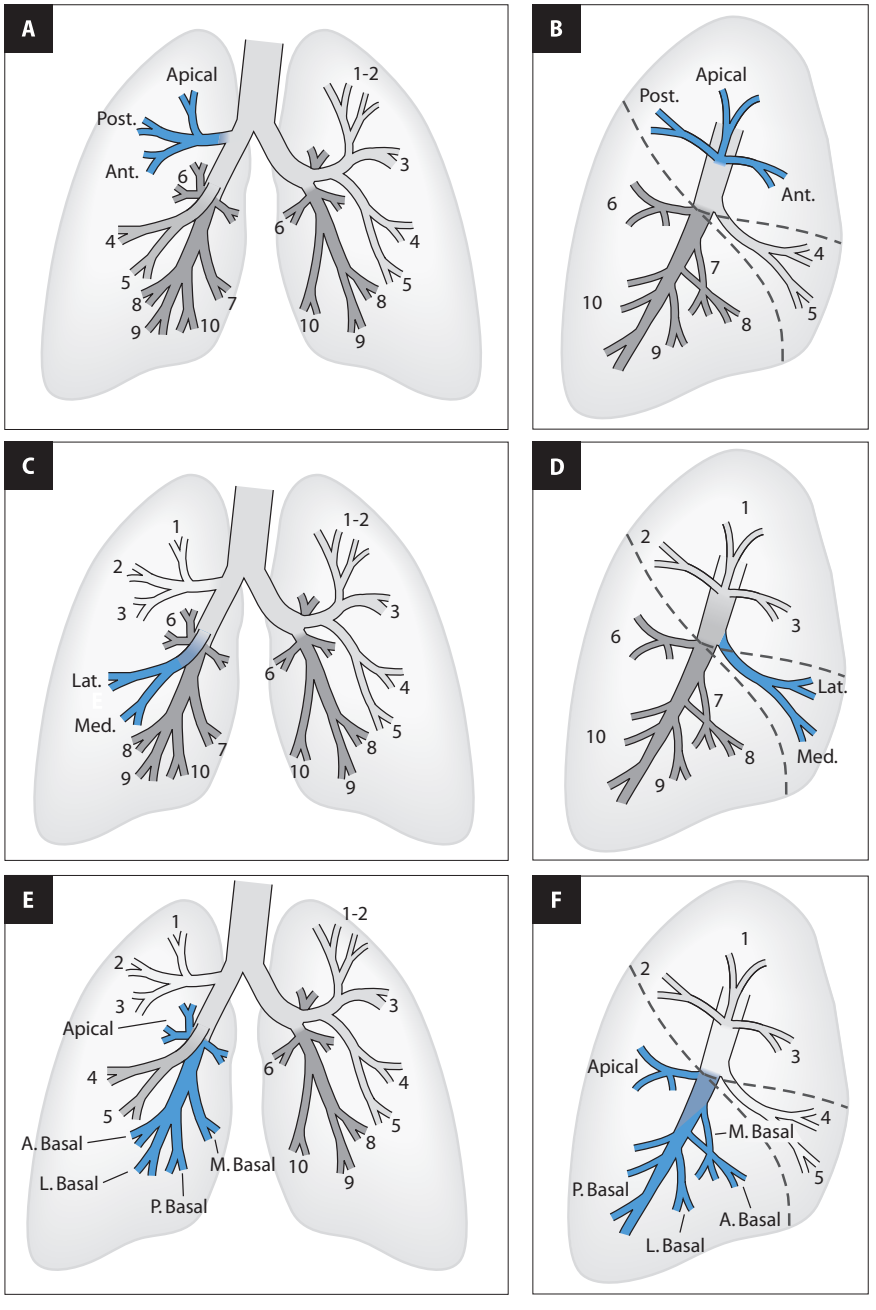


Figure 1-6. A, Upper lobe, anterior view. **B,** Right upper lobe, lateral view. Dashed lines indicate lateral and horizontal fissures. **C,** Right middle lobe, anterior view. **D,** Right middle lobe, lateral view. Dashed lines indicate lateral and horizontal fissures. **E,** Right lower lobe, anterior view. **F,** Right lower lobe, lateral view. Dashed lines indicate lateral and horizontal fissures.

Abbreviations: A.Basal, anterior basal; Ant., anterior; L.Basal, lateral basal; Lat., lateral; M.Basal, medial basal; Med., medial; P.Basal, posterior basal; Post., posterior.

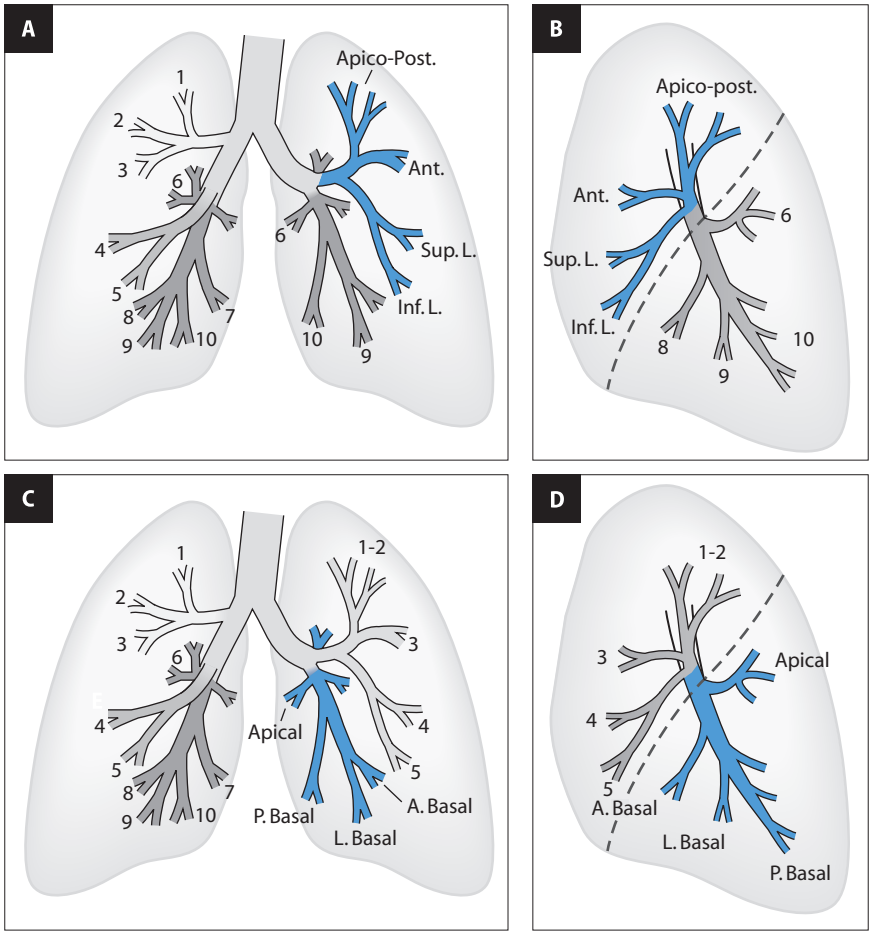


Figure 1-7. A, Left upper lobe (includes lingula), anterior view. **B,** Left upper lobe (includes lingula), lateral view. **C,** Left lower lobe, anterior view. **D,** Left lower lobe, lateral view.

Abbreviations: A.Basal, anterior basal; Ant., anterior; Apico-Post., apicoposterior; Inf. L., inferior lingual; L.Basal, lateral basal; P.Basal, posterior basal; Sup. L., superior lingual.

The lungs are covered by the visceral pleura (also called *pulmonary pleura*), and this membrane extends into the fissures. The parietal pleura lines the inner surface of the thoracic cavity, and the visceral and parietal pleurae join at the root of the lung (hilum). There is an expandable space between the 2 layers that contains a small amount of pleural fluid.

Mediastinum

The mediastinum lies within the thoracic cavity between the pleurae of the 2 lungs, with the anterior boundary of the sternum and posterior border of the vertebral column. The superior mediastinum is above the pericardium and contains the thymus, trachea, esophagus, and upper great vessels.

Below the pericardium there are 3 parts. In front of the pericardium is the anterior mediastinum, which contains the thymus; the middle mediastinum contains the heart and pericardium; and the posterior mediastinum is behind the heart and contains the esophagus (**Figure 1-5B**).

The hila of the lungs are where the structures of the lung enter from the mediastinum. The usual level of the hilum is anterior to the third to fourth costal cartilage and posterior to the fifth to seventh thoracic vertebrae.

Intercostal Muscles and Diaphragm

The muscles of respiration are the intercostals and the diaphragm. The anatomy of the diaphragm is shown in **Figure 1-8.** The right hemidiaphragm overlies the liver and is higher than the left hemidiaphragm, which overlies the stomach and spleen. There are 3 major openings in the diaphragm, including the inferior vena cava at thoracic vertebral level T12, the esophagus at T10, and the aorta at T12. The diaphragm's anterior opening is the foramen of Morgagni, and the diaphragm's posterior opening is the foramen of Bochdalek. These 2 foramina are the sites of diaphragmatic hernia, with the Bochdalek hernia being the most common and known as the *posterolateral diaphragmatic hernia* (it is mostly [80%–85%] on the left). The Bochdalek hernia tends to be more severe and may be associated with pulmonary hypoplasia and pulmonary hypertension.

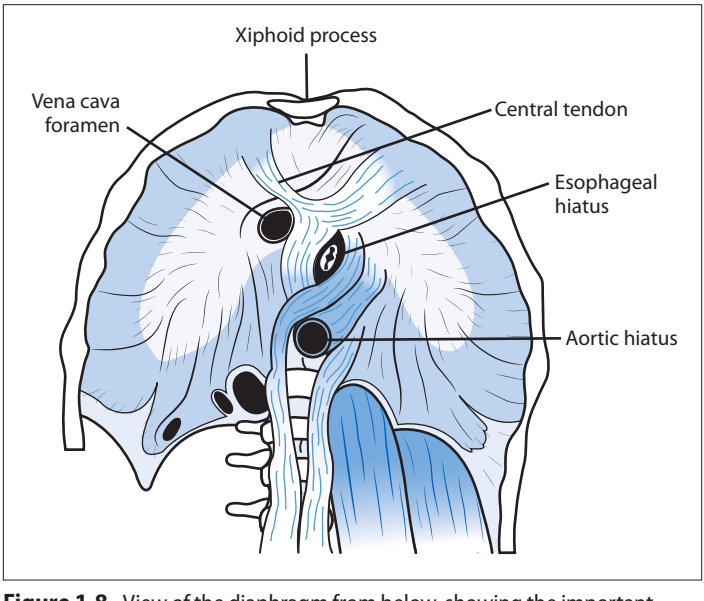


Figure 1-8. View of the diaphragm from below, showing the important openings.

It is important to understand the surface anatomy of the lungs, which is shown in **Figure 1-9.** Knowing the area of the lung below the surface while percussing and auscultating the lungs is important in localizing disease. The diaphragm is attached to the lower costal margin, and the muscular leaves are dome shaped. With inspiration, the diaphragm flattens and the lower border of the lungs correspondingly descends. This movement results in a different level of the lower lung border, which changes by several centimeters during deep breathing.

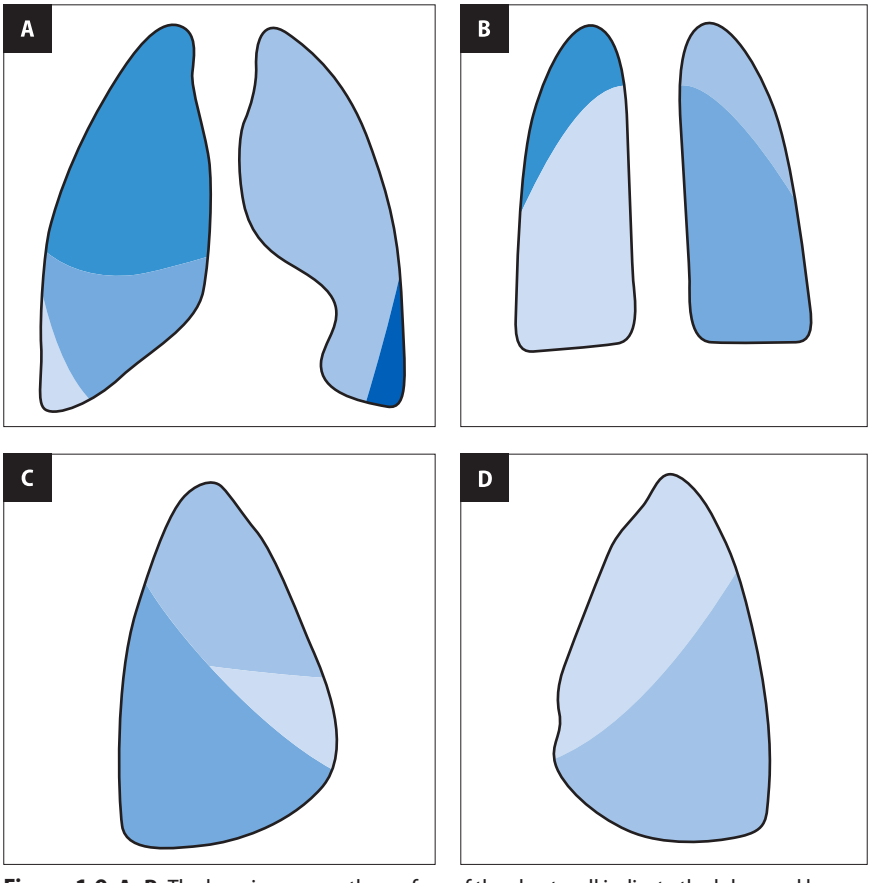


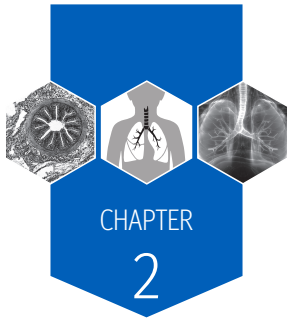
Figure 1-9. A–B, The lung images on the surface of the chest wall indicate the lobes and lungs at full inspiration. With tidal breathing and full expiration, the images will be moderately smaller and much smaller, respectively. **C–D,** The lung images on the surface of the chest wall indicate the lobes and lungs at full inspiration. With tidal breathing and full expiration, the images will be moderately smaller and much smaller, respectively.

key points

- Lung development occurs in 5 phases. Extrauterine life can be sustained at 20 to 22 weeks of gestation.
- The airways branch from the trachea. The first 19 branches are the conduction airways, and the 20th to 27th branches are the gas-exchanging units.
- It is important to know the surface position of lung anatomy to aid in localizing lung diseases.

Reference

1. Gould SJ. The respiratory system. In: Keeling JW, ed. *Fetal and Neonatal Pathology.* Springer; 1993:403–428



CHAPTER 2

Pulmonary Physiology

Pnina Weiss, MD, MHPE, FAAP

Introduction

The primary function of the respiratory system is to provide oxygen to arterial blood to nourish the body's tissues and to remove carbon dioxide from the returning venous blood. Gas exchange takes place at the level of the alveoli surrounded by a network of thin capillaries. Oxygen and carbon dioxide move between the air and blood by a process of diffusion. Air is brought to the alveoli by branching bronchi and bronchioles. The muscles of respiration act as a pump to move air in and out of the lungs. Elastic properties of the lung and chest wall and airway resistance affect the work and efficiency of the system. Disease processes that alter these relationships can lead to respiratory failure, defined as failure of the lungs to oxygenate and/or ventilate adequately.

Gas Exchange

The tensions or pressures of dissolved oxygen or carbon dioxide in the blood are designated as P_{O_2} and P_{CO_2} (individual partial pressures of the gases), respectively. **Table 2-1** shows the partial pressures of gases in the atmosphere and the lung. Dry atmospheric air is composed primarily of nitrogen. Oxygen constitutes 20.93% of the atmosphere; there is a minimal amount of carbon dioxide.[1]

Table 2-1. Partial Pressure of Gases in the Atmosphere and the Lung

Gas	Air (mm Hg)	Humidified Air (mm Hg)	Alveoli (mm Hg)
Oxygen	159	149	104
Carbon dioxide	0.3	0.3	40
Nitrogen	600.6	564	569
Water vapor	0	47	47

Adapted with permission from Levitzky M. *Pulmonary Physiology.* 4th ed. McGraw-Hill, Inc; 1995:74–75.

Dry atmospheric air is humidified as it travels down the airways into the lungs. The P_{O_2} in the alveoli is determined by the balance between the amount that flows in and the amount that is removed by the pulmonary capillaries. It will be decreased if barometric pressure is low (ie, high altitude), if there is no fresh supply of air (ie, atelectasis), or if P_{CO_2} is elevated (ie, hypoventilation).

As gas moves in and out of the alveolus, blood flows through the pulmonary capillary vessels, which provide a large surface for gas exchange. **Figure 2-1** depicts how gas exchange occurs in the alveolus. The driving force for gas exchange is the difference in pressures of P_{O_2} and P_{CO_2} between the venous blood and alveoli. Under normal conditions, the gases equilibrate fully, and the P_{O_2} and P_{CO_2} of pulmonary capillary blood equal those of the alveoli.[2]

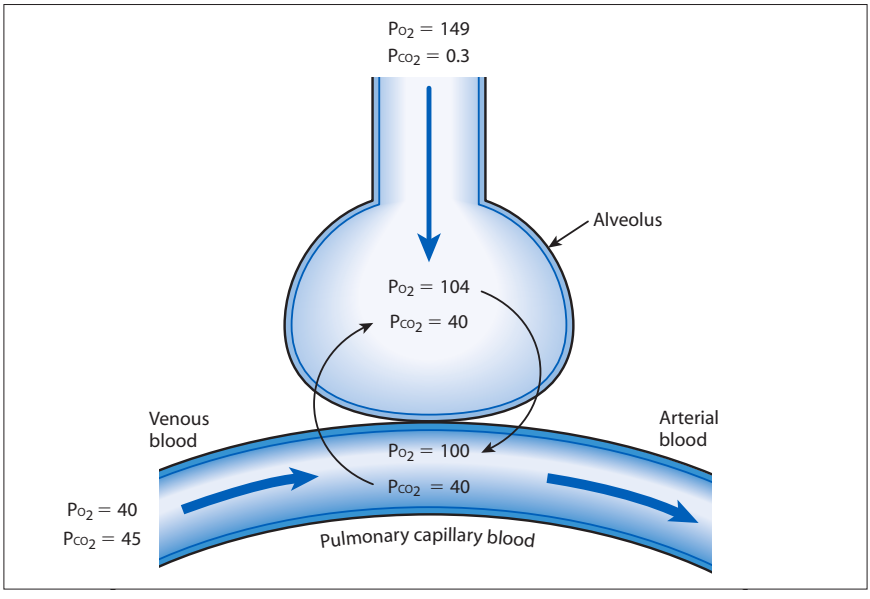


Figure 2-1. Gas exchange in the alveolus (values in mm Hg). Oxygen and carbon dioxide diffuse across the alveolar-capillary membrane. There is little carbon dioxide in the atmosphere. The P_{O_2} in the alveolus is high, and oxygen diffuses into the capillary blood. P_{CO_2} is high in the venous blood, and carbon dioxide diffuses into the alveolus.

Oxygen Consumption and Carbon Dioxide Production

The total amount of oxygen taken up by the body in 1 minute is called the *oxygen consumption,* and the amount of carbon dioxide produced is the *carbon dioxide production.* Oxygen consumption and carbon dioxide production increase with exercise. The ratio between them is known as the *respiratory quotient* and is approximately 0.8. The respiratory quotient increases (ie, more carbon dioxide is produced for each molecule of oxygen consumed) on a high carbohydrate diet. For patients in respiratory failure, low carbohydrate and high lipid formulas are suggested to decrease the respiratory quotient and decrease carbon dioxide production.[3]

Ventilation

The process of ventilation brings air in and out of the lungs. During inspiration, the size of the thoracic cavity increases and air moves into the lungs. The fresh air is carried through conducting airways to the alveoli, which are responsible for gas exchange.

Alveolar and Dead Space Ventilation

The volume of a breath is known as the *tidal volume*.[2] However, only part of the breath is used for gas exchange. Only the air that reaches the alveolus is involved in gas exchange; this is known as *alveolar volume* and is shown in **Figure 2-2.** The conducting airways are not involved in gas exchange, and the volume of air in them is known as *dead space*. About 30% of each breath ends up in dead space.[4] In some disease processes, the dead space volume increases, and less air is available in each breath for gas exchange.

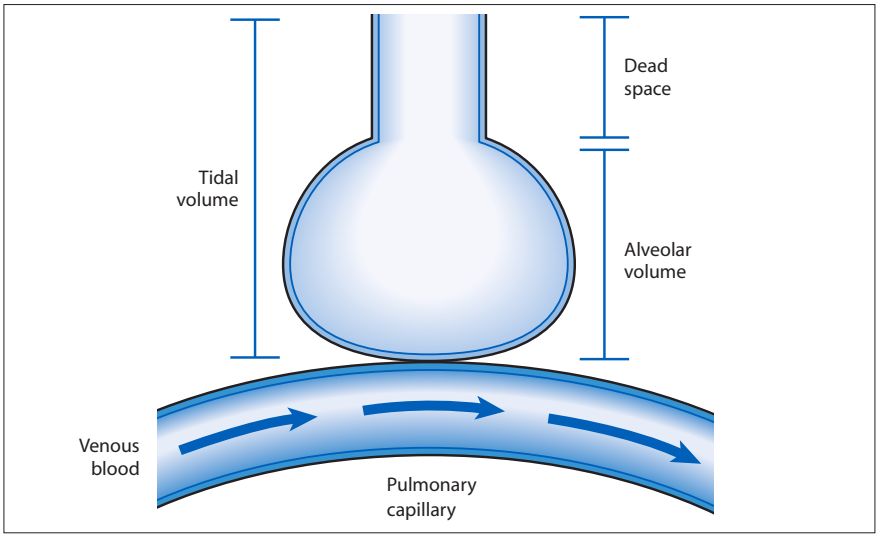


Figure 2-2. The relationship of tidal volume to dead space and alveolar volume. In each breath (tidal volume), some of the air goes into the alveoli (alveolar volume) and is available for gas exchange. The rest remains in the conducting airways and is known as dead space.

Total ventilation is the total volume of fresh air that reaches the lung each minute. It is determined by the volume of each breath multiplied by the number of breaths per minute. The relationship of tidal volume, respiratory rate, and total ventilation is shown in **Figure 2-3.** If a child has a tidal volume of 100 mL and is breathing 15 breaths/min, then the total ventilation is 1,500 mL/min. *Alveolar ventilation* is the total volume of air that reaches the alveoli and is available for gas exchange each minute. Thus, if a disease process decreases the respiratory rate and/or the volume of each breath or increases the dead space, it will decrease the effective ventilation. Total

ventilation is easy to quantify because tidal volume is easily measured; alveolar ventilation is more difficult to quantify because dead space is more difficult to measure.

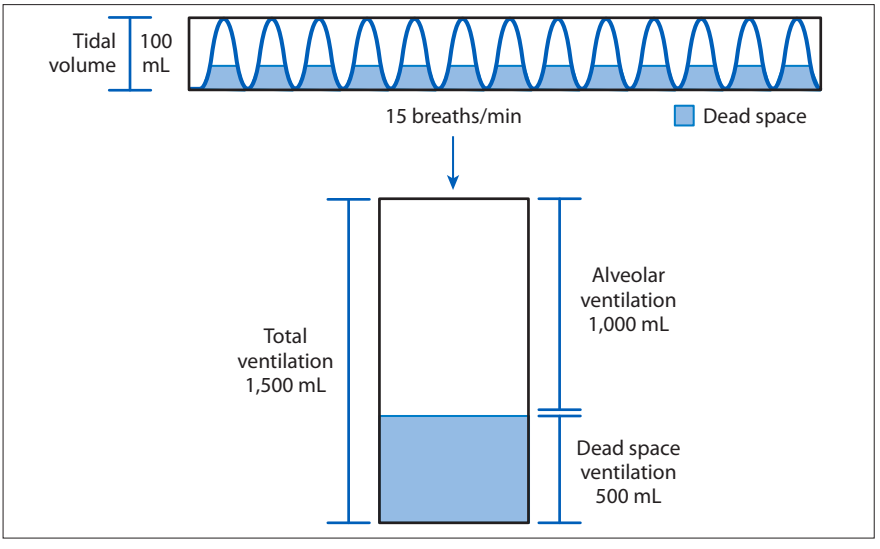


Figure 2-3. Components of total ventilation: tidal volume, respiratory rate, alveolar ventilation, and dead space ventilation. Total ventilation is determined by the volume of each breath multiplied by the number of breaths per minute. In this diagram, dead space is one-third of total volume.

Relationship of Ventilation to Arterial P_{CO_2}

The removal of carbon dioxide from the blood depends on alveolar ventilation. If alveolar ventilation increases, then the elimination of carbon dioxide increases, and its concentration in the arterial blood decreases.[1] This relationship is shown in **Figure 2-4.** If alveolar ventilation decreases, then the elimination of carbon dioxide decreases, and it accumulates in the arterial blood. There is an inverse relationship between the alveolar ventilation and the arterial carbon dioxide concentration: if alveolar ventilation doubles, the arterial carbon dioxide concentration is halved. If the alveolar ventilation decreases by 50%, then the arterial carbon dioxide concentration doubles.

The effect of changes in respiratory rate, tidal volume, and dead space on ventilation and arterial carbon dioxide level are depicted in **Table 2-2.** A wide variety of factors can cause decreased alveolar ventilation with an increase in arterial carbon dioxide tension. A decrease in respiratory rate or tidal volume can result from drugs such as opiates, benzodiazepines, or alcohol; central nervous system infection; trauma; seizures; or sepsis. Preterm infants can have cessation of breathing or apnea of prematurity. In congenital central hypoventilation syndrome, children have a decreased central drive to breathe and, consequently, hypoventilation. Children with obstructive sleep apnea have a

relative decrease in their tidal volume because they cannot effectively breathe in. Chest wall trauma or deformity, neuromuscular weakness, and lung disease can also decrease the tidal volume and impair ventilation. Disease processes, such as acute respiratory distress syndrome, scoliosis, pulmonary embolus, or general anesthesia, can increase the dead space and thus impair the proportion of effective ventilation.

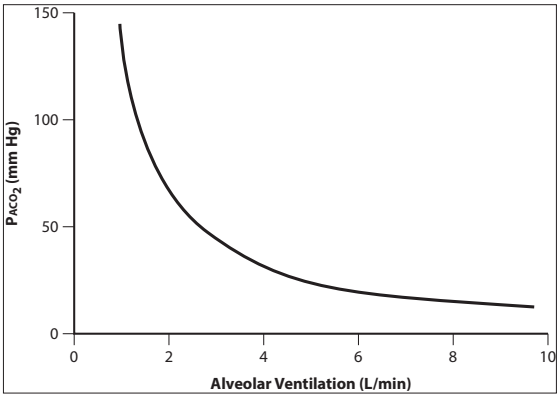


Figure 2-4. The relationship between ventilation and carbon dioxide levels in the lung. Increases in alveolar ventilation will decrease carbon dioxide levels; conversely, decreases in ventilation will increase carbon dioxide levels. P_{ACO_2} is the P_{CO_2} in the alveolus.

Adapted from Lumb AB. *Nunn's Applied Respiratory Physiology.* 5th ed. Edinburgh, Scotland: Butterworth Heinemann; 2000, with permission.

Table 2-2. Effect of Changes in Respiratory Rate, Tidal Volume, and Dead Space on Total Ventilation and Arterial Carbon Dioxide Level

Respiratory Rate (breaths/min)	Tidal Volume	Dead Space	Total Ventilation	Arterial P_{CO_2}	Causes
↓	↔	↔	↓	↑	Medications, alcohol, central nervous system infections, seizures, apnea
↔	**↓**	↔	↓	↑	Chest wall trauma, neuromuscular weakness, lung disease
↔	↔	**↑**	↔	↑	Acute respiratory distress syndrome, scoliosis, pulmonary embolus
↑	↔	↔	↑	↓	Metabolic acidosis, salicylate overdose, anxiety, pain
↔	**↑**	↔	↑	↓	Metabolic acidosis, salicylate overdose, anxiety, pain
↔	↔	**↓**	↔	↓	Mechanical ventilation, deep breathing

The primary events are shown in bold arrows; the effects on total ventilation and arterial PCO_2 are listed. Decreases in respiratory rate and tidal volume decrease total ventilation and increase arterial carbon dioxide tension. Increases in respiratory rate and tidal volume increase total ventilation and decrease arterial carbon dioxide tension. Changes in dead space do not affect total ventilation; they will, however, affect alveolar ventilation and carbon dioxide levels.

Increased alveolar ventilation results in a decrease in P_{CO_2}. Causes for increasing respiratory rate and tidal volume are depicted in **Table 2-2.** The most common causes include metabolic acidosis, salicylate ingestion, anxiety, central nervous system disorders, and pain. There are also some instances in which the dead space can be decreased.

Regulation of Arterial P_{CO_2}

The arterial carbon dioxide concentration reflects a balance between carbon dioxide production and elimination. More carbon dioxide is produced when the metabolic rate is increased. Fever or increased muscle activity (shivering, seizures) produces more carbon dioxide and can produce elevations in arterial carbon dioxide levels unless ventilation is increased.

Ventilation is controlled by sensors called chemoreceptors, which are located in the brain and aortic bodies (at the common carotid artery and aortic arch, respectively). These receptors sense changes in arterial carbon dioxide concentration. They respond by activating effectors that alter ventilation to keep arterial carbon dioxide concentration normal.

Acid-Base Status

Carbon dioxide is transported in the blood in 3 forms: dissolved, bicarbonate, and combined with proteins such as carbamino compounds. In arterial blood, most carbon dioxide is carried as bicarbonate (90%).[5]

$$CO_2 + H_2O \xrightarrow[\text{Carbonic Anhydrase}]{} H_2CO_3 \leftrightarrows H^+ + HCO^-_3$$

Carbon dioxide and water are converted to carbonic acid by the enzyme carbonic anhydrase in red blood cells. Carbonic acid spontaneously dissociates into hydrogen ions (acid) and bicarbonate.

The pH of the blood depends on the relationship of bicarbonate and carbon dioxide. As the arterial P_{CO_2} increases, the pH decreases, which is known as *respiratory acidosis*. As the arterial P_{CO_2} decreases, the pH increases, which is known as *respiratory alkalosis*.

The lungs regulate the concentration of carbon dioxide, and the kidneys control the bicarbonate concentration. In response to respiratory acidosis, the kidneys will compensate over 3 to 5 days by conserving bicarbonate and will create a secondary metabolic alkalosis. **Table 2-3** provides a list of primary acid-base disorders and their secondary compensation. In contrast, in response to respiratory alkalosis, the kidneys will eliminate excess bicarbonate and create a secondary metabolic acidosis in compensation.

Table 2-3. Primary Acid-Base Disorders and Compensation

Disorder	Carbon Dioxide Level	pH	Bicarbonate Level
Acute respiratory acidosis	↑	↓	↑
Chronic respiratory acidosis	↑	↓	↑
Acute respiratory alkalosis	↓	↑	↓
Chronic respiratory alkalosis	↓	↑	↓
Metabolic acidosis	↓	↓	↓
Metabolic alkalosis	↑	↑	↑

The primary events are shown in bold arrows; the secondary effects are listed, and the arrow lengths are proportional to the magnitude of the change. For example, in acute respiratory acidosis, the primary event is an elevation in arterial P_{CO_2}. There is a concomitant decrease in pH and a very small increase in bicarbonate. In chronic respiratory acidosis, there is renal compensation and bicarbonate increases. As a result, the P_{CO_2} is still elevated, but the pH is not as dramatically low as in acute respiratory acidosis.

It is possible to determine the primary acid-base disorder and the compensation by plotting the values on a nomogram as exemplified in **Figure 2-5.**[6] In general, for acute respiratory acidosis, an increase in P_{CO_2} of 10 mm Hg will decrease the pH by 0.08 and the bicarbonate by 1 mmol/L (1 mEq/L). In chronic respiratory acidosis, after renal compensation, the bicarbonate will increase by a total of 4 mmol/L (4 mEq/L) for each increase in P_{CO_2} of 10 mm Hg. In acute and chronic respiratory alkalosis, similar changes in the opposite direction occur. Remembering the relationship between change in P_{CO_2} and pH can be useful in determining whether a patient has compensated, partially compensated, or uncompensated respiratory acidosis. For example, a patient with a severe acute asthma exacerbation may present to the emergency department with a pH of 7.24, P_{CO_2} of 60 mm Hg, and bicarbonate level of 22 mmol/L (22 mEq/L), which indicates acute uncompensated respiratory acidosis. If the patient's ventilation does not improve, over the course of 2 to 3 days the kidneys will start to compensate, and a follow-up blood gas measurement may have a pH of 7.30, P_{CO_2} of 60 mm Hg, and bicarbonate level of 25 mmol/L (25 mEq/L), which reflects partial compensation. In contrast, an infant with bronchopulmonary dysplasia who has chronic respiratory failure may have a blood gas measurement with a pH of 7.35, P_{CO_2} of 60 mm Hg, and bicarbonate level of 28 mmol/L (28 mEq/L), which indicates compensated respiratory acidosis.

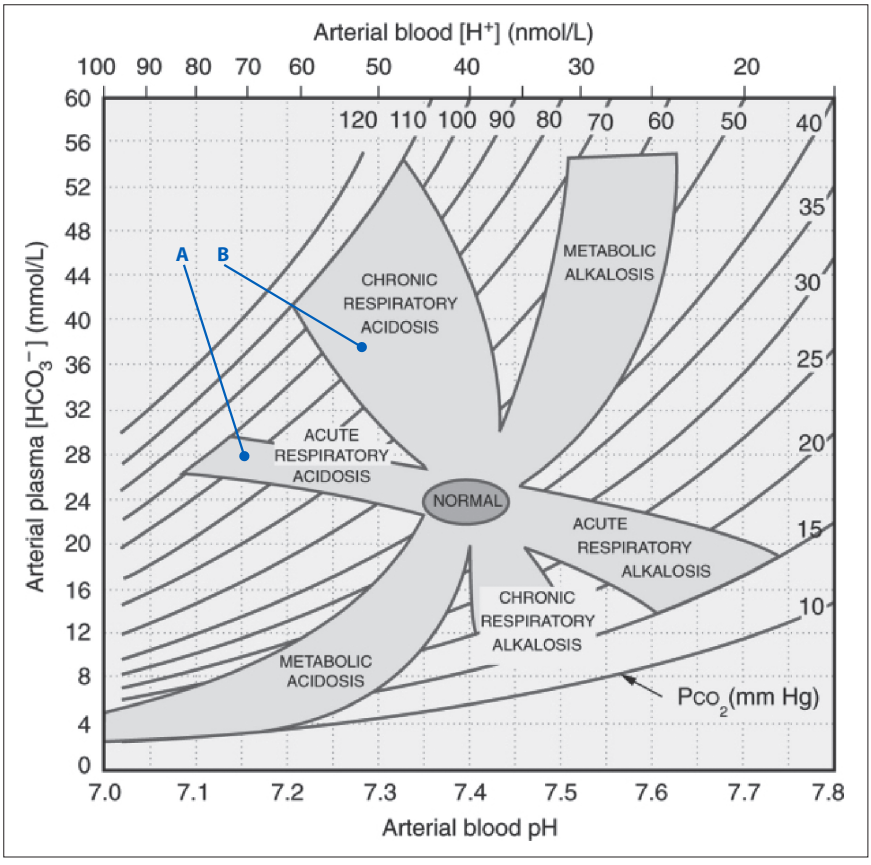


Figure 2-5. Nomogram of acid-base abnormalities. From this nomogram, the primary acid-base abnormality can be determined. **A.** Patient A has a pH of 7.18, P_{CO_2} of 80 mm Hg, and bicarbonate (HCO^-_3) of 26 mmol/L, which is consistent with acute respiratory acidosis. **B.** Patient B has a pH of 7.3, P_{CO_2} of 80 mm Hg, and HCO^-_3 of 37 mmol/L, which is consistent with chronic respiratory acidosis.

Adapted from DuBose TD. Disorders of acid-base balance. In: Brenner BM, ed. *Brenner and Rector's The Kidney.* Philadelphia, PA: Saunders Elsevier; 2007, with permission from Elsevier.

Oxygenation

Oxygen reaches the alveoli through the conducting airways, where it diffuses across the very thin membrane to the capillary blood. Under normal circumstances, oxygen composes approximately 21% of air. The amount of oxygen in the alveolus is determined by the presence of other gases such as carbon dioxide, a supply of fresh air, and changes in barometric pressure. The P_{O_2} decreases when the P_{CO_2} increases. The P_{O_2} depends on a fresh flow of air; if there is no airflow, such as in cases of mucous plugging, atelectasis, or apnea, then the P_{O_2} in the alveolus decreases. In addition, the P_{O_2} depends on the atmospheric pressure. At high altitudes, the atmospheric pressure is lower,

and there is less oxygen available, which accounts for the development of hypoxemia, or low arterial oxygen level, at Mount Everest or when flying.

Oxygen is primarily bound to hemoglobin in the red blood cell; a small amount is dissolved in plasma. A red blood cell takes about three-quarters of a second to transverse the pulmonary capillary bed; under normal conditions, it takes about one-quarter of a second for oxygen to be transferred fully to the red blood cell.[2] If the capillary membrane is thickened, then transfer may take longer and may not be complete by the end of its transit time. This delay may be aggravated by exercise; as the blood moves more quickly through the lungs, it may not have adequate time to become fully saturated.[7]

Mechanisms of Hypoxemia

The primary processes that contribute to hypoxemia are hypoventilation; diffusion impairment; shunt; ventilation/perfusion ($\dot{V}/\dot{Q}$) mismatch; and, under some conditions, low venous blood saturation.[8] These processes are depicted in **Figure 2-6.** In addition, as mentioned in the prior section, hypoxemia may result from low inspired P_{O_2}, which may occur at high altitudes or in the laboratory under experimental conditions.

Hypoventilation

If ventilation is inadequate, the P_{CO_2} in the alveoli increases and the P_{O_2} decreases. Inadequate ventilation may be caused by depressed respiratory drive (medications, sepsis, brain trauma), damage to the chest wall, or weakness of the respiratory muscles.

The relationship between the increase in arterial carbon dioxide and decrease in oxygen tension can be seen from the alveolar gas equation, which is often simplified as follows:

$$P_{AO_2} = P_{IO_2} - Pa_{CO_2}/R,$$

where P_{AO_2} is the alveolar P_{O_2}, P_{IO_2} is the inspired P_{O_2}, Pa_{CO_2} is the arterial P_{CO_2}, and R is the respiratory exchange ratio of carbon dioxide and oxygen, which is estimated to be 0.8 for the whole lung. Therefore, every increase in alveolar P_{CO_2} of 10 mm Hg would decrease the P_{O_2} by approximately 12.5 mm Hg. For example, if a child without lung disease with a resting P_{CO_2} of 40 mm Hg and P_{O_2} of 100 mm Hg has an episode of apnea and the P_{CO_2} increases to 80 mm Hg, the P_{O_2} will decrease to 50 mm Hg.

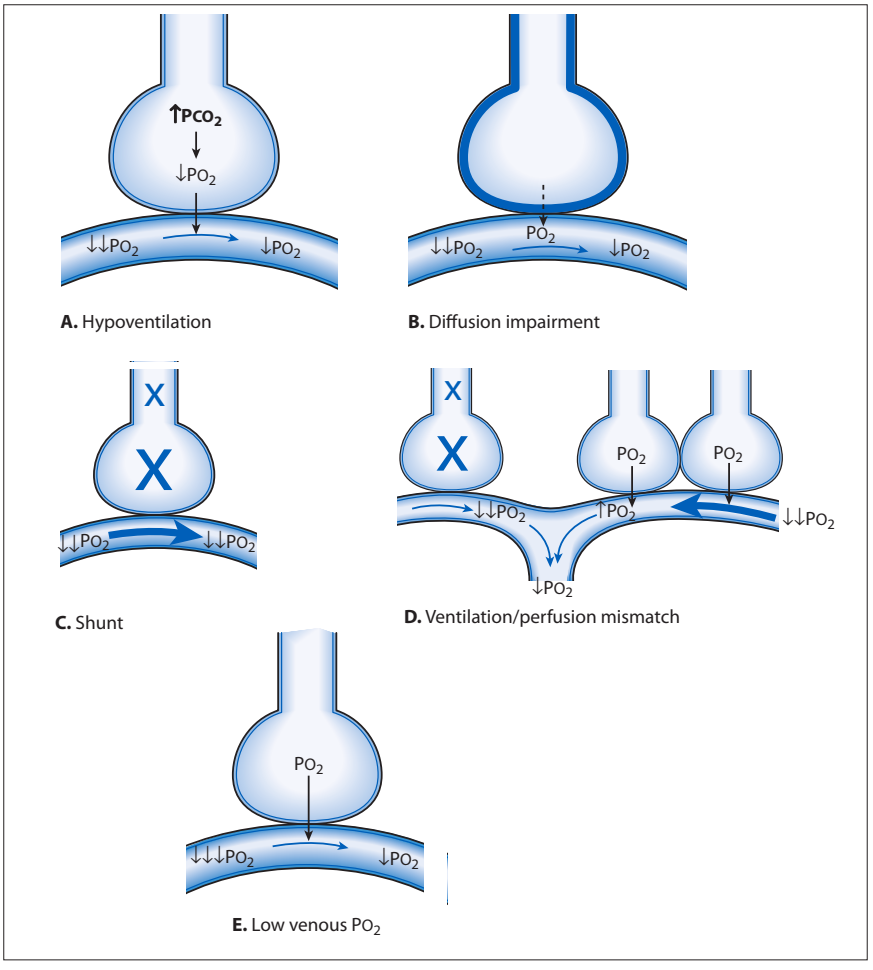


Figure 2-6. Causes of hypoxemia. **A,** Hypoventilation: Ventilation is decreased, and P_{CO_2} is increased. Consequently, the P_{O_2} in the alveolus decreases. **B,** Diffusion impairment: Diffusion across the alveolar-capillary membrane to the hemoglobin in the red blood cells is decreased. **C,** Shunt: Pulmonary venous blood bypasses the lung without being oxygenated. This may occur in congenital cardiac disease or arteriovenous malformation where there is a right-to-left shunt. **D,** Ventilation/perfusion mismatch: Some areas of the lung are nonfunctional and poorly oxygenate the venous blood. Blood from functioning alveolar units mixes with the venous blood. **E,** Low venous P_{O_2}: The P_{O_2} in the venous blood may be abnormally low because of anemia, fever, or decreased cardiac output. In the presence of lung disease, shunt, or exercise, the venous blood may not be fully oxygenated as it completes its course through the lung.

Diffusion Defects

Pediatric patients can have problems with diffusion. Diffusion of a gas through tissues depends on the cross-sectional area, the partial pressure difference across the tissue and the thickness of the tissue, and inherent characteristics of the gas (its solubility and molecular weight). Diffusion can be impaired if the surface area of the lung is decreased (such as in a lobectomy or emphysema) or

the capillary basement membrane is thickened (such as in pulmonary edema or interstitial fibrosis). Problems with diffusion can be detected by using carbon monoxide as a surrogate marker and testing the diffusing capacity of the lung for carbon monoxide (D_{LCO}). The D_{LCO} may be low in the aforementioned conditions and also with reduced thoracic blood volume or reduced hemoglobin.

Infants and children have lower diffusion capacities, related to their smaller body length and lung volumes, than adults do. Infants and children with chronic lung disease of prematurity have a decrease in D_{LCO} likely related to arrested alveolarization and decreased surface area.[9–11] Despite immature alveolarization, it does not appear as though prematurity per se is associated with a decrease in D_{LCO}.[12]

Shunt

Shunt occurs when deoxygenated blood bypasses the lungs and flows directly into the arterial circulation.[2] Small shunts exist under normal physiological conditions. Deoxygenated blood from the bronchial arteries drains directly into the pulmonary veins, and the coronary veins drain directly into the left ventricle through the Thebesian veins. In some circumstances, there can be an abnormal connection between the veins and arteries (arteriovenous malformation). In addition, a right-to-left shunt can occur with congenital heart disease (eg, pulmonary atresia with ventriculoseptal defect, pulmonary hypertension with an atrial septal defect or patent foramen ovale). The amount of blood going through the shunt can be calculated from the following equation:

$$\frac{\dot{Q}S}{\dot{Q}T} = \frac{Cc'O_2 - CaO_2}{Cc'O_2 - C\bar{v}O_2}$$

where $\dot{Q}S/\dot{Q}T$ is the fraction of blood going through the shunt, $Cc'O_2$ is the pulmonary capillary oxygen content, CaO_2 is the arterial oxygen content, and $C\bar{v}O_2$ is the mixed venous oxygen content. Shunt fractions can also be calculated from nomograms (**Figure 2-7**).

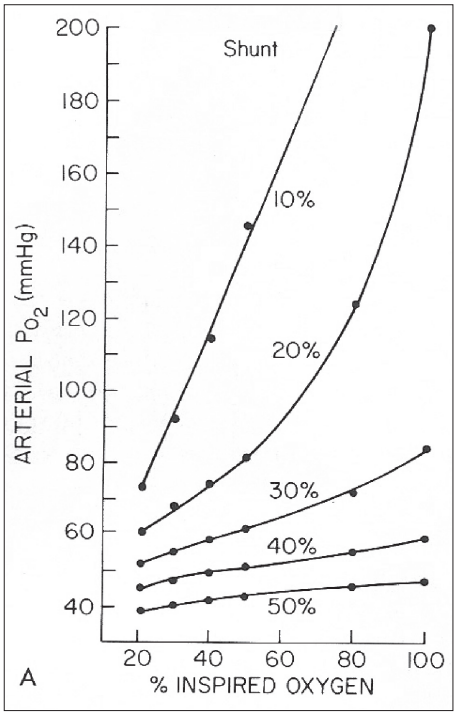


Figure 2-7. Effect of changing inspired oxygen concentration on arterial P_{O_2} in lungs with shunts of varying degrees from 10% to 50%. In larger shunts, administering supplemental oxygen has little effect on arterial P_{O_2}. Addition of 100% oxygen has little effect on arterial P_{O_2} when the shunt is greater than 30%.

From Dantzker DR. Gas exchange in the adult respiratory distress syndrome. *Clin Chest Med.* 1982;3:57–67, with permission from Elsevier.

A shunt will result in decreased oxygen concentration but does not usually produce elevated arterial carbon dioxide levels. The chemoreceptors normally sense the elevation of arterial carbon dioxide and respond by increasing ventilation.

$\dot{V}/\dot{Q}$ Mismatch

$\dot{V}/\dot{Q}$ mismatch is one of the most difficult of the causes of hypoxemia to understand. If blood flow and ventilation are not matched in areas of the lung, then inadequate gas exchange occurs. If an area of the lung is perfused but not ventilated, as in the case of pneumonia or atelectasis (lung collapse), then it acts like a small shunt. Deoxygenated blood goes through the nonfunctional lung without being oxygenated and then mixes with blood from other areas of the lung that are oxygenated.

A shunt can be distinguished from $\dot{V}/\dot{Q}$ mismatch by the hyperoxia test. In the case of the latter, addition of 100% oxygen will increase the arterial oxygen saturation. However, if a true shunt exists, the supplemental oxygen will raise the arterial saturation by only a small amount (usually $<5\%$).[2]

Low Venous P_{O_2}

The normal P_{O_2} of venous blood is 45 mm Hg and has a saturation of 75%. If venous blood has an unusually low P_{O_2}, then the blood may not be fully oxygenated by the time it finishes its course through the pulmonary capillaries. Low venous P_{O_2} may result when the body extracts more oxygen from the blood than usual, such as in anemia, fever, and low cardiac output. Normally, the lung can compensate for the abnormally low venous P_{O_2}. However, it may not during exercise or if there is another superimposed problem, such as $\dot{V}/\dot{Q}$ mismatch, shunt, or diffusion impairment.

Oxygen Transport

Oxygen is primarily carried in the blood bound to hemoglobin; a very small amount is dissolved in plasma. The total amount carried by the blood is called the *oxygen content.* The maximum amount of oxygen that can be combined with hemoglobin is called the *oxygen capacity.* One gram of hemoglobin can combine with 1.34 mL of oxygen.[2] The oxygen capacity for a normal child with a hemoglobin concentration of 14 g/100 mL is 19.5 mL oxygen/100 mL of blood.

The oxygen saturation is the percentage of binding sites of hemoglobin that have oxygen attached. The normal oxygen saturation is 98% for arterial blood and 75% for venous blood. In general, oxygen saturation increases as the P_{O_2} of the blood increases. The dissociation curve for oxygen is S-shaped and is shown in **Figure 2-8.** Between an oxygen tension of 20 and 75 mm Hg, there is a sharp, linear increase in oxygen saturation. After that, large increases in arterial P_{O_2} cause small increases in oxygen saturation. The P_{50} is the oxygen tension at which 50% of the hemoglobin is saturated.

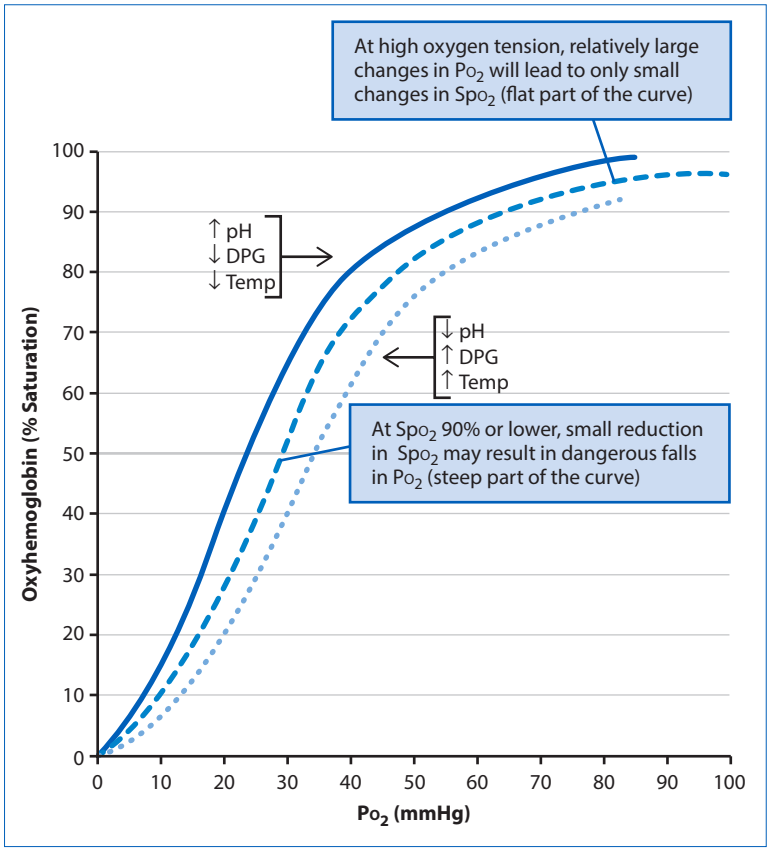


Figure 2-8. Oxygen dissociation curve. The oxygen dissociation curve is shown for a pH of 7.4, P_{CO_2} of 40 mm Hg, temperature of 37 °C, and hemoglobin concentration of 15 g/100 mL (dashed line). Many factors can shift the oxygen dissociation curve to the right and cause oxygen to bind less avidly to hemoglobin (dotted line): increased temperature, acidosis, hypercarbia, and increased 2,3-diphosphoglycerate (2,3-DPG) levels. Conversely, decreased temperature, alkalosis, low carbon dioxide levels, and decreased 2,3-DPG levels shift the curve to the left (solid line); thus, oxygen binds more avidly to the hemoglobin, and the effect is decreased delivery to the tissues. Spo_2, oxygen saturation as measured by pulse oximetry. P_{50} is the oxygen tension when hemoglobin is 50% saturated with oxygen. When hemoglobin-oxygen affinity increases, the oxyhemoglobin dissociation curve shifts to the left and decreases P_{50}. When hemoglobin-oxygen affinity decreases, the oxyhemoglobin dissociation curve shifts to the right and increases P_{50}.

Adapted from Krishnan S. Oximetry and capnography. In: Stokes DC, Dozor AJ, eds. *Pediatric Pulmonology, Asthma, and Sleep Medicine: A Quick Reference Guide.* Itasca, IL: American Academy of Pediatrics; 2018: 63–67.

Factors That Alter the Affinity of Hemoglobin for Oxygen

Many factors can affect the affinity of hemoglobin for oxygen. Acidosis, hypercarbia, hyperthermia, and increased 2,3-diphosphoglycerate (2,3-DPG) levels can decrease the affinity. The result is a shift in the oxygen dissociation curve to the right, which is shown in **Figure 2-8.** As a result, the hemoglobin is less saturated at a given oxygen tension. The converse is also true: alkalosis, hypocarbia, hypothermia, and decreased 2,3-DPG levels shift the oxygen dissociation curve to the left, and the hemoglobin has a higher saturation at a given oxygen tension.

Another common reason for altered oxygen affinity is alterations in the hemoglobin itself. The hemoglobin in patients with sickle cell disease has less affinity for oxygen than that in those with normal hemoglobin, so patients with sickle cell disease may have a lower oxygen saturation in room air.[13,14] In contrast, fetal hemoglobin or red blood cells that have been stored in a blood bank have a higher affinity for oxygen because of a decreased level of 2,3-DPG.[15] The saturation of oxygen can also be lower because it is bound by other molecules, such as in carbon monoxide poisoning or methemoglobinemia.

Decreases in oxygen capacity and, consequently, impaired oxygen delivery to tissues can be caused by a decrease in oxygen saturation or anemia. As previously described, decreases in oxygen saturation can be caused by decreases in arterial oxygen concentration (pneumonia, atelectasis, lung disease, high altitude), decreases in affinity of hemoglobin for oxygen, or sites on the hemoglobin being bound by other molecules.

Assessment of Oxygenation and Ventilation

It is extremely difficult to assess the adequacy of oxygenation and ventilation by means of physical examination. The most specific sign of impaired oxygenation is cyanosis, which can usually be detected at an oxyhemoglobin saturation of 80%.[16] However, it may be difficult to assess in children with anemia or dark-colored skin. Signs of hypoxemia include tachypnea and tachycardia, and progression may be associated with confusion, motor incoordination, and agitation. Impaired ventilation is even more difficult to determine. Certainly, when a patient is apneic or has an extremely low respiratory rate, an impairment of ventilation is likely. Tidal volume is difficult to determine from examination of chest excursion; dead space cannot be assessed.[17] Other late signs of impaired ventilation are hypotension, flushed skin, diaphoresis, tachycardia, and lethargy.

Noninvasive Monitoring of Oxygen and Carbon Dioxide

Both oxygenation and ventilation can be assessed noninvasively. Pulse oximetry is the most common way to assess oxygenation and is based on the principle that oxyhemoglobin and reduced hemoglobin have different light

absorption spectra. Pulse oximetry detects arterial pulsations and measures the arterial oxygen saturation. However, it has a few deficiencies. It is insensitive to changes at high arterial P_{O_2} (because of the shape of the oxygen dissociation curve) and inaccurate at low arterial oxygen saturation (Sa_{O_2}). Pulse oximetry may be less sensitive to hypoxemia in patients with more darkly pigmented skin. There is also a delay in response to changes in Sa_{O_2}, particularly when the oximeter is placed on an extremity. In addition, a number of factors can give spurious results; these factors are listed in **Box 2-1.**[18,19]

Box 2-1

Causes of Inaccuracies in Pulse Oximetry

- Carboxyhemoglobin
- Methemoglobin
- High-intensity ambient light
- Impaired perfusion
- Nail polish and artificial nails
- Intravenous dyes
  - Methylene blue
  - Indigo carmine
  - Indocyanine green

End-tidal carbon dioxide monitoring (capnography) can be used to assess ventilation.[20] The carbon dioxide in exhaled air is measured by means of infrared light absorption or mass spectrometry. A representative capnograph is shown in **Figure 2-9.** In healthy individuals, the carbon dioxide in the exhaled

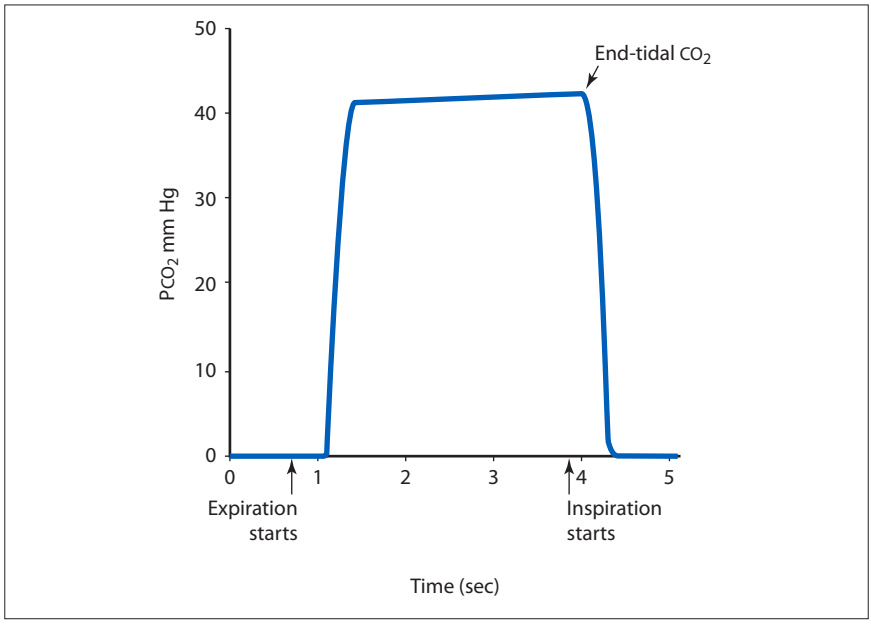


Figure 2-9. Normal capnograph. Carbon dioxide is measured in the exhaled air. The beginning of the breath is filled with dead space volume. At the end of the breath, the end-tidal P_{CO_2} reflects alveolar P_{CO_2}. It is a noninvasive way of monitoring arterial P_{CO_2}.

From Levitzky M. Pulmonary Physiology. 4th ed. New York: McGraw-Hill, Inc; 1995:73, with permission.

air will be slightly less than the arterial P_{CO_2}. Larger differences may occur in disease states in which there is more dead space, such as in patients who are anesthetized or those with pulmonary embolism.[21]

Another noninvasive method to estimate arterial P_{O_2} and P_{CO_2} is by using a transcutaneous monitor, which measures skin-surface P_{O_2} and P_{CO_2}. The transcutaneous monitor increases the local temperature of the skin, producing hyperperfusion, and determines the P_{O_2} and P_{CO_2} by using a sensor.[22] Because of the widespread use of pulse oximetry and the potential risk of thermal injury, the transcutaneous monitor is usually used only to estimate arterial P_{CO_2} and is referred to as *transcutaneous* P_{CO_2} (TcP_{CO_2}). This technique has advantages and disadvantages. TcP_{CO_2} values are typically higher than the true arterial P_{CO_2}. Inaccurate readings may occur in patients with hyperoxemia, hypoperfusion, or skin edema and from improper electrode placement.[22] However, TcP_{CO_2} values may provide a better estimate of arterial P_{CO_2} than does end-tidal P_{CO_2}, particularly in neonates and preterm infants in whom end-tidal P_{CO_2} measurements often lead to underestimation of the true arterial P_{CO_2}.[23] Transcutaneous P_{CO_2} monitoring is especially useful in neonatal and pediatric intensive care units, sleep laboratories, and operating rooms.[22–25]

Arterial Blood Gas Analysis

The gold standard for assessing both oxygenation and ventilation is arterial blood gas analysis.[26] The actual value of measured arterial P_{O_2} is important. However, in patients with hypoventilation or receiving supplemental oxygen, it is also useful to compare it with what it should ideally be. The difference between the predicted arterial P_{O_2}, calculated from the alveolar P_{O_2} (P_{AO_2}), and what is measured is known as the *alveolar-arterial (A-a) gradient;* it is usually less than 10 mm Hg.[27] The P_{AO_2} can be calculated from the simplified alveolar gas equation as follows:

$$P_{AO_2} = P_{IO_2} - Pa_{CO_2}/R,$$

and because $P_{IO_2} = F_{IO_2}(Patm - P_{H_2O})$,

$$P_{AO_2} = F_{IO_2}(Patm - P_{H_2O}) - Pa_{CO_2}/R,$$

where P_{AO_2} is the alveolar P_{O_2}, P_{IO_2} is the inspired P_{O_2}, Pa_{CO_2} is the arterial P_{CO_2}, and R is the respiratory exchange ratio of carbon dioxide and oxygen (which is estimated to be 0.8 for the whole lung). F_{IO_2} is the percentage of oxygen, Patm is atmospheric pressure (760 mm Hg at sea level), and P_{H_2O} is water vapor pressure (47 mm Hg at 37° C). So, for example, a patient breathing 40% oxygen with an arterial P_{CO_2} of 35 mm Hg has a P_{O_2} of 100 mm Hg. However, on the basis of the equation, the patient should have an arterial P_{O_2} of 240 mm Hg at sea level. The A-a gradient is extremely elevated at 140 mm Hg. There are other ways to assess impairment of oxygenation by using the P_{AO_2} as well as other variables[27–31] (**Table 2-4**).

The adequacy of ventilation can be assessed by measuring arterial blood gas; there is an inverse correlation between ventilation and the arterial P_{CO_2}. However, the number must be assessed in the context of the clinical picture. For example, a patient with asthma who is in severe distress with a respiratory rate of 60 breaths/min has a P_{CO_2} of 40 mm Hg. Although this is a normal value, it implies impending respiratory failure in a patient with this degree of tachypnea and work of breathing.

Measurement of arterial blood gases is invasive and may be technically difficult and painful. Surrogate measures involve using either a venous or a capillary blood sample. In the latter, a finger or toe is pierced with a lancet and the blood collected. Neither measure is useful for assessing arterial oxygenation because the samples are mixed with venous blood. Because venous blood has a higher P_{CO_2}, both samples will lead to overestimation of the true arterial P_{CO_2} (and indicate the worst-case scenario). In cases of cardiac arrest, the discrepancy between the 2 values widens.[32]

Table 2-4. Measures of Impairment in Oxygenation

Name of Index	Equation	Normal Values
A-a oxygen gradient	$P_{AO_2} - Pa_{O_2}$	< 10 mm Hg
A-a oxygen ratio	Pa_{O_2}/P_{AO_2}	> 0.75
Pa_{O_2}:F_{IO_2} ratio	Pa_{O_2}/F_{IO_2}	300–500 mm Hg
Oxygenation index	$F_{IO_2} \times$ mean airway pressure $\times$ 100/Pa_{O_2}	< 5
Oxygen saturation index	$F_{IO_2} \times$ mean airway pressure $\times$ 100/Sp_{O_2}	< 6.5

Normal values are from references [27–31].

Mechanics of Breathing

The muscles of respiration act like a pump to move air in and out of the lungs. The efficiency of the pump is determined by the elastic properties of the chest wall and lungs and the resistance of the airways. Disease processes can alter these relationships and lead to respiratory failure.

Muscles of Breathing

The muscles of breathing are depicted in **Figure 2-10.** The diaphragm is the primary muscle of inspiration. It is a dome-shaped muscle and is responsible for two-thirds of the air that enters the lungs during quiet breathing. When it contracts, it forces the abdominal contents down and widens the rib cage. When it is paralyzed, as in the case of phrenic nerve or cervical spine injury, it moves up instead of down during inspiration. Other muscles of inspiration are the external intercostal muscles and other accessory muscles, such as the scalene and sternocleidomastoid muscles.

In normal quiet breathing, expiration is passive; the recoil of the lungs forces the air out. However, in active breathing, such as with exercise, coughing, or singing, or in lower airway obstruction, expiratory muscles are recruited.[1] The muscles of expiration are the abdominal and internal intercostal muscles. Neuromuscular disease, abdominal muscle weakness, or postoperative abdominal pain may impair cough, leading to a decreased ability to clear secretions.

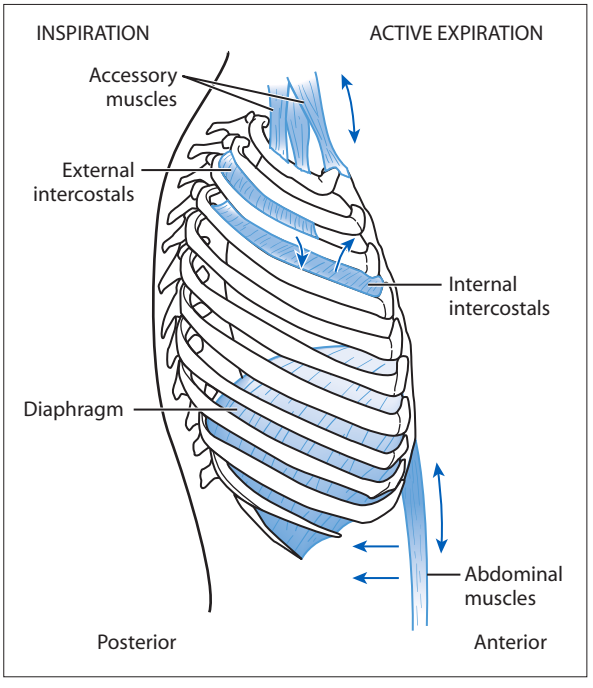


Figure 2-10. Muscles of breathing. The inspiratory muscles are the diaphragm, external intercostals, and accessory muscles such as the sternocleidomastoid and scalene. Expiration with quiet breathing is passive. Active expiration requires the use of the abdominal and internal intercostal muscles.

Elastic Properties of the Lung and Chest Wall

The interaction of the lungs and chest wall determines the effectiveness of the pump. The lungs and individual alveoli act like balloons. Pressure is required to inflate the lungs; without it, they would tend to collapse. At low volumes, it is difficult to overcome the elastic forces and to inflate the lung; high pressures are required. At medium volumes, less pressure is required to inflate the lungs. At high volumes, it is again more difficult, and higher pressures are required. The ease with which the lungs can be stretched is known as compliance. Reduced lung compliance can be seen in conditions such as fibrosis, pulmonary edema, and acute respiratory distress syndrome. Increased lung compliance is seen in emphysema and aging. One of the important functions of surfactant, a phospholipid produced by the lung, is to increase lung compliance by reducing the surface tension of the alveoli. Consequently, in preterm neonates in whom there is a developmental decrease in surfactant production, there is a decrease in lung compliance and the development of neonatal respiratory distress syndrome.

The chest wall has elastic properties and its own compliance. Its inherent tendency is to expand, which counterbalances the tendency of the lungs to collapse. The relationship between the forces of the chest wall and lung volume is shown in **Figure 2-11.** The resting lung volume (functional residual capacity) represents the equilibrium between the 2 forces (**Figure 2-11A**). Lung volumes are smaller if the compliance of either the chest wall (**Figure 2-11B**) or the lung (**Figure 2-11C**) is decreased.

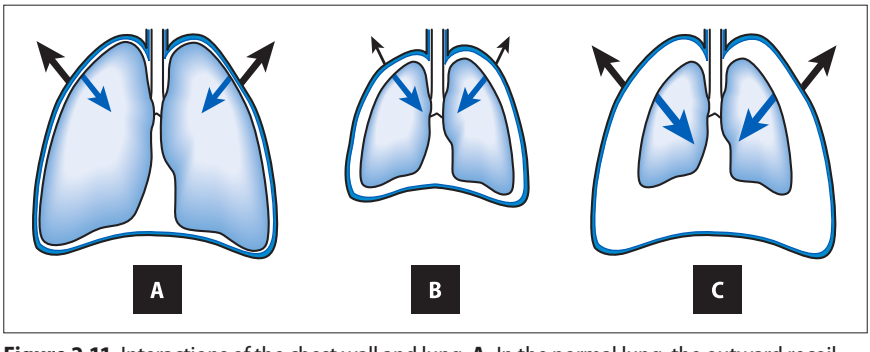


Figure 2-11. Interactions of the chest wall and lung. **A,** In the normal lung, the outward recoil of the chest wall balances the inward recoil of the lung. The final volume of the lung depends on the equilibrium between them. **B,** If the chest wall becomes less compliant and more stiff, there is less outward force to balance out the inward recoil of the lungs. The result is a smaller lung volume. Examples include obesity, neuromuscular weakness, and trauma to or defects in the chest wall. **C,** If the lungs become less compliant, they overcome the outward force of the chest wall and have a smaller resting volume. Examples include pulmonary edema, interstitial fibrosis, and acute respiratory distress syndrome.

Airway Resistance

Resistance is the force that opposes the forward motion of the airflow. Approximately 25% to 40% of the total resistance to airflow is located in the upper airway: nose and mouth passages and larynx.[1,5] The airways and lung tissue provide the remainder of the resistance. Air flows through the airways as if they were tubes. In some areas, the flow is very orderly and is known as laminar flow. In some places, such as in narrowed or branch points, it is disorganized and is known as turbulent flow. In laminar flow, resistance is directly proportional to the radius^4 of the airways. Consequently, if the radius of an airway is narrowed by one-half, the resistance increases by 16-fold. In an infant's or child's airway, which is already narrow relative to an adult's, small changes in caliber produce large changes in the degree of obstruction. Turbulent flow depends on gas density. Thus, gases with a low density, such as helium, are administered to decrease resistance in patients with airway obstruction.[33]

Work of Breathing

The work involved in breathing is proportional to the tidal volume and the change in pressure required to move the air. The work of breathing increases when the compliance of the chest wall or lung is decreased; more negative pressure is required to breathe. In addition, the work of breathing increases with increased airway resistance, such as with asthma or upper airway obstruction. Infants and young children are at a mechanical disadvantage; their respiratory system works less efficiently than an adult's. Their chest walls are more compliant, and their diaphragms are flatter and more likely to fatigue, which predisposes them to respiratory failure.

Assessment of Lung Mechanics

An alteration in lung mechanics may result in signs of respiratory distress. Decreases in lung and chest wall compliance are usually heralded by tachypnea. Increased effort of breathing is manifested by recruitment of accessory muscles, such as the sternocleidomastoid or scalene muscles. Retractions, bowing in of the muscle and soft tissue of the chest wall with inspiration, indicate that high pressures are generated to move air through the airways. They can be seen subcostally, intercostally, and in the suprasternal notch. The higher the retractions, the more severe the respiratory distress. Nasal flaring is an attempt to decrease the resistance of breathing by decreasing the resistance of the nasal passages.

Airflow, lung volumes, and airway resistance can be measured by means of pulmonary function testing and will be further described in Chapter 6, Pulmonary Function Testing.

key points

Gas Exchange

- The P_{O_2} in the alveoli is determined by the balance between the amount that flows in and the amount that is removed in the pulmonary capillaries.

Ventilation

- In each breath (tidal volume), some of the air goes into the alveoli (alveolar volume) and is available for gas exchange, while the rest remains in the conducting airways and is known as dead space.
- The arterial P_{CO_2} is inversely proportional to alveolar ventilation.
- Increases in arterial P_{CO_2} can be caused by decreased tidal volume, decreased respiratory rate, increased dead space, or increased carbon dioxide production.
- In chronic respiratory acidosis, after renal compensation, the bicarbonate will increase by a total of 4 mEq/L for each 10-mm increase in P_{CO_2}.
- Arterial P_{CO_2} can be approximated noninvasively by end-tidal carbon dioxide or transcutaneous carbon dioxide monitoring.

Oxygenation

- Hypoxemia, or low arterial P_{O_2}, may be caused by low inspired partial pressure of oxygen (ie, high altitude), hypoventilation, diffusion impairment, shunt, $\dot{V}/\dot{Q}$ mismatch, and abnormally low venous blood saturation (under certain conditions).
- Oxygen is primarily carried in the blood bound to hemoglobin; a very small amount is dissolved in plasma.
- The P_{50} is the oxygen tension at which 50% of the hemoglobin is saturated.
- The affinity of hemoglobin for oxygen can by altered by changes in blood pH, P_{CO_2}, temperature, and 2,3-DPG levels.
- Arterial oxygen saturation can be approximated noninvasively by using pulse oximetry.
- The degree of impairment in oxygenation can be assessed by calculating the A-a oxygen gradient or other indexes such as A-a oxygen ratio, P_{aO_2}:F_{IO_2} ratio, oxygenation index, and oxygen saturation index.

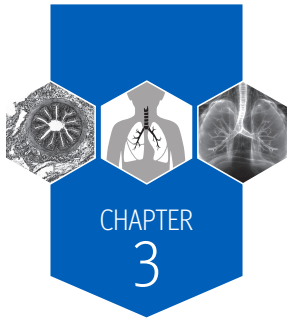
Mechanics of Breathing

- The diaphragm is the primary muscle of inspiration.
- The ease with which the lungs can be stretched is known as *compliance,* which is decreased in conditions such as pneumonia, pulmonary edema, and acute respiratory distress syndrome.
- In laminar airflow, which normally occurs only in small airways, resistance is directly proportional to the radius^4 of the airways, and small changes in the airway caliber produce large changes in resistance.
- The work of breathing increases when the compliance of the chest wall or lung is decreased or airway resistance is increased.
- Infants and young children are at higher risk of respiratory failure in part because their chest walls are more compliant and their diaphragms are flatter and more prone to fatigue.

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CHAPTER
3

Applied Pulmonary Physiology

Maki Ishizuka, MD
Christopher M. Cielo, DO, MS

Exercise Physiology

Understanding exercise physiology in children is important because of the increasing participation of young children in competitive sports. The energy to power skeletal muscle depends on adenosine triphosphate (ATP). Combined with water, hydrolysis splits one of the phosphate groups, which results in the formation of adenosine diphosphate. To replenish the limited stores of ATP, phosphorylation adds a phosphate group to adenosine diphosphate. If phosphorylation occurs in the presence of oxygen, the reaction is aerobic metabolism; in the absence of oxygen, the reaction is anaerobic metabolism.

The ventilatory response to exercise results from increased demand for oxygen and excretion of carbon dioxide (CO_2). Exercise results in an almost immediate increase in oxygen consumption, and without oxygen stores in the body, the carotid chemoreceptors register hypoxemia. Ventilation appears to increase before there is hypoxemia and is probably driven by a neural response. Hypoxemia results in higher minute ventilation, which is the tidal volume (the volume of air inspired and expired during a passive breath) multiplied by the number of breaths per minute (frequency). Both tidal volume and frequency increase in response to increased metabolic demands. There is also an increase in blood flow to the lungs and an increase in lung diffusion capacity, which is a measure of the transport of oxygen passing from the alveolus across the alveolar-capillary membrane into the pulmonary circulation. The frequency increases from the resting rate of 12 to 15 breaths/min to 45 to 70 breaths/min depending on age. The tidal volume increases to levels that may reach 50% to 60% of the vital capacity, which is the largest active breath than can be inspired and expired. As the degree of exercise increases, there is a linear increase in tidal volume that reaches a maximum, and increased minute ventilation then results from an increase in the frequency of breathing.

The cardiac responses to exercise are increased heart rate and stroke volume, which increase cardiac output. Cardiac output increases more slowly than does ventilation during exercise. Resting heart rate averages 60 to 80 beats/min and

increases in direct proportion to the degree of exercise to a maximum that is approximately 220 minus the age in years. Stroke volume also increases with exercise intensity, and training can increase this volume significantly. The increase in cardiac output results in increased pulmonary arterial and venous pressure, which accounts for the recruitment and distention of pulmonary capillaries.

The point at which the oxygen consumption does not increase with increasing exercise intensity is $\dot{V}O_2max$, which is also known as *maximal oxygen uptake* or *aerobic capacity*, expressed as milliliters of oxygen per kilogram of body weight per minute. The expression relative to weight or body surface area is useful in comparing a child with other children (and adults of different sizes).

There is a great deal of variety in $\dot{V}O_2max$, and genetics plays a major role in these differences.[1] Responders to training make substantial improvement, and nonresponders make little or no progress in $\dot{V}O_2max$. Maximal ventilation increases to some extent with training, but at submaximal levels of exercise, ventilation is consistently lower after training.[2] In children, both aerobic and anaerobic work capacity increase with training as measured by increase in $\dot{V}O_2max$ and decreased lactate production for a given workload.[3]

High-Altitude Illness

Ascending to high altitude (ie, > 1,500 m [5,000 ft]) results in hypoxia because the P_{O_2} of inspired air decreases with ascent. Mild altitude elevation is considered to be higher than 1,500 m (5,000 ft); moderate, 2,000 to 3,500 m (6,700–11,700 ft); very high, 3,500 to 5,500 m (11,700–18,300 ft); and extreme, higher than 5,500 m (18,300 ft). **Table 3-1** shows the approximate alveolar oxygen (ie, the oxygen concentration at the level of the gas exchange portion of the lung) at different altitudes. The physiological effect of the reduced inspired oxygen depends principally on the rate of ascent and to a lesser extent on the medical history of the individual. High-altitude illness is a spectrum of cerebral and pulmonary syndromes induced by the hypoxic stress of high altitude. The susceptibility of children to altitude illness is comparable with that of adults. However, children with a history of cardiopulmonary conditions, at increased risk of pulmonary hypertension, or with a recent upper respiratory illness should not travel to high altitude. Such travel should also be avoided for infants during the first 4 to 6 weeks after birth, or longer for those born prematurely, especially those with lung diseases.

Table 3-1. Altitude and Oxygen Tensions

Altitude	Meters (Feet)	Approximate Alveolar Oxygen Tension (mm Hg)
Sea level	0	100
Mild elevation	1,500–2,000 (5,000–6,700)	80
Moderate elevation	2,000–3,500 (6,700–11,700)	60
Very high elevation	3,500–5,500 (11,700–18,300)	40
Extreme elevation	> 5,500 (> 18,300)	< 40

Acclimatization

The percentage (fraction) of oxygen in inspired air remains approximately 21% (0.21), but during ascent the Po_2 decreases with the decrease in barometric pressure. Compensatory responses to acute hypobaric hypoxia are known as *acclimatization*. The physiological response to hypoxia occurs both immediately and over time. The immediate response is an increase in minute ventilation when the carotid and aortic bodies register the hypoxemia. As alveolar ventilation increases, there is resultant decrease in $Paco_2$, which causes a mild respiratory alkalosis and a reduction in the degree of hyperventilation. Over time, renal compensation for the respiratory alkalosis causes excretion of bicarbonate, which normalizes the pH. This ventilatory acclimatization takes place over 3 to 4 days. After a rapid and sustained increase in altitude, circulatory changes involving systemic, cerebral, and pulmonary vasculature occur. Sympathetic activity increases cardiac output, blood pressure, heart rate, and venous tone. Hypoxia causes pulmonary vasoconstriction and an increase in cerebral blood flow.

Hemoconcentration results from reduction in plasma volume caused by fluid shifts and diuresis, which improves the oxygen-carrying capacity of the blood. Hypoxemia stimulates the production of erythropoietin, resulting in increased red blood cell production over time.

Acute Mountain Sickness

Acute mountain sickness (AMS) is a clinical syndrome characterized by headache plus 1 of several other symptoms including anorexia, nausea, dizziness, malaise, and sleep disturbance. Symptom onset tends to be 6 to 12 hours after ascent greater than 2,000 m (6,700 ft) but can be as early as 1 to 2 hours or as late as 24 hours. There are no approved clinical measures for diagnosing AMS, but several tools have been studied in a research context. The simplest screening tool for assessing AMS is the Clinical Functional Score; the 2018 Lake Louise Acute Mountain Sickness Score may be used to assess the severity of AMS as shown in **Box 3-1.**[4] Children are at risk for AMS but not necessarily more than adults are.

Box 3-1

AMS Scores

Clinical Functional Score

Overall, if you had AMS symptoms, how did they affect your activities?

0. Not at all
1. Symptoms present, but did not force any change in activity or itinerary
2. My symptoms forced me to stop the ascent or to go down on my own power
3. Had to be evacuated to a lower altitude

2018 Lake Louise Acute Mountain Sickness Score

Headache

0. None at all
1. Mild headache
2. Moderate headache
3. Severe headache, incapacitating

Gastrointestinal symptoms

0. Good appetite
1. Poor appetite or nausea
2. Moderate nausea or vomiting
3. Severe nausea and vomiting, incapacitating

Fatigue and/or weakness

0. Not tired or weak
1. Mild fatigue/weakness
2. Moderate fatigue/weakness
3. Severe fatigue/weakness, incapacitating

Dizziness/light-headedness

0. No dizziness/light-headedness
1. Mild dizziness/light-headedness
2. Moderate dizziness/light-headedness
3. Severe dizziness/light-headedness, incapacitating

An AMS Clinical Functional Score of 2 or higher indicates AMS. On the basis of the 2018 Lake Louise Acute Mountain Sickness Score, AMS is indicated if the sum of the scores is 3 points or higher, including headache (mild AMS, 3–5 points; moderate AMS, 6–9 points; severe AMS, 10–12 points).

Abbreviation: AMS, acute mountain sickness.

From Roach RC, Hackett PH, Oelz O, et al; Lake Louise AMS Score Consensus Committee. The 2018 Lake Louise Acute Mountain Sickness Score. *High Alt Med Biol.* 2018;19(1):4–6.

High-Altitude Cerebral Edema

High-altitude cerebral edema (HACE) may be associated with AMS or high-altitude pulmonary edema. The major symptoms are ataxia and altered consciousness; HACE is essentially the severe form of AMS. The cerebral edema may cause papilledema or retinal hemorrhage and even cranial nerve palsy. Drowsiness is followed by stupor. Death may occur from brainstem herniation.

High-Altitude Pulmonary Edema

High-altitude pulmonary edema (HAPE) is a noncardiogenic pulmonary edema. As noted previously, hypoxia causes pulmonary vasoconstriction, and pulmonary hypertension results. The combination of increased pressure and hypoxia-related increased capillary permeability leads to leakage of fluid in the lungs. Some children may have a genetic predisposition to HAPE. Genes affecting the renin-angiotensin-aldosterone system pathway, the nitric oxide pathway, and the hypoxia-inducible factor pathway may all be associated with increased susceptibility to HAPE.[5] In addition, the presence of preexisting pulmonary hypertension before the ascent exacerbates the effect of hypoxia. The risk of HAPE is increased by exercise because of the increased cardiac output and oxygen deficit. Travel to high altitude should be avoided during the first 4 to 6 weeks after birth in children with a history of cardiopulmonary conditions or Down syndrome, at increased risk for pulmonary hypertension, or with a recent upper respiratory illness. In children with a history of prematurity, travel to altitude should be done with caution, even at older ages.

High-altitude pulmonary edema usually occurs 2 to 4 days after the ascent and tends to be worse at night. The primary symptom is cough with progressive dyspnea. In children, HAPE manifests as increasing respiratory distress over 1 to 2 days, but it may develop more precipitously. Cough and decreased exercise ability are usually the first symptoms to manifest, and only late in the illness does production of frothy bloodstained sputum occur. Young children may develop only pallor and depressed consciousness or other nonspecific symptoms such as increased fussiness, crying, decreased appetite, decreased playfulness, disrupted sleep, and possibly vomiting. Low-grade fever may be present, so a diagnosis of pneumonia may be incorrectly considered. In children with HAPE, chest radiography typically shows unilateral or bilateral patchy infiltrates with a normal heart size.

Reentry HAPE occurs when persons who live at high altitude leave for a time and then return. Children are more susceptible than adults. Symptoms develop as rapidly as 24 hours after returning. It is diagnosed and managed the same as HAPE.

It is important to recognize HAPE because it has the potential to be life-threatening within a few hours. The Lake Louise Consensus Definition for HAPE is summarized in **Box 3-2.**[6] Fifty percent of people with HAPE have AMS, and 14% have HACE.

Box 3-2

Lake Louise Consensus Definition for HAPE

At least 2 of the following symptoms and at least 2 of the following signs are necessary for diagnosis.

Symptoms

Weakness or decreased exercise ability
Cough
Dyspnea at rest
Chest tightness or congestion

Signs

Crackles or wheezing in at least 1 lung field
Central cyanosis or arterial oxygen desaturation relative to altitude
Tachycardia
Tachypnea

Abbreviation: HAPE, high-altitude pulmonary edema.

Derived from Hackett PH, Oelz O. The Lake Louise Consensus on the definition and quantification of altitude illness. In: Sutton JR, Houston CS, Coates G, eds. *Hypoxia and Mountain Medicine.* Queen City Press; 1992:327–330.

Chronic Mountain Sickness

Chronic mountain sickness (CMS) occurs with persons born at high altitude as well as lowlanders who spend a prolonged period at high altitude. The symptoms are related to polycythemia and include headache, dizziness, lethargy, difficulty sleeping, and impaired mentation and memory. The disorder is incompletely understood because actual hematocrit levels tend to be higher than expected considering the oxygen saturation. In addition, there is hypoventilation and blunted hypoxic ventilatory response. Pulmonary hypertension may develop. The first consideration is to descend to a lower altitude, but this may not be practical. The management of CMS is lowering the red blood cell volume by means of phlebotomy. Low-flow oxygen may be beneficial.[7]

Management of Altitude Sickness

Descent remains the single best treatment for AMS, HACE, or HAPE. Symptoms of AMS may improve with a descent as small as 500 to 1,000 m (1,700–3,300 ft). The first treatment of AMS is supplemental oxygen to raise peripheral capillary oxygen saturation greater than 90%. Symptoms can be reduced with acetazolamide, effective within 24 hours. Dexamethasone is

equivalently effective, with a response within about 12 hours. Acetazolamide is also used as a preventive treatment, especially in those with a history of AMS or HAPE, but it is not used in the treatment of HAPE. The headache associated with AMS responds well to ibuprofen; however, ibuprofen is not proved to improve the full spectrum of AMS symptoms. Nifedipine should be used for HAPE treatment when descent is delayed or access to supplemental oxygen is limited. Nifedipine can be also used for HAPE prevention for susceptible individuals. Early diagnosis of HAPE is essential because it is the cause of most deaths from high-altitude illness. It is important not to exacerbate hypoxia during the descent by additional exertion. **Table 3-2** presents medical therapies for high-altitude sickness, but caution is necessary for children because data are limited. Supplemental oxygen to keep peripheral capillary oxygen saturation greater than 90% may be used to treat AMS, HACE, or HAPE. Portable hyperbaric chambers are effective for treating severe altitude illness. A rapid pressurization of the patient simulates a descent of about 1,500 to 2,500 m (5,000–8,300 ft). However, use of a portable hyperbaric chamber should not delay descent.

Table 3-2. Therapy for High-Altitude Illness

Agent	Indication	Route	Dosage
Acetazolamide	AMS, HACE prevention	Oral	125 mg every 12 h **Pediatrics:** 2.5 mg/kg every 12 h
	AMS treatment	Oral	250 mg every 12 h **Pediatrics:** 2.5 mg/kg every 12 h (Maximum: 125 mg per dose)
Dexamethasone	AMS, HACE prevention	Oral	2 mg every 6 h or 4 mg every 12 h **Pediatrics:** Should not be used for prophylaxis
	AMS, HACE treatment	Oral, IV, IM	**AMS:** 4 mg every 6 h **HACE:** 8 mg once, then 4 mg every 6 h **Pediatrics:** 0.15 mg/kg every 6 h (Maximum: 4 mg per dose)
Ibuprofen	AMS prevention	Oral	600 mg every 8 h
Nifedipine	HAPE prevention	Oral	30 mg extended-release every 12 h or 20 mg extended-release every 8 h
	HAPE treatment	Oral	30 mg extended-release every 12 h or 20 mg extended-release every 8 h

Abbreviations: AMS, acute mountain sickness; HACE, high-altitude cerebral edema; HAPE, high-altitude pulmonary edema; IM, intramuscular; IV, intravenous.

Adapted from Luks AM, Auerbach PS, Freer L, et al. Wilderness Medical Society clinical practice guidelines for the prevention and treatment of acute altitude illness: 2019 update. *Wilderness Environ Med.* 2019;30(4S):S3–S18.

Underwater Medicine

Shallow Water Blackout

Hyperventilation before diving lowers CO_2 levels, which reduces the stimulus to breathe and prolongs the breath-holding time, but it can be dangerous. It occurs when free diving because as the diver descends, alveolar P_{O_2} and P_{CO_2} increase, but CO_2 is so soluble that it diffuses into the tissues. The P_{O_2} increases artificially, prolonging the breath-holding time, and then when the diver ascends, the P_{O_2} decreases dramatically so that unconsciousness may occur before the diver reaches the surface. The risk is increased because of simultaneous hypocapnic vasoconstriction of the cerebral vessels. This combination is thought to explain many of the accidents that occur in swimming pools. Advice to parents should include telling children not to hyperventilate before swimming underwater and to avoid prolonged breath holding.

Thoracic Squeeze

This condition results during breath-hold diving, also known as *free diving*. Taking a full breath and free diving to 10 m (33 ft) would cause the lungs to be one-half of their original size. At 20 m (66 ft), they would be one-third, and at 30 m (99 ft) they would be one-fourth. The air within the lungs is compressed during descent, and it is possible to compress to a volume smaller than the residual volume of the lungs. The chest wall will not be able to be compressed further, and the squeeze results in blood being forced into the alveoli because of the negative pressure within the lungs. The result is wheezing and hemoptysis. Free divers attempt to improve their ability to dive to deeper levels by *packing* or *stacking*, which consists of glossopharyngeal breathing whereby the tongue and pharynx force air into the lung to exceed total lung capacity. A nontrained free diver risks lung injuries, blackouts, and potentially drowning, so training specific to free diving should be considered to improve safety.

Scuba Diving

Scuba is an acronym for *self-contained underwater breathing apparatus*, and the sport of scuba diving is very popular. There are limits of lower age set by the 2 major certifying agencies in North America. The Professional Association of Diving Instructors (PADI) requires that a child be 10 years or older to take the certification course. Students younger than 15 will receive the PADI Junior Open Water Diver certification, which can then be upgraded to PADI Open Water Diver certification on reaching age 15. The minimum age for the National Association of Underwater Instructors' course is also 10 years.

The effect of underwater pressure on gases is described by Boyle's law, which states that as the pressure of a gas increases, the volume decreases

proportionately. By going from the surface (1 atm) to 10 m (33 ft) (2 atm), the volume of air within the lungs is halved. This law helps explain the principles behind diving-related barotrauma and air embolism. Charles's law states that if the pressure is constant, the volume of gas alters with temperature, expanding with heating and contracting with cooling. This means that when a scuba tank is filled, it will have less air if it is filled at a high temperature and later cools than will a tank that is filled at a low temperature. Charles's law is important when nitrogen in the tissues is expelled as gas in the lungs. If a diver is close to the bends (see Decompression Sickness later in this chapter) and is warmed, there will be increased risk of the bends. If a scuba tank is left in a hot car, it is more at risk for bursting (as the temperature increases, with the volume constant, the pressure increases). Also important is Dalton's law, which states that in a mixture of gases, the total gas pressure is equal to the sum of the individual pressures, implying that as air is compressed into the scuba tank, the percentages of each gas will remain the same. Many of the complications of diving are related to Henry's law, which states that the amount of gas that dissolves in a liquid is a function of the partial pressure of the gas and how easily the liquid absorbs gas. As a result, when a diver is at great depths, the amount of nitrogen absorbed into blood and tissues increases because of the increased pressure, which explains in part why the risk of decompression sickness (DCS) and nitrogen narcosis is greater at depths of 30 m (100 ft) than 10 m (33 ft).

Complications of Scuba Diving

Nitrogen Narcosis

Nitrogen narcosis is caused by an increased partial pressure of nitrogen. Symptoms include euphoria, difficulty concentrating, and poor judgment. Because it happens at depths greater than 30 m (100 ft), this can be a dangerous situation for the diver. It is called *rapture of the deep* because the symptoms are similar to the effects of alcohol. It resolves very quickly during the ascent.

Oxygen Toxicity

Oxygen toxicity is caused by exposure to high-pressure oxygen during diving and can manifest as both respiratory and central nervous system symptoms, including cough, shortness of breath, tremor and seizure, nausea, and tunnel vision. These effects may not occur until lower depths if the diver is using nitrox, a blend of oxygen and nitrogen. The advantage of nitrox is that there is less risk of nitrogen narcosis and DCS because the percentage of nitrogen decreases as the percentage of oxygen increases.

Decompression Sickness

During descent, nitrogen under pressure is absorbed into tissues throughout the body. The amount is increased more in adipose tissues and tissues with

good blood flow and less in other tissues, such as cartilage and tendons. During ascent, the nitrogen is released again; with slow ascent, the nitrogen travels to the lung and is exhaled. If the ascent is too rapid, the nitrogen forms bubbles in the blood that can block circulation in blood vessels, producing symptoms, commonly known as the *bends*, that result from blockage in the small veins of joints, especially the elbow, knee, and shoulder joints.

Type I DCS is the nonneurogenic form, which causes itching, rashes, joint pains, fatigue, and vertigo. Type II DCS is the more severe form, when the bubbles interfere with the cerebral and spinal circulation resulting in weakness, paralysis, and behavioral changes. Decompression sickness occurs within a short time after the dive. Thalmann[8] reported 42% within 1 hour, 60% within 3 hours, and 98% within 24 hours, so that later symptoms are unlikely to be due to DCS.

Preventing Decompression Sickness

Good diving practice is the most important way to prevent DCS, although there are differences in age, body size and shape, and degree of fitness that may make certain individuals more susceptible. Dive tables indicate how much time can be spent at a certain depth, and dive computers are helpful to define these depths, particularly if multiple dives are attempted. The rate of ascent is very important, and decompression stops should be routine, including a stop at one-half of the maximum dive and a safety stop at 5 m (15 ft). Divers should wait 12 to 48 hours before flying, depending on number of dives.

Treating Decompression Sickness

The treatment for DCS includes administration of 100% oxygen and hydration. Positioning the patient in the left decubitus and mild Trendelenburg positions prevents preferential entry of bubbles into cerebral circulation. Hyperbaric oxygen therapy is the gold standard treatment for DCS.[9] The recompression dissolves the bubbles, which can then be gradually eliminated by slow decompression.

Barotrauma

As every diver is aware, breath holding during ascent is extremely dangerous. Air in the lung expands, especially in the last 10 m (30 ft), and if it is unable to escape can produce an arterial gas embolism, pneumothorax, pneumomediastinum, or subcutaneous emphysema. These complications are more likely to occur if there is air trapping. The presence of lung bullae or cysts, cystic fibrosis, pulmonary fibrosis, or a history of pneumothorax or pneumomediastinum should be considered absolute contraindications to diving. Arterial gas embolism is the most serious complication, whereby the alveolar sacs rupture and air enters the pulmonary capillary circulation. Bubbles travel to the left ventricle and then into the systemic circulation. The bubbles form

an embolus with ischemia distal to the obstruction. Immediate recompression is necessary to reduce the size of the bubble causing the obstruction.

Diving and Asthma

Not uncommonly, parents and patients will inquire about the safety of underwater sports for children with asthma. Several factors occurring naturally in the course of undertaking scuba diving may put individuals with increased airway hyperresponsiveness at risk of acute asthma exacerbation. These include the inspiration of cold and dry gas, increased airway resistance, increased inspired P_{O_2}, possible gas contamination with allergens and irritants, saltwater aspiration, and extreme exertion.[10] Airway obstruction may be localized to the distal airways, preventing gas elimination. Uncontrolled expansion of the distal airway may result in pulmonary barotrauma. Epidemiological studies do not seem to show a greater risk of barotrauma, DCS, or arterial gas embolism in patients with asthma.[11]

Patients with severe asthma should not dive, and only those with well-controlled asthma should be considered for clearance to dive. Patients with asthma should not dive within 48 hours of having asthma symptoms or needing to use a rescue bronchodilator. The Undersea and Hyperbaric Medical Society in the United States recommends that children with exercise-induced bronchospasm should not dive. All divers with asthma should have an annual review of their fitness for diving. The diver with asthma should not dive until peak flow measurement is within 10% of the best values. Patients with normal lung function and well-controlled asthma should be able to scuba dive successfully.[12]

Drowning

Drowning is a process resulting in primary respiratory impairment from submersion or immersion in a liquid medium.[13] The spectrum of drowning ranges from brief entry of liquid into the airways resulting in minor temporary injury to prolonged presence of liquid in the lungs resulting in pulmonary dysfunction, hypoxia, neurological and cardiac abnormalities, and death. Fatal drowning results in death, and nonfatal drowning occurs when the person is rescued. The highest rate of drowning occurs in 1- to 4-year-olds left unattended in or near swimming pools. Worldwide, more than 500,000 deaths occur annually from drowning, and it is the leading cause of death in boys 5 to 14 years old. The prognosis for cerebral recovery is dependent on the pH upon arrival in the emergency department.

The composition of the body usually allows individuals to float in water with about 3% of their volume above the surface. If a breath is taken, then more of the body can be above water; conversely, on deep expiration, the body will sink somewhat. This is one of the reasons that shouting while drowning may cause a person to sink. In addition, restrictive lung disease will reduce buoyancy.

An important factor relating to drowning is the temperature of the water. Immersion in cold water results in hypothermia, which may have the potential to prolong survival. The mammalian dive reflex results from immersion of the face in cold water. This dive reflex leads to an immediate response with reduced physiological functioning of various body systems, including the respiratory, cardiac, and nervous systems, entering a state of near suspended animation.

The sequence of events in a drowning accident is usually immersion followed by a sharp inspiration, initially resulting in a spasm of the larynx preventing water from entering the lungs. Hypoxia leads to unconsciousness, with subsequent laryngeal relaxation allowing water to enter the lungs. The major contribution to mortality and morbidity is the degree and duration of hypoxia with resultant cerebral injury. The pulmonary effects are from aspiration. The amount of aspirated fluid is usually small, and the distinction between salt water and fresh water drowning is no longer considered important. Aspirated fluid can wash out surfactant and cause alveolar instability. Decreased surfactant levels result in decreased lung compliance, ventilation/perfusion ($\dot{V}/\dot{Q}$) mismatching, and intrapulmonary shunting, leading to hypoxemia. Acute respiratory distress syndrome is an important complication of drowning. Bronchospasm is often seen in those who experience nonfatal drowning, and most cases rapidly improve with inhaled β-adrenergic agonists. Pneumonia complicates recovery from drowning, especially when the submersion is in stagnant or polluted water and the organisms responsible for infection may be unusual, including *Burkholderia pseudomallei, Chromobacterium violaceum,* and *Pseudallescheria boydii,* as well as the more expected *Escherichia coli, Streptococcus pneumoniae,* and *Haemophilus influenzae.* There is no good evidence to support the routine use of glucocorticoids, prophylactic antibiotics, or exogenous surfactant in nonfatal drowning patients. The initial management should focus on reversing anoxia from submersion through the use of rescue breaths or bag-mask ventilation with 100% oxygen and rewarming if there is hypothermia.

The cause of drowning needs to be evaluated because other injuries may be present including traumatic injury (intentional, or perhaps unintentional, head injury), seizures, syncope, or cardiac disease. Hypoglycemia or alcohol intoxication may also have been involved.

Inhalation Injury

Inhalation of Products of Combustion

Inhalation injury most commonly occurs during the inhalation of smoke containing chemicals and particulates and/or steam from fires but also may occur with the inhalation of oils or corrosive chemicals. For pediatric patients

with a severe burn injury, inhalation injury significantly increases mortality and affects approximately 20% to 30% of patients.[14] A multicenter review of pediatric burn patients with inhalation injury showed that overall mortality was 16% and that most patients died from pulmonary dysfunction and sepsis.[15]

Injury from inhalation is caused by both chemical and thermal exposures, with most of the thermal injury occurring in the upper airway. The exception to this is steam, which can carry thermal injury to the lower airways because of its large heat capacity. Tracheobronchial damage below the vocal cords occurs owing to chemical injury, which results from incomplete products of combustion and release of various substances that may combine with water vapor to form corrosive substances. These include compounds such as nitrous oxide and sulfur dioxide forming nitric and sulfuric acids. Children are at risk of airway compromise because of the small size of the airway, and the threshold for intubation should be low. Stridor from upper airway edema and increased airway hyperreactivity with reflex bronchoconstriction increase airway resistance, significantly increasing the work of breathing.

Damage to the lung parenchyma is delayed and usually manifests at least 24 hours after the initial injury. Small airway damage may occur directly or as a result of the effects of hypoxemia and hypotension. Edema of the interstitium, alveoli, and alveolar vessels can occur, and acute pulmonary edema often ensues owing to increased vascular permeability. Atelectasis from both obstruction of small airways and loss of pulmonary surfactant, and loss of hypoxic vasoconstriction may complicate $\dot{V}/\dot{Q}$ mismatching, leading to significant hypoxemia. Patients who die from acute injury have severe necrotizing bronchitis and bronchiolitis, intra-alveolar hemorrhage, hyaline membrane formation, and massive pulmonary edema.[16]

Bronchoscopic evaluation, especially in children and youth with facial burns, can reveal the extent and level of the thermal injury and may also provide a means to clear debris from the airway and enhance ventilation and oxygenation. The pathological lesions encountered include bronchial erythema with vascular engorgement, edema, and epithelial necrosis, with formation of obstructing bronchial casts composed of sooty debris, exudated fibrin, and other circulatory-derived products, including inflammatory cells. Superinfection may eventually affect both the damaged airways and lungs.

Significant airway injury may require endotracheal intubation and mechanical ventilation with positive end-expiratory pressure to reduce pulmonary edema from vascular leak. Awake and cooperative patients with lesser pulmonary involvement and few facial burns may benefit from noninvasive ventilation with continuous positive airway pressure devices. Attention to fluid management and antibiotics as needed for superinfection is important. The long-term

prognosis after thermal, chemical, and smoke inhalation injury is guarded. Inhalation injury limits exercise endurance and leads to reduced lung function for 3 to 8 years after injury.[17,18]

Carbon Monoxide Toxicity

Carbon monoxide (CO) and cyanide toxicity are early and immediate causes of morbidity and mortality due to hypoxia. Carbon monoxide is the most common gas resulting from incomplete combustion of carbon-containing materials such as wood. It is responsible for 50% of fire-related fatalities and should be an immediate concern for caregivers of people who have been burned. Carbon monoxide combines with great affinity to hemoglobin (with approximately 250 times the affinity of oxygen), forming carboxyhemoglobin (COHb). COHb shifts the oxyhemoglobin dissociation curve to the left, impairing release of oxygen at the tissues and use of oxygen in mitochondria, leading to tissue hypoxia. It is important to understand that the oxygen content of the blood is reduced, but the Po_2 on a blood gas measurement will not reflect this. In addition, pulse oximetry will be inaccurate, as it measures both saturated normal hemoglobin and COHb; co-oximetry is needed to distinguish between them. The CO level measured in blood can indicate the severity of exposure, with expected associated symptoms as outlined in **Table 3-3.** Treatment consists of administration of 100% oxygen, which reduces the half-life of COHb from 120 to 200 minutes to 30 minutes. Patients should continue 100% oxygen until COHb levels return to normal. Hyperbaric oxygen has been used to treat CO poisoning in children; however, evidence for its use in children is inconclusive.[19]

Table 3-3. Signs and Symptoms Associated With Carbon Monoxide Intoxication

Carboxyhemoglobin Level (%)	Signs and Symptoms
Mild (< 20%)	Headache, slight dyspnea, decreased visual acuity, decreased coordination, slowed thinking
Moderate (20%–40%)	Irritability, nausea, decreased vision, impaired judgment, rapid fatigue
Severe (> 40%)	Confusion, hallucination, ataxia, coma
Critical (> 60%)	Death

Hydrogen Cyanide Toxicity

If synthetic materials are also burned in the fire, hydrogen cyanide is released and may be a significant component of the inhaled smoke. Cyanide also produces hypoxia at the cellular level; however, the mechanism is different from that of CO. Cyanide disrupts mitochondrial generation of ATP through binding of ferric ions in cytochrome c oxidase. Cyanide poisoning is difficult to confirm because the symptoms are nonspecific and cyanide levels usually

cannot be measured quickly enough to be clinically meaningful. For treatment, hydroxocobalamin has shown some efficacy in lowering cyanide levels; however, current evidence remains limited.[20]

Effect of Pregnancy on Pulmonary Function

Normal pregnancy is associated with a 20% increase in oxygen consumption and a 15% increase in metabolic rate. When the uterus expands, the diaphragm is displaced as much as 4 cm (1.6 in) higher in the thoracic cavity. The function of the diaphragm remains normal. The thoracic cavity expands at its lower level by increasing circumference. The major physiological effect on pulmonary function is reduction in the functional residual capacity by about 20% during the latter one-half of pregnancy. This results from reduction in both expiratory reserve volume and residual volume. The changes in vital capacity tend to be small, and the forced expired volume in 1 second is essentially unchanged.

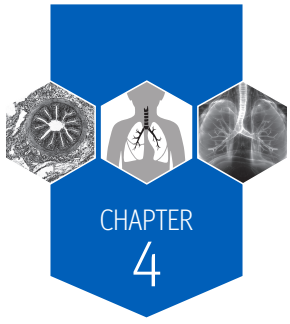
The minute volume increases by nearly 50% at term as a result of increased tidal volume with respiratory rates that do not increase. This effect is thought to be related to increased levels of progesterone. The change in minute volume is associated with a corresponding decrease in arterial P_{CO_2}, which tends to be about 30 mm Hg at term, and an increase in Pa_{O_2} because of reduced alveolar CO_2 levels.

key points

- The definitive treatment of AMS, HACE, and HAPE is descent to lower altitude.
- Individuals may be particularly susceptible to AMS, HACE, and HAPE and can experience recurrence on ascent to altitude.
- Shallow water blackout can occur with hyperventilation before swimming and diving; children and adolescents should be warned against this practice.
- Qualified diving instruction and good diving practice help prevent DCS.
- Scuba diving is contraindicated in patients with a history of pulmonary blebs or bullae, moderate to severe persistent asthma, and acute asthma symptoms with abnormal pulmonary function.
- Children are at high risk of upper airway obstruction from thermal inhalation injury.
- Pulse oximetry is inaccurate in measuring CO toxicity; oxygen should be administered for suspected cases of CO toxicity to reduce COHb.
- Compensatory increase in minute volume prevents hypoxemia in pregnancy because of reduction in functional residual capacity.

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Taking the Pulmonary History

Christopher E. Harris, MD, FAAP

Pulmonary History

In the evaluation of children with respiratory concerns, it is crucial to obtain a complete and thorough history. This history should be considered a supplement to the general pediatric history, a guide to which can be found in several comprehensive texts.[1,2] The pulmonary history is an information-gathering process; sensitivity is key to the formation of a good therapeutic relationship. Parents and other care providers are often under great stress, especially when dealing with a chronic illness. Multiple people may care for the patient, and, with appropriate parental or guardian consent, attention should be given to getting information from grandparents, teachers, and others in the child's life to obtain a clear picture of the symptom complex. Sensitivity and humility must also be shown to cultural aspects of the child and family. This may include the nuances of language that trained translators can provide. Finally, ingrained beliefs about conditions are often present and may influence how a parent or care provider is able to understand and trust the information given. For instance, parents may not believe that their active child has asthma because of a long-held idea that asthma causes children to be sickly and inactive. Assurance that persons with asthma may be Olympic-class athletes helps dispel this idea.

History of Present Illness

As in the general pediatric history of present illness, determining *onset* (gradual or acute), *duration* (chronic ≥3 weeks), *recurrence* (periods of wellness alternating with periods of illness) or *persistence,* and *triggers* (eg, viral upper respiratory infection, activity) is essential, all obtained in chronological fashion. Because the lungs are in constant contact with the external environment, the *environmental history* is particularly important. Indoor exposures (environmental tobacco smoke [ETS], woodstoves, pets, stuffed animals in the bedroom, etc) and outdoor exposures (animals, cold air, industrial pollutants, etc) must be carefully sought. Exposure to ETS will adversely affect children's lung health. Parents and other caregivers should be questioned about tobacco use, with a strong recommendation to quit, with use of a brief intervention, or, at minimum, removing all secondhand smoke from a child's environment

(eg, not smoking in the house or car, sitting in nonsmoking areas of restaurants, avoiding family gatherings where smoke cannot be avoided, or asking family members to smoke away from the child). Teen smoking is a growing problem, and all teens and preteens, starting in the middle school years, should be questioned about primary smoking. Also, information about the use of electronic nicotine delivery systems (vape devices such as JUUL, SMOK Infinix, or Suorin Air) must be carefully sought. (See Chapter 61, Nicotine and Tobacco.) Additional environmental inquiry should include the age of the home; type of construction; and sources of heating, cooling, and ventilation.

Family History

Family history of respiratory illness is very important because many diseases manifesting in childhood have a genetic basis. Various conditions result in pulmonary abnormalities. The Mendelian defects are single gene defects that may be autosomal dominant, autosomal recessive, X-linked dominant, and X-linked recessive. In addition, there are chromosome and multifactorial disorders that may result in pulmonary abnormalities. Some examples are shown in **Box 4-1.** If there appears to be a genetic basis for disease, an extended family tree may be useful.

Box 4-1

Genetic or Chromosomal Defects That Result in Pulmonary Disorders

Dominant
- Marfan syndrome
- Neurofibromatosis 1
- Achondroplasia
- Familial pulmonary fibrosis

Recessive
- Cystic fibrosis
- Primary ciliary dyskinesia
- Sickle cell disease
- Mucopolysaccharidoses
- Spinal muscular atrophy

X-linked

Dominant
- Rett syndrome

Recessive
- Duchenne muscular dystrophy
- Hemophilia

Chromosomal
- Down syndrome
- Other trisomy

Other (multifactorial)
- Cleft lip and palate
- Asthma
- Allergic rhinitis
- Gastroesophageal reflux
- Autoimmune disorders
- Diabetes mellitus type 1
- Heart disease
- Interstitial lung disease

Medical History

The neonatal history may indicate a reason for persistent or recurrent respiratory disease, especially in infancy, although even teens may have chronic airway obstruction as a result of neonatal disease such as infant respiratory distress syndrome or bronchopulmonary dysplasia. Precise details of the antenatal history and clinical course after delivery are key to providing

rational and appropriate care. Attention should be paid to birth weight and gestational age, both of which are known antecedents to neonatal lung disease. The pregnancy history should include maternal use of tobacco and other substances. Other important points include maternal complications during pregnancy, such as pregnancy-induced hypertension or diabetes mellitus. Problems at the time of delivery are relevant because they may immediately place the neonate at risk for lung disease and injury. For instance, a prolonged labor increases the risk for fetal distress and the antenatal passage of meconium. With sufficient stress, meconium aspiration syndrome may occur, which can be associated with significant lung injury and pulmonary hypertension. In addition, details of treatment in the intensive care nursery aid in understanding how severely the child's lungs may have been affected by both antenatal factors and postnatal treatment. Certainly the neonate born with transient tachypnea of the newborn and a 12-hour intubation is very different from the 500-g neonate born at 26 weeks' gestation who underwent intubation and mechanical ventilation for weeks. Finally, the total length of oxygen therapy can provide information regarding the degree of lung injury.

Surgical History

Surgical procedures relevant to the respiratory tract, including cardiac, gastrointestinal, otolaryngological, orthopedic, and urological and renal procedures, may be a clue to persistent respiratory problems. For example, repair of a tracheoesophageal fistula may leave significant residual airway problems in the form of localized tracheomalacia. Tympanostomy (ear tubes) or tonsillectomy and adenoidectomy may not be declared without prompting the parent or caretaker.

A history of contact with the medical system and the use of medical resources can give valuable information about the severity, chronicity, and control of a respiratory condition. For example, hospitalizations and emergency department visits provide important information about the patient's history.

Quality health care includes efficient use of resources and limiting unnecessary repeat studies. Many times, a few precisely directed calls will yield valuable information regarding previous studies and investigations that can be summarized quickly. This information will often obviate the need for repeating some studies, allowing further diagnostic testing to be streamlined, lowering cost, and lessening the burden of health care visits on the family. In some cases, however, repeat studies are necessary. For example, if a sweat chloride test for cystic fibrosis (CF) is not performed according to Cystic Fibrosis Foundation standards by experienced personnel (most often found in a CF care center), the results may be suspect, and the test should be repeated. Similarly, relying solely on the result of a newborn screening test for CF may miss the diagnosis of a case caused by less common mutations.

The past response to various therapeutic trials is also helpful information for pediatricians and other physicians. For example, if a child has chronic cough that fails to respond to oral antibiotics but that responds well after a several day course of corticosteroid, then a diagnosis of asthma is supported. Alternatively, if the cough responds well to oral antibiotics, then conditions such as chronic sinusitis, CF, bronchiectasis, or possible aspirated foreign body are more likely. Medication delivery information is also critical because inadequate delivery may lead to a lack of response to therapy. For example, it is appropriate to inquire whether nebulized medications were administered with a blow-by method rather than with a properly fitted mask. Furthermore, was there an attempt to give a metered-dose inhaler to a small child who lacks the skill or proper equipment to use it?

Social History

Additional social history will supplement the environmental history. For example, an appropriate social history should determine whether a child spends time in different households. Exposure to ETS in one home may make asthma control difficult, and education of all caregivers is essential. Other questions to ask include the following:

- Who is caring for the child or youth?
- Is there an adult in the home who can supervise administration of medication and provide for early medical intervention when symptoms are exacerbated?
- Is the child receiving treatments as prescribed, or are there any challenges to adhering to recommended treatment?
- Does the family have any barriers to follow-up appointments?
- Are there financial barriers that prevent adherence to a therapeutic regimen or that may promote emergency department use rather than primary or subspecialty follow-up care?
- Is there a history of any medical or mental illness of the caregiver that could interfere with adherence to therapeutic recommendations?
- Are there educational or language barriers that prevent the family from reading and understanding educational and instructional information regarding illness treatment and prevention?

A medical social worker can help sort through possible barriers to quality care and help families obtain the resources necessary to treat respiratory conditions with minimal stress.

As in the general pediatric history, *immunization* and specific *medication allergy history* are important to record. The child with chronic respiratory disease is at particular risk from influenza, so yearly influenza vaccination should be administered as recommended by the Centers for Disease Control and Prevention and the American Academy of Pediatrics. Occasionally, travel

may expose a patient to an infectious agent that is not common in a local area. Certain fungal pathogens have a particular propensity for a geographic region, so it is helpful to know about a patient's travel history. Foreign travel can increase risk for *Mycobacterium tuberculosis* exposure with varying degrees of susceptibility to antimicrobials.

Copies of previous medical records, including imaging studies, will help avoid unnecessary tests, confirm response or lack thereof to medication or other therapeutic trials, and confirm the severity and frequency of symptoms and chronicity of a condition. A list of elements of the pediatric pulmonary history is found in **Box 4-2.**

Box 4-2

Elements of the Pediatric Pulmonary History

Present Illness

Onset

Duration

Recurrence

Persistence

Triggers

Medical History

Birth history

Immunizations

Medication and environmental allergy

Hospitalizations and ED visits

Response to therapeutic interventions

Imaging and laboratory test results

Family History

Allergy or allergic rhinitis, bronchitis, asthma, cystic fibrosis, sinus diseases, pneumonia, tuberculosis, inflammatory bowel disease, childhood cancer, HIV or immune problems, eczema, congenital heart disease, juvenile-onset diabetes mellitus, early-onset emphysema, liver disease

Environmental History

Smoke and other toxic exposures

- Primary and secondhand environmental tobacco smoke exposure
- Woodstoves
- Industrial and household aerosols
- Dust, mold, construction dust, and debris
- Other toxins

Allergen exposure

- Age and condition of the house and the child's bedroom
- Stuffed toys
- Pets
- Heat source, humidifiers, air filters
- Other environments including a second household and child care
- Attempts at allergy reduction

Travel

Social History

Family dynamics

- Who are the caregivers?
- Is the child supervised in taking medications?
- Educational and reading level
- Barriers to treatment such as language, transportation, caregiver illness, or health literacy

Financial Support

Are medications affordable to the patient and family?

Are follow-up visits avoided because of finances or other logistic problems (eg, co-pays or lack of transportation)?

ED use because of financial hardship

Abbreviation: ED, emergency department.

Review of Systems

A complete review of systems is always necessary for the thorough evaluation of a new patient. The review of systems relevant to the respiratory tract is listed in **Box 4-3.** Important information not otherwise gleaned in the history of present illness may become evident here and may shed light on the current illness.

Box 4-3

Review of Systems Relevant to the Respiratory Tract

Constitutional

Fever, weight loss or gain, night sweats, fatigue, pain

Skin

Eczema, other rashes, urticaria

Head, Eyes, Ears, Nose, Throat

Sinusitis, otitis media, congestion

Respiratory

Cough, wheeze, stridor, shortness of breath, chest discomfort or pain, hemoptysis, sputum production, chest tightness, symptoms with exercise, pneumonia diagnosis

Cardiovascular

Congenital heart disease, hypertension, syncope, previous surgery

Gastrointestinal

Stool volume and consistency, constipation, diarrhea, regurgitation or gastroesophageal reflux disease, choking or gagging with feedings, food intolerance, hematochezia

Genital and Urinary

Urinary anomalies, poly- or oligohydramnios, renal disease, recurrent infection

Neurological

Known neuromuscular disease, known developmental disabilities, choking or gagging, stridor

Musculoskeletal

Scoliosis, chest wall deformity, previous chest wall surgery, muscle weakness, joint pain or swelling, chest wall pain or discomfort

Allergy and Immunology

Wheezing or known asthma, chronic cough, chronic congestion, itching and sneezing, recurrent infection, HIV infection or other viral exposures, skin or serum test results

Blood Disorders

Sickle cell disease, coagulopathies, bleeding, cancer, other blood dyscrasias, transfusion history

Endocrine

Diabetes, thyroid, parathyroid disease, growth parameters

Common Symptoms Related to the Pulmonary System

Pediatricians commonly encounter symptoms that include cough, wheezing and stridor, chest pain, dyspnea (shortness of breath), and cyanosis. Although considerable overlap may occur, the causes of these symptoms may vary by the child's age. Details about the various causes presented here can be found in the specific diseases discussed in other chapters of this book and in other pediatric pulmonary texts.[3]

Cough

Coughing arises from an irritation of the airways where receptors are concentrated at airway bifurcations. It occurs in a phased sequence involving a deep inspiration, closure of the glottis and relaxation of the diaphragm along with contraction of muscles of expiration, and sudden opening of the glottis with forceful expired airflow. Cough can be classified as acute or, if symptoms continue beyond 3 weeks, chronic.

Cough during infancy most commonly accompanies infection, usually viral, and is productive of thin, white mucus resolving over about 10 days. Croup syndrome produces a brassy, seal-like cough as part of an upper airway infection. Exposure to irritants such as ETS and woodstoves may produce acute cough in infants. Chronic cough in infants requires a more extensive and comprehensive evaluation. Causes include CF, infections (*Bordetella pertussis*, *Chlamydia*, *Mycoplasma*), aspiration due to developmental disabilities or traumatic birth injury (suck-swallow discoordination, recurrent laryngeal nerve injury, complications of neonatal intubation), gastroesophageal reflux disease (GERD), the sequelae of neonatal lung injury (bronchopulmonary dysplasia), and congenital lung malformations (bronchogenic cyst, congenital pulmonary airway malformation, congenital hyperlucent lung, and pulmonary sequestration).

Cough in childhood, like in infancy, is most often caused by infectious agents. Cystic fibrosis may manifest with cough at this age, although newborn screening usually allows for this diagnosis to be determined earlier. Foreign body aspiration becomes a more common cause of acute cough in early childhood. Chronic causes of cough include infections (tuberculosis if exposed to infected individuals), primary ciliary dyskinesia, chronic sinusitis, aspiration (especially with developmental disabilities), GERD, ETS and other toxic exposures, congenital lung and airway malformations, and the use of angiotensin-converting enzyme inhibitor drugs. Functional or habit cough (psychogenic cough) may begin in late childhood but is more common in adolescents. Asthma may manifest only as cough (cough variant asthma) at almost any age and can be proved with a bronchial challenge, such as methacholine, or by response to a trial of asthma treatment. Acute cough in adolescents is also most often caused by infectious agents but may result from acute toxic exposures, such as primary smoking and exposure to ETS or other aerosols. Postnasal drip

and chronic sinusitis are a cause of throat clearing and nighttime–early morning cough. In adolescents with cough, a history of exposure to irritating inhalants should be sought if substance use is suspected; certainly the recent surge of cases of e-cigarette, or vaping, product use-associated lung injury has raised awareness of these dangerous products. Occasionally, a congenital malformation, such as a bronchogenic cyst, will not become evident until the teen years when recurrent or chronic infection occurs.

Wheezing and Stridor

Stridor and wheezing due to respiratory infections (bronchiolitis and croup) are very common during infancy, although CF may also manifest with chronic wheezing. Infants with disabilities may aspirate silently, so a strong index of suspicion should be maintained when recurrent pulmonary symptoms occur in this group of infants. Gastroesophageal reflux disease with retrograde aspiration can occur and may be found with congenital causes of stridor, such as laryngomalacia. When tracheomalacia or bronchomalacia is present, chronic coarse expiratory wheeze also occurs. Rarely, airway lesions, such as laryngeal hemangiomas, laryngeal webs, subglottic stenosis, and laryngo-esophageal clefts, cause stridor in infancy. Intermittent stridor beyond early childhood most often occurs in children with atopic dermatitis and is termed *spasmodic croup.* Allergy is a rare cause of wheezing in infancy but is a more common cause in childhood. Other causes of wheezing in children include aspirated foreign body, CF, inhalation injury, bronchiectasis from any cause, aspiration syndromes, and mediastinal and airway malformations or neoplasms. Stridor with or without expiratory wheezing is a common finding in vocal cord dysfunction (see Chapter 44, Functional Respiratory Disorders), which is transient, not life-threatening, often associated with exercise, and most common in adolescents. Adolescents can also experience the other causes mentioned for children, although asthma and wheezing as a result of intentional or nonintentional inhalation of irritating aerosols or smoke are more common in adolescents.

Chest Pain

Chest pain can originate in chest wall structures or within the lung as a result of inflammation of the lung-covering membranes (pleura). Infants clearly cannot express specific pain, but tenderness on palpation along with skin changes that might be related to trauma can be elicited and noted during a careful examination. Chest wall pain is commonly associated with prolonged and vigorous coughing and is commonly found in children with CF who are experiencing a pulmonary exacerbation. Other causes of chest pain in children include pleurisy, most often associated with coxsackievirus B (pleurodynia) and bacterial pneumonias. Occasionally, both GERD and asthma will be causes of chest pain or discomfort in children and adolescents; certainly the

acute chest pain associated with sickle cell crisis is well known in pediatrics and must be treated aggressively. Adolescents in athletic activities such as weight lifting can present with acute or chronic chest wall pain localized over the costochondral junctions (costochondritis). Rib fractures caused by chest wall trauma or vigorous activities such as competitive rowing can occur in teens. Although spontaneous pneumothorax as a cause of chest pain can occur at other ages, it is most common in adolescents and should be suspected when an otherwise healthy teen complains of sudden onset of sharp, unilateral chest pain with shortness of breath (dyspnea). Herpes zoster as a cause of chest wall pain is readily identifiable by its characteristic rash found along a chest wall dermatome. Rarely, previously undiagnosed coronary artery anomalies and mitral valve prolapse, as well as myocarditis, can manifest in this age group as well as in younger children.

Dyspnea

Increased depth of respiration, often with increased respiratory rate (tachypnea), can occur at any age and is produced by both pulmonary and nonpulmonary causes. Any cause of airway obstruction in infancy can lead to dyspnea, although sudden onset is more likely caused by infection or cardiac disease. Acidosis is a cause of nonpulmonary dyspnea and may occur with inborn errors of metabolism or with dehydration. Rarely in infants but more commonly in children and adolescents, dyspnea is associated with ketoacidosis as an initial manifestation of diabetes mellitus or with inadequate diabetic control leading to severe hyperglycemia. In childhood as well as adolescence, acute asthma becomes a common cause of dyspnea, and acute toxic ingestion (eg, salicylates) can also manifest as dyspnea. Cyanosis and hemoptysis, along with dyspnea, often occur with pulmonary embolism due to traumatic lower extremity injury, heart disease, or other coagulopathy. Anxiety (hyperventilation with panic attacks—see Chapter 44, Functional Respiratory Disorders) and substance ingestion (eg, suicide attempt with salicylates) are more common in adolescents.

Cyanosis

Central cyanosis (blue mucous membranes) should be distinguished from peripheral cyanosis (blue extremities) because the former is associated with important cardiopulmonary disease. Any pulmonary disease that causes significant mismatching of lung ventilation and perfusion or reduced functional residual capacity (expiratory reserve volume plus residual volume) will lead to oxygen desaturation and, eventually, visible central cyanosis. In newborns, this occurs during infant respiratory distress syndrome (hyaline membrane disease), which reduces functional residual capacity, and any significant lung inflammation, such as neonatal pneumonia or meconium aspiration. Space-occupying lesions, such as lung malformations (congenital hyperlucent lung,

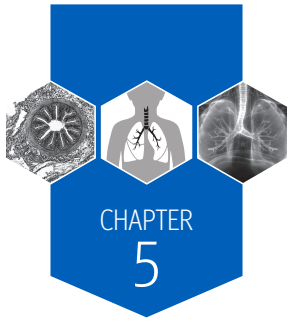
congenital pulmonary airway malformation, pulmonary sequestration, bronchogenic cyst, gastroenteric cyst, etc), may compress acutely on the ipsilateral healthy portion of the lung or the contralateral lung, leading to decreased ventilation and perfusion. If present prenatally, lung malformations and oligohydramnios can lead to lung hypoplasia, which may cause cyanosis. Any right-to-left shunt caused by vascular malformation or intrinsic cardiac disease may lead to cyanosis. In older children and adolescents, cyanosis is most commonly associated with acute pulmonary disease (eg, acute asthma or pneumonia). Cyanosis is a late manifestation of chronic, destructive pulmonary disease such as is found in CF. Because of increased survival of children with CF, cyanosis is unusual in infancy or childhood. Cyanosis is also a late finding of degenerative neurological disease such as Duchenne muscular dystrophy. Acute inhalation of smoke or other toxic substances, such as hydrocarbons, can lead to cyanosis stemming from severe acute lung inflammation. A space-occupying thoracic neoplasm may produce enough pressure on surrounding lung or airways to compromise ventilation and perfusion significantly, producing cyanosis.

key points

- Careful questioning and listening, with cultural sensitivity and humility, lead to an accurate picture of the patient's condition and how it affects individual and family ability to adapt to the respiratory illness.
- Genetics and environment play a large role in childhood respiratory disease.
- Information about onset, duration, recurrence, persistence, and triggers helps lead the diagnostician first to determine acuteness and chronicity and, second, to determine a likely cause of a pediatric respiratory condition.
- Toxic exposures, particularly ETS or primary smoking, are important causes of acute and chronic respiratory conditions as children age.
- Asthma is a common cause of chronic cough as well as wheeze.
- Response to previous therapeutic interventions, including medications, can be a valuable clue to the cause of an underlying pulmonary condition.

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CHAPTER 5

The Pulmonary Physical Examination

Christopher E. Harris, MD, FAAP

Introduction

Every clinical encounter must begin with a thorough history. As outlined in Chapter 4, Taking the Pulmonary History, details of the present condition, its time course and past management, other medical and surgical conditions, and family history should be completely reviewed. Social, environmental, and immunization histories and a complete review of systems are necessary to completely evaluate a child with a pulmonary concern.

The pediatric physical examination should vary according to the age and developmental stage of the child. In young children, the passive examination, where possible, is always more productive; for example, a child should be lying down to bring out wheezing by lowering lung volumes and thus reducing airway caliber. Examinations such as the heart and lungs that are more difficult in a crying child should be done first, and the less tolerated examinations, such as ears and throat, should be saved for last. Young children often are most comfortable when seated in the lap of a parent or caretaker. The time- honored principles of inspection, palpation, auscultation, and percussion apply well to the pulmonary examination of children and youth at any age.[1–3]

Upper Airway

The head, ears, nose, and throat examination is an important part of the respiratory tract examination. Chronic otitis media may be a first sign of immune deficiency and is often present in children with primary ciliary dyskinesia. Nasal examination is also very important in children presenting with respiratory diseases. Children with allergic conditions, such as allergic rhinitis, often have mucosal pallor or edema along with the presence of clear secretions. Aggressive treatment of upper airway allergies may improve lower airway signs and symptoms.[4] Sinusitis may also be a common problem in children presenting with chronic cough. Because the paranasal sinuses are lined by pseudostratified columnar epithelium (the same cells lining the airway), it stands to reason that conditions affecting the airway may also affect the sinuses.[5] For example, chronic sinusitis is nearly universal in

children with cystic fibrosis (CF) and primary ciliary dyskinesia. Patients with allergic rhinitis may also have mucosal edema, preventing the sinus ostia from draining readily. Nasal polyps may also complicate both allergic rhinitis and CF. Polyps, which have a characteristic clear to white bulbous appearance, may be quite large but cause the child relatively few symptoms, probably because of the gradual nasal obstruction that occurs with polyp growth.

The diagnosis of sinusitis can be rather difficult to establish solely on clinical grounds. Nasal secretions are usually thick and purulent. However, if post-nasal drip is present, secretions may not be issuing from the nares. Therefore, the oropharynx should be examined carefully for mucoid material draining from above. A cobblestoned oropharynx may be noted with postnasal drip. Sinus tenderness with palpation of the maxillary and frontal sinuses may be helpful in diagnosing a sinus infection in older children. Reports of sinus pressure, especially when the patient bends over, are also common with sinus infections.

Examination of the mouth and oral cavity is important in respiratory medicine because of congenital anomalies and other conditions that affect sleep. Many dysmorphologies affect orofacial structures. Common examples include the Pierre Robin sequence, Stickler syndrome, Treacher Collins syndrome, and Crouzon syndrome. Infants with these conditions may present with cleft palate, making early nutritional and feeding intervention of prime importance. Conditions associated with relative or absolute macroglossia, such as Down syndrome, congenital hypothyroidism, and glycogen storage diseases, may place the child at risk of obstruction of the upper airway during sleep. Careful questioning of the caretakers and a low threshold for referral for sleep evaluation and polysomnography are needed in caring for these children. Tonsillar size is also very important to assess in all children, especially during the preschool years. Frequent infections of the upper respiratory tract during these years cause the lymphoid tissues in the head and neck to proliferate. This hyperplasia, along with the normal small size of the upper airway, puts children at risk for sleep-disordered breathing, including obstructive sleep apnea. In addition, the increasing prevalence of obesity among children further contributes to increased risk for obstructive sleep apnea.[6] Therefore, careful inspection of tonsillar size and degree of oropharyngeal filling must be noted in all children, especially for those with sleep-related concerns.

Characterization of the voice is another important part of the pulmonary examination. Lesions in the area of the larynx may impede normal vocal fold function and cause hoarse voice along with inspiratory stridor. For example, respiratory papillomas caused by infection with human papillomavirus may cause a hoarse voice. Also, injury to the nerves innervating the larynx may

cause vocal disturbance and stridor. Repair of congenital heart defects, especially ligation of the ductus arteriosus, may be associated with at least temporary vocal cord paresis. Of much greater consequence are abnormalities of the central nervous system (CNS) that may compress the brainstem and cranial nerves. Arnold-Chiari malformations are well known to be associated with bilateral vocal cord paralysis. Signs include a soft, breathy voice and stridor. Demonstration of cough by the child should be elicited when there is concern about laryngeal innervation. Stridor has different causes at different ages and depends on whether it is intermittent or continuous. Inspiratory stridor usually indicates lesions of the glottis or above, and expiratory coarse wheeze or stridor indicates lesions below the level of the glottis. Biphasic stridor may occur with severe glottic lesions. Causes of stridor in different age groups are listed in **Table 5-1.**

Table 5-1. Causes of Stridor in Children and Adolescents

Patient	Intermittent	Persistent
Infant	Aspiration Viral croup Electrolyte abnormality	Laryngeal anomaly Mediastinal mass Vascular ring Lung or gastrointestinal cyst Intubation trauma Neck or surgical trauma to RLN
Child	Viral croup Spasmodic croup Aspiration Vocal cord dysfunction (rare)	Vascular ring Laryngeal anomaly Mediastinal mass Inhalation injury Neck or surgical trauma to RLN Foreign body aspiration
Adolescent	Vocal cord dysfunction Spasmodic croup	Mediastinal mass Inhalation injury Neck or surgical trauma to RLN Foreign body aspiration Glottic trauma

Abbreviation: RLN, recurrent laryngeal nerve.

Extremities

Examination of the extremities for clubbing and the Schamroth sign is also important (**Figure 5-1**). These signs may be found in patients with chronic lung, heart, and liver disease and are also a clue to the chronicity of a respiratory condition in children. Potential causes of digital clubbing are listed in **Box 5-1.**

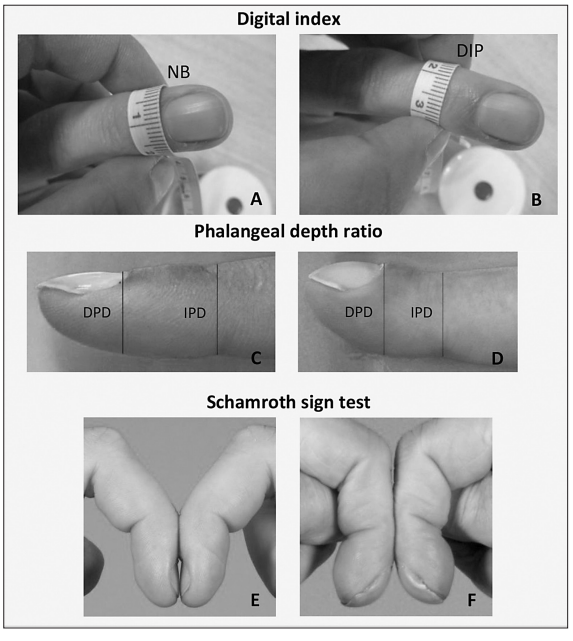


Figure 5-1. Clubbing measuring methods. DIP, distal interphalangeal joint; DPD, distal phalangeal depth; IPD, interphalangeal depth; NB, nail bed.

From van Manen MJG, Vermeer LC, Moor CC, Vrijenhoeff R, Grutters JC, Veltkamp M, Wijsenbeek MS. Clubbing in patients with fibrotic interstitial lung diseases. *Respir Med.* 2017;132:226–231, with permission from Elsevier.

Box 5-1

Causes of Clubbing

Pulmonary

- Cystic fibrosis
- Bronchiectasis
- Pulmonary abscess
- Empyema
- Neoplasms
- Interstitial lung disease
- Alveolar proteinosis
- Chronic pneumonia

Cardiac

- Cyanotic congenital heart disease
- Bacterial endocarditis

Gastrointestinal and Hepatic

- Inflammatory bowel disease (ulcerative colitis and Crohn disease)
- Polyposis
- Biliary cirrhosis
- Biliary atresia

Thyrotoxicosis

Familial

Eupnea and Dyspnea

The chest and lung examination is of primary importance for patients with respiratory concerns. Inspection of the chest should begin as soon as the examiner enters the room. Findings of respiratory distress depend on the patient's age. Increased respiratory rate (*tachypnea*) is often the first indication of respiratory distress at all ages; however, normal rates will vary over a wide range according to age (**Table 5-2**). Normal respiratory rates are also highly variable in infants and toddlers depending on sleep state and the presence of fever. Breathing pattern is important: *Hyperpnea* (abnormally deep respiration) may accompany acidosis and CNS dysfunction. *Hypopnea* can occur in sleep-disordered breathing and again with CNS disease. *Eupnea* is normal, unlabored breathing, and *dyspnea* is difficulty breathing.

Dyspnea, which is shortness of breath or difficulty "catching" one's breath, is found with true lung disease, such as acute asthma, but also occurs with hyperventilation secondary to panic attack or panic disorder.

Table 5-2. Respiratory Rate by Age

Age	Respiration (breaths/minute)
Newborn	30–60
1–6 weeks	30–60
6 months	25–40
1 year	20–40
3 years	20–30
6 years	12–25
10 years	12–20

Adapted from Burbulys DB. Respiratory distress. In: Berkowitz CD, ed. *Berkowitz's Pediatrics: A Primary Care Approach.* 6th ed. American Academy of Pediatrics; 2021:501–505.

Lungs and Thorax

The highly compliant chest wall of the young infant leads to significant retractions (suprasternal, intercostal, subcostal) with increased respiratory effort. Retractions occur when the skin overlying the neck or chest is drawn in during inspiration. Even with the patient clothed, retractions within the suprasternal notch may be readily apparent in the older child and adolescent. This group may also demonstrate intercostal retractions as well as use of accessory muscles of respiration (sternocleidomastoid and scalene muscles) during periods of respiratory distress. Infants may also demonstrate nasal flaring with respiratory distress.

Inspection and palpation of the chest wall may reveal abnormalities. The trachea should normally deviate slightly to the right when a finger is placed in the suprasternal notch. Changes in the position of the trachea may provide important information during the physical examination. In conditions in which either air or liquid fills the pleural space, the lung may move away from its normal position with the trachea also shifting in the same direction. Conversely, in complete atelectasis of a lung, the trachea may shift toward the side of collapse. In lung agenesis or hypoplasia, the trachea may deviate to the affected side. Absence of a pectoralis muscle is seen in Poland syndrome, and rib or thoracic vertebral anomalies may lead to chest wall asymmetry. Severe scoliosis may lead to respiratory compromise due to restriction of normal lung expansion, which may be accompanied by kyphosis, and both conditions may be seen in children with neuromuscular disease. Pectus carinatum (pigeon breast) or pectus excavatum are both common reasons for referral for evaluation, although they affect cardiopulmonary functioning only when severe (**Figure 5-2**). Children with significant obstructive sleep apnea may develop a Harrison groove, which is an indentation along the site of diaphragmatic insertion of the anterior ribs. Furthermore, certain genetic syndromes may be associated with a small thoracic cage. For example, Jeune syndrome, spinal muscular atrophy type I, or other congenital myopathies may show a small bony thorax.

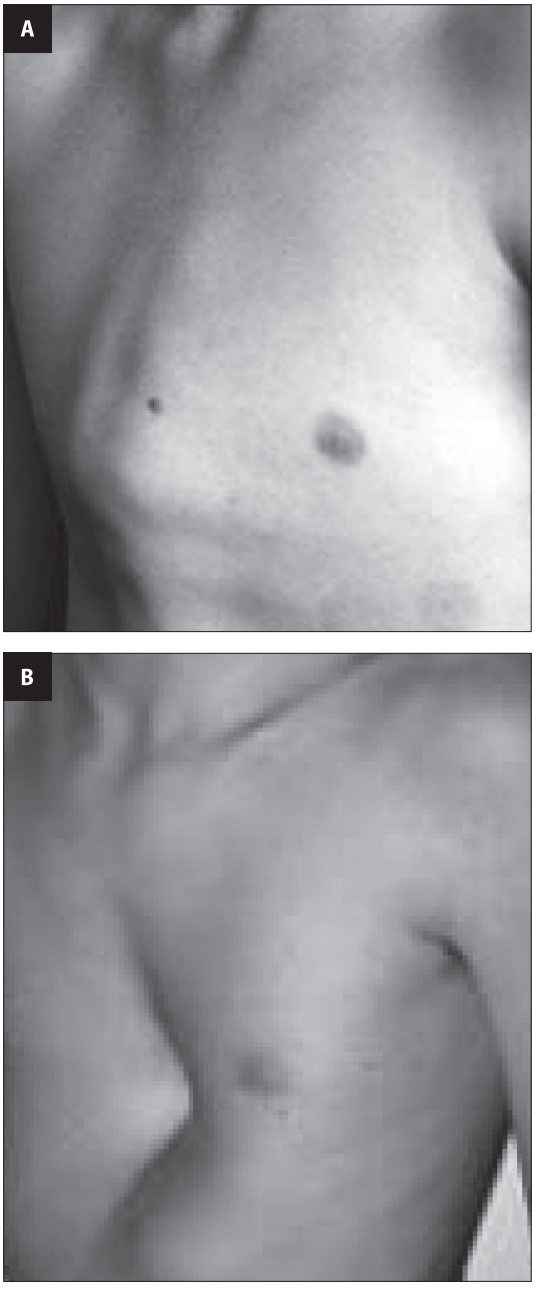


Figure 5-2. Pectus carinatum (**A**) and pectus excavatum (**B**).

Percussion of the chest gives the clinician vital information about underlying structures (**Figure 5-3**). Percussion may be difficult in the small, uncooperative infant and may precipitate crying, so percussion and palpation should always follow auscultation in this age group. Usually, normal lungs will provide a resonant note with a low pitch and slightly long duration. When pleural effusion, consolidating pneumonia, or an intrathoracic mass is present, the note is flat with a high pitch and shorter duration. Conversely, when a pneumothorax has occurred, one will find a high-pitched, loud note. Obstructive lung disease with air trapping, such as asthma or CF, may also produce a hyperresonant pitch. In particular, when percussing the chest, always remember to compare one side with the other.

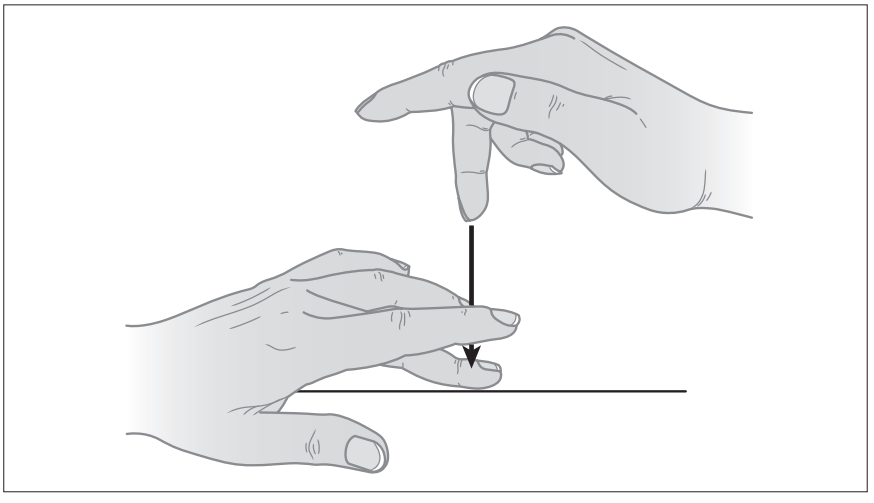


Figure 5-3. Technique of chest percussion.

After percussion, auscultation of the lungs is performed during physical assessment (except in the infant and small child, when auscultation should precede percussion and palpation). With normal breathing and with larger tidal volumes, normal breath sounds or adventitial sounds may be detectable. Normal vesicular breath sounds are low-pitched and heard mostly throughout inspiration, continuing approximately one-third of the way into exhalation. During certain clinical conditions, other breath sounds may replace the normal vesicular breath sounds. Bronchial breath sounds are abnormal sounds that are often louder than vesicular breath sounds; they may be shorter during inspiration and longer during exhalation. In addition, they may be slightly louder and more high-pitched during expiration. These are the sounds of large airways transmitted through lung parenchyma that is consolidated or atelectatic. Three different types of adventitious sounds are generally acknowledged and agreed on in present medical teaching. First, *crackles* or *rales* are short,

intermittent sounds. Two types of crackles are described: Fine crackles are similar to hairs being rubbed together near the ears; coarse crackles, as the name implies, are louder and harsher, more like rubbing 2 pieces of tissue paper together. Fine crackles are more commonly associated with interstitial lung disease. Coarse crackles are often heard in pneumonia or CF. *Wheeze*, the sound most commonly associated with asthma, is a continuous sound and is often musical. *Rhonchi* are also continuous sounds but much lower in pitch and may clear with coughing. These sounds are probably caused by secretions in the large airways. A pleural rub may also occasionally be heard during chest examination. More often heard during inspiration, these low-pitched continuous sounds are the result of pleural inflammation. Often described as a creaky noise, they may also sound like leather being stretched.

During auscultation is an opportune time to examine the cardiovascular system, which begins with inspection of mucous membranes and nail beds for signs of central cyanosis. Next is auscultation of the heart tones; children with congenital heart disease may present with murmurs heard during the entire cardiac cycle. Full characterization of murmurs may require evaluation by a pediatric cardiologist. Dysrhythmias, both bradycardic and tachycardic, may be noted during cardiac auscultation.

Additional Examinations

Additional systems may give important clues to chronic respiratory disease. These include the abdominal, dermatologic, musculoskeletal, and neurological systems.

The abdominal examination should include accurate assessment of liver and spleen size. Hepatomegaly may occur in patients with CF and may be a potentially life-threatening complication. Cirrhosis may occur because of biliary tract obstruction, leading to hepatocyte damage and subsequent fibrosis. Secondary splenic congestion due to hepatic insufficiency may also occur occasionally and requires expert skill to ascertain fullness in the left upper quadrant of the abdomen reliably. Any mass or fluid in the abdomen may restrict thoracic excursion through elevation of the diaphragm and thus lead to respiratory compromise.

Sequelae of neurological complications often affect the respiratory system. Severe neurological dysfunction may interfere with respiratory control, leading to apnea or hypoventilation. Much more commonly, patients are seen with more subtle neurological involvement, most frequently involving swallowing. Patients with cerebral palsy often are at risk for aspiration pneumonia, and particular care should be paid to the patient's ability to handle oral secretions. Evaluating the strength and duration of an elicited gag reflex may provide clues to aspiration risk because both prolonged and absent gags are abnormal.

Silent aspiration can occur often in children with severe neurological deficits, and a strong index of suspicion should be maintained; bronchoscopy and radiographic deglutition studies (best with a physical or speech therapist present) can help delineate aspiration risk. Any condition leading to thoracic muscle weakness can lead to progressive respiratory compromise and, eventually, respiratory failure requiring support. At the first sign of sleep disturbance or with recurrent respiratory infection, children with muscle weakness should be referred for pulmonary and sleep evaluation.

Examining the skin may yield important clues to underlying systemic disease with a respiratory component. Eczema in infancy may be associated with food allergy and rarely is associated with respiratory disease. However, as children age, eczema is more often associated with asthma, allergic rhinitis, and inhalation allergy. Severe asthma, with eczema and recurrent *Staphylococcus aureus* infection, occurs with the immunodeficiency of the hyper-IgE syndrome. Cyanosis of nail beds and mucous membranes is always a significant physical finding and should prompt a thorough investigation.

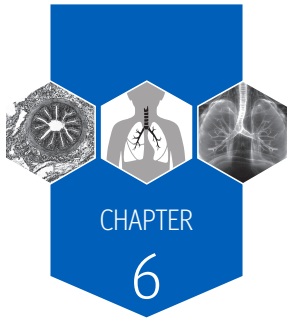
Assessing the musculoskeletal system is the final portion of the physical examination. Many patients with developmental delay or genetic conditions are prone to kyphoscoliosis. Careful examination of the back is of prime importance in children of all ages. Key points to assess include the linearity of the spine, asymmetry of the back and shoulders, and range of motion (flexion, extension, and lateral bending). Digital clubbing, if not previously assessed, should be evaluated at this time.

key points

- Respiratory rates in children vary over a wide range with activity and age; this vital sign should be compared against standard tables.
- The heart and lung examinations are best performed first in young children to increase the chance of an adequate examination.
- Characterization of breath sounds and their location can lead to efficient and accurate diagnosis of acute or chronic pulmonary conditions.
- Children with developmental disabilities can aspirate silently, leading to recurrent pneumonia; therefore, a strong index of suspicion with appropriate testing is in order.
- Other systems affect or are affected by the lungs, including the cardiovascular, neurological, dermatologic, and musculoskeletal systems; these must be evaluated along with the pulmonary tract during the complete physical evaluation, which is especially important in the preparticipation examination for children and teens seeking to undertake athletics. This examination is discussed in detail in the American Academy of Pediatrics publication *Preparticipation Physical Evaluation*.[7]

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CHAPTER 6

Pulmonary Function Testing

Carol J. Blaisdell, MD
Allen J. Dozor, MD, FAAP

Pulmonary function tests (PFTs) offer clinicians useful objective functional information that can aid in the diagnosis and management of known or suspected lung or respiratory system disease in children. Symptoms of shortness of breath (dyspnea), chest pain, cough, and wheezing have many potential causes. As part of a clinician's evaluation, the choice of an appropriate objective and reproducible test of pulmonary function may confirm a working diagnosis. Many children are prescribed asthma medications with potential adverse effects for years or even decades. Pulmonary function tests can assure patients, parents, and clinicians that the diagnosis is correct. In addition, PFTs are important in assessing the progression of known lung disease and response to therapy. Some tests are readily available in the primary care office, while others are most often restricted to pulmonary function laboratories or, more recently, the offices of pediatric pulmonologists. Procedures should follow American Thoracic Society[1] guidelines referenced to healthy populations. Indications are listed in **Box 6-1.**

Box 6-1

Indications for Pulmonary Function Tests

- **To determine the nature of the respiratory dysfunction (obstructive versus restrictive disease)**
- **To evaluate respiratory function associated with signs and symptoms**
- **To quantify the extent or progression of known pulmonary disease**
- **To provide an objective measure to determine the appropriateness of reducing therapy for asthma**
- **To measure the effect of occupational exposure**
- **To identify benefits, adverse effects, or consequences of withdrawal or step-down of therapy**
- **To assess the presence of airway hyperreactivity**
- **To assess preoperative lung function**
- **To use as a research objective or measure**

Peak Expiratory Flow Rate

Peak expiratory flow rate (PEFR) is a useful measure for monitoring lung function in the primary care management of obstructive lung diseases, particularly asthma. It is inexpensive and can be used at the patient's home or workplace, at the clinician's office, and in the acute care setting of the emergency department (ED) and hospital. However, there are important limitations.[2]

To use a peak flow meter, the child should blow out as quickly as possible from maximal inhalation with his or her mouth closed tightly on the mouthpiece. The highest of 3 attempts should be recorded. The performance of PEFR depends highly on effort and is affected by large-airway dysfunction. Patients who do not keep a tight seal on the mouthpiece will produce a falsely low PEFR, and those who put their tongue in the mouthpiece while exhaling (essentially performing a "blow-dart" maneuver) may have falsely elevated PEFR measurements. Consistency of the values with 3 trials at a time suggests reproducible results that can be interpreted. If variability is greater than 20% with 3 efforts performed at one time, the clinician should suspect that there is a problem with the patient's technique.

Normative PEFR data based on standing height are available to assess flow limitation compared with that in healthy control subjects; however, these data are fairly old and vary with the PEFR devices used.[2–4] If the values are less than 80% of the expected or the patient's personal best PEFR (discussed in the next paragraph), airflow obstruction should be suspected. This result could be consistent with subjective concerns of a patient with asthma or may be unexpected in a patient with poor perception of his or her disease.

Like all PFTs, PEFR is much more useful in detecting changes over time than in asking the question, "Is this normal?" In a patient with poorly controlled asthma who frequently accesses acute care in an ED, PEFR can be used to set criteria for contacting the clinician for impending asthma exacerbations. The asthma action plan, which defines adjustment in home asthma management in response to early symptoms of asthma (cough, dyspnea, chest pain), may also document the target PEFR for each individual.[5] The convention is to determine the patient's personal best PEFR when asthma is under best control in the clinician's office or with home monitoring and to review these data with the provider.

Using a peak expiratory flow meter to determine whether there is significant airflow obstruction in adolescents who complain of exercise-induced dyspnea can be useful. A 20% change in the PEFR between before and after exercise that elicits dyspnea is consistent with exercise-induced asthma. Peak expiratory flow rate values greater than 80% of the personal best or expected for height usually suggest reasonable control if symptoms are absent. When PEFR decreases to less than 80% of personal best or there is greater than 20% variability from morning to evening PEFR measurements on the same

day, then adjustments to asthma medications should be considered. Adjustments could include initiating short-acting β-agonist therapy, such as albuterol; increasing the dose of inhaled corticosteroids; adding a long-acting β-agonist, such as salmeterol or formoterol to inhaled corticosteroids; or adding a leukotriene receptor antagonist such as montelukast. If PEFR measurements decrease to less than 50% of predicted or personal best, and a dose of short-acting β-agonist does not resolve the symptoms and increases the PEFR to 50%, patients should contact a physician. Evaluation and management in an urgent care setting are often needed, and a short course of systemic corticosteroids will most likely be necessary.

Spirometry

Unlike PEFR, spirometry is helpful in inferring lung volumes as well as a measure of flows. It is the most useful test for determining whether respiratory symptoms are attributable to underlying obstructive versus restrictive lung disease, although confirmation when restrictive disease is suspected usually requires measurement of complete lung volumes. Abnormal spirometry results do not provide a specific diagnosis; rather, they place a patient in a specific physiological category. The most common obstructive lung disease in children is asthma, affecting about 10% of the US population.[6,7] Cystic fibrosis (CF) is also an obstructive lung disease that often presents to the clinician as recurrent cough, bronchitis, or pneumonia. Restrictive lung diseases include chronic lung diseases that decrease effective lung volumes (eg, bronchopulmonary dysplasia, sickle cell disease), chest wall disorders (eg, pectus deformities, scoliosis), and neuromuscular disorders (eg, Duchenne muscular dystrophy). Normal spirometry results do not exclude lung disease, but they can provide reassurance that the disease is not significantly limiting pulmonary function at rest.

Most children as young as 6 years can perform spirometry adequately for interpretation, and, with practice, some can perform adequately even younger. Preschoolers may be able to perform simple maneuvers with good coaching from staff who help the child feel comfortable and motivated to perform the test.[8] It is possible to obtain reproducible forced expiratory maneuvers in infants, but this is technically challenging and possible only in pediatric PFT laboratories with experience in this specialized technique. The raised volume rapid thoracoabdominal compression technique produces forced expiratory maneuvers in infants that simulate adult-type flow-volume curves. Forced expiratory flows measured with raised volume rapid thoracoabdominal compression in infants with CF are often lower than those in healthy infants and appear to be useful for early detection of CF airway dysfunction.[9,10]

Measures of forced vital capacity (FVC), forced expiratory volume in the first second of expiration (FEV_1), and the ratio of these 2 (FEV_1/FVC) are a useful start in distinguishing between obstructive and restrictive lung disorders.

Patterns of spirometry results are listed in **Table 6-1**. The vital capacity is the largest volume of air that a person can inspire or expire from the lungs. The maneuver required to measure FVC involves taking a maximal inhalation and forcefully exhaling with the mouth tightly closed around a mouthpiece with the nose closed with a nose clip until the entire lung volume is exhaled. The volume exhaled in the first second is the FEV_1 (**Figure 6-1**) and is decreased compared with normal if there is obstruction to exhaled airflow (as with asthma and CF). Flows in the midportion of the forced-exhalation maneuver, a forced expiratory flow between 25% and 75% of the FVC ($FEF_{25\%–75\%}$), are sensitive to small-airway function in children and are the first affected in obstructive lung diseases such as asthma and CF.

Table 6-1. Patterns of Spirometry Results

Measure	Obstructive	Restrictive
FVC	Normal or increased	Reduced
FRC	Increased	Normal or reduced
TLC	Increased	Reduced
FEV_1	Decreased	Normal or decreased
FEV_1/FVC	Decreased	Normal or decreased
$FEF_{25\%–75\%}$	Decreased	Normal or decreased

Abbreviations: $FEF_{25\%–75\%}$, forced expiratory flow between 25% and 75% of the FVC; FEV_1, forced expiratory volume in 1 second; FRC, functional reserve capacity; FVC, forced vital capacity; TLC, total lung capacity.

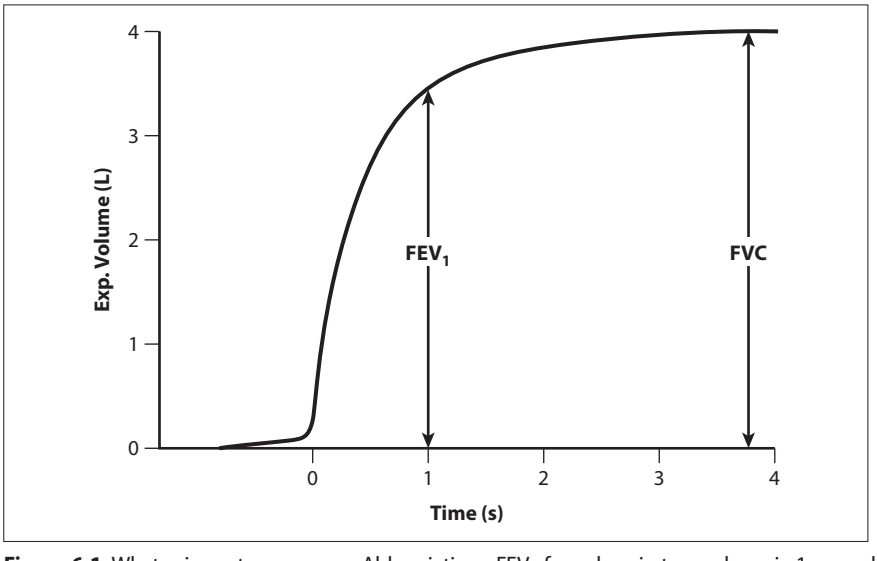


Figure 6-1. What spirometry measures. Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

The results of the expiratory maneuver that generates the measurements of FEV_1 and FVC are displayed most commonly as a flow-volume loop or can be displayed as a volume-versus-time graph (**Figure 6-2**).

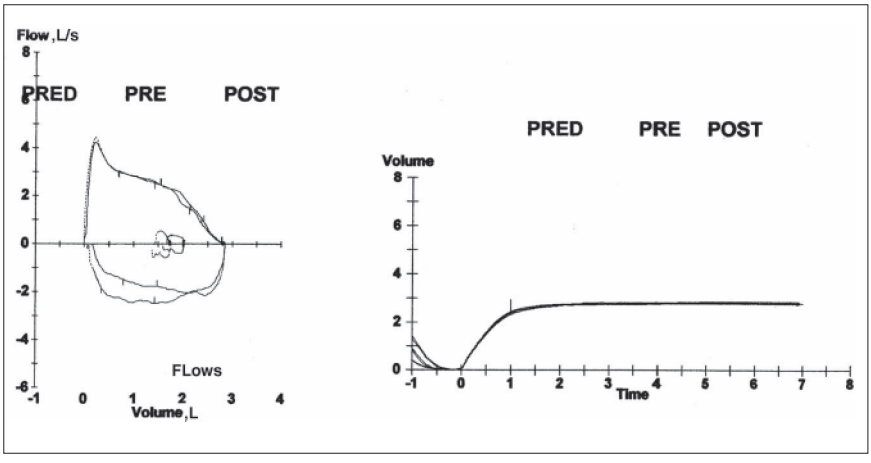


Figure 6-2. Flow-volume loop and volume-versus-time graph of a spirogram. There was good patient effort on the maneuvers, American Thoracic Society criteria were met, and 2 puffs of albuterol were administered with a holding chamber.

Abbreviations: Pre, before bronchodilator; pred, predicted; post, after bronchodilator.

In obstructive lung diseases, there may be a reduced rate of airflow at any given lung volume, and the FEV_1/FVC is lower than normal. Criteria for assessing for an adequate flow-volume loop include (1) instantaneous start of exhalation and rapid increase in flow to peak; (2) normal sharp peak, indicating maximal effort; (3) smooth, continuous exhalation to zero flow; and (4) reproducible results (**Box 6-2**, **Figure 6-3**).

Box 6-2

Characteristics of Flow-Volume Loops

Acceptable flow-volume loop

Instantaneous start of exhalation and rapid increase in flow to peak

Normal sharp peak, indicating maximal effort and no large conducting central airway obstruction

Smooth, continuous exhalation to residual volume

Reproducible results

Unacceptable flow-volume loop

Poor start of exhalation with slow or erratic increase to peak

Broad or flat peak, which may indicate less-than-optimal effort; if it is smooth and reproducible, it may indicate central conducting airway obstructions

Erratic exhalation with cough or abrupt flow changes

Exhalation not complete (ie, flow decreases abruptly to zero without a gradual return to zero)

Curve features not reproducible

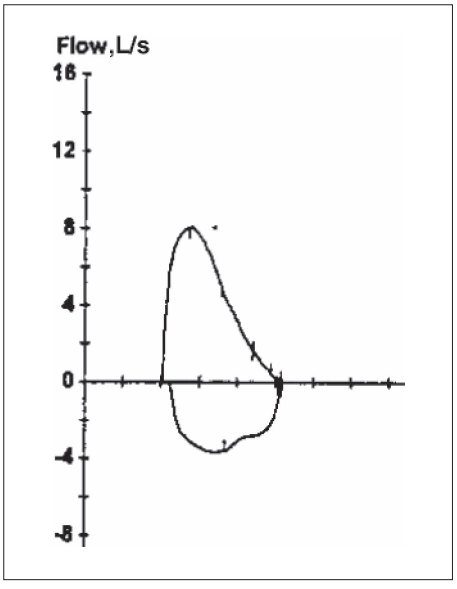


Figure 6-3. Acceptable flow-volume loop: rapid increase during expiration, a normal sharp peak, smooth exhalation, and gradual return to zero flow.

An unacceptable flow-volume curve is shown in **Figure 6-4**, which demonstrates erratic flows during exhalation that are attributable to coughing. Without a reliable flow-volume loop, the results of the spirometric maneuver should be questioned. Careful inspection of the expiratory flow-volume curve provides a more sensitive indication of small-airway obstruction than does evaluating only the quantitative measurements. The early reduction of flow and the flattening of the slope are characteristic of obstruction, which appears as a concave expiratory flow tracing (**Figure 6-5**). Pulmonary function laboratories should always follow standards set by the American Thoracic Society, and PFTs in children are more likely to be reproducible and useful when obtained in laboratories or other settings with significant experience with children.

Spirometry has become so ubiquitous that it may seem as if it is the only PFT available. It is relatively inexpensive and easy to perform and has become the primary end point for almost all clinical trials. However, there are many limitations, particularly in children.

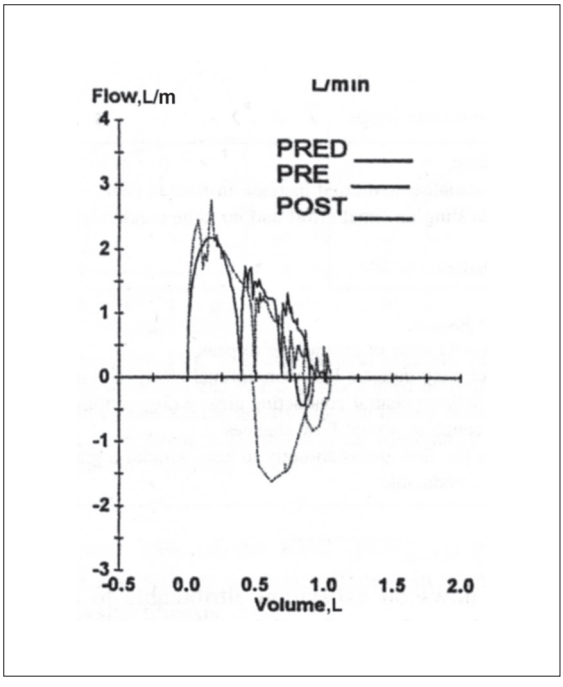


Figure 6-4. Unacceptable flow-volume loop: poor start, erratic exhalation with cough that led to inhalation during expiratory phase, and abrupt return to zero.

Abbreviations: Pre, before bronchodilator; pred, predicted; post, after bronchodilator.

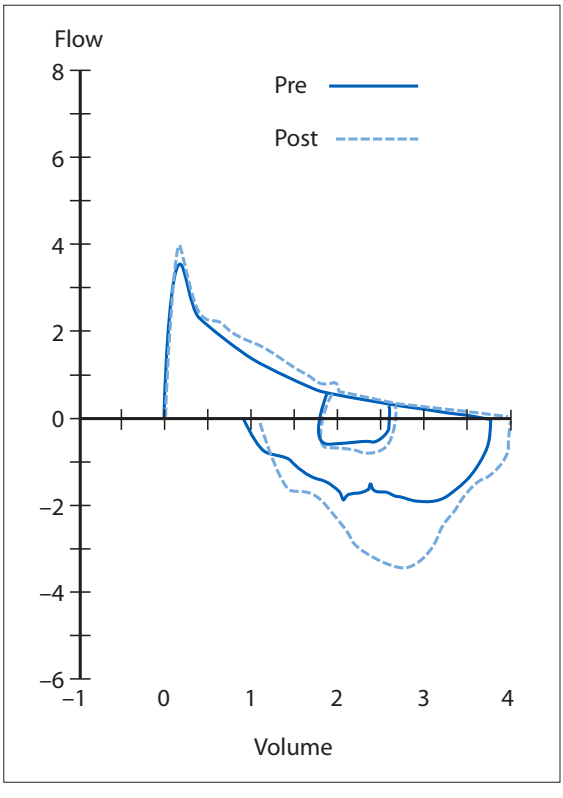


Figure 6-5. Severe airflow obstruction. The flow-volume loop demonstrates flow limitation at all lung volumes, with concave tracings on the expiratory loop. There was no improvement in flows after use of a bronchodilator.

Abbreviations: Pre, before bronchodilator; post, after bronchodilator.

Reference Values

Pulmonary function test results may indicate patterns of lung function consistent with obstructive or restrictive lung disease. The results should be compared with reference values from healthy populations. Norms and standards for interpretation[11,12] should be chosen from a study in a healthy population similar to the patient. It is important to obtain an accurate standing height (or arm span if the patient cannot stand or has significant scoliosis) because the interpretation of normal versus abnormal is based on height in addition to age, sex, and race. If the pulmonary function laboratory does not provide a qualitative interpretation of the data, then fixed-percent predicted cutoffs of less than 80%, 80%, and 60% are reasonable for identifying abnormalities of FVC, FEV_1, and $FEF_{25\%–75\%}$, respectively. Grades of impairment compared with predicted norms are shown in **Table 6-2.** An FEV_1 or FVC of less than 80% of that predicted has generally been considered abnormal, though recently more expert bodies, including the American Thoracic Society, recommend moving to calculation of *z* scores and considering a *z* score less than −2 (2 SDs below the normal mean) to be abnormal. As a general rule, spirometric measurements are considered mildly abnormal if they are between 70% and 79% of predicted values, though a healthy child younger than 12 years usually has an absolute FEV_1/FVC ratio of 0.85 or greater. **Table 6-2** includes one classification of severity of obstruction based on spirometric values expressed as percentage of predicted values, though these are not universally accepted. An example of how predicted values can vary depending on the reference group used for comparison is represented in **Table 6-3**. For the spirometric data in the same patient, according to National Health and Nutrition Examination Survey III references,[4] FVC and FEV_1 were 64% of that predicted, or moderately abnormal. According to the European Respiratory Society 1993 standards,[13] which do not include Black counterparts, the FVC and FEV_1 were 56% and 57% of that predicted, respectively, or moderate to severely abnormal.

The development of reference ranges for PFTs, particularly spirometry and diffusing capacity, has improved significantly. One of the more vexing problems for pediatricians has been the lack of a single set of reference equations that can be used for children of all ages. In the past, clinicians had to switch reference ranges midway through childhood, which could result in significant confusion and misinterpretation. Now, there are internationally accepted equations for patients of all ages (from age 3 years and up) for spirometry and diffusing capacity. An international group of experts developed these equations as part of the Global Lung Function Initiative (GLI), as nicely summarized in the review article by Cooper et al.[14] Not all current spirometers have these newer equations built into their memory, but

continued advocacy efforts for their wide adoption are critical to achieve health equity. However, although GLI is a step in the right direction to eliminate race-based medicine, the normative values on which it relies remain limited by small sample sizes of African Americans, particularly children, as well as many other ethnic groups and nationalities throughout the world. Using race-based reference equations for the interpretation of pulmonary function tests in Black patients (see **Table 6-3**) can result in underdiagnosing lung disease, which can perpetuate health disparities in many respiratory diseases and respiratory complications of several diseases, such as sickle cell disease.[15–18] When comparing results in an individual patient over time, it is important to compare absolute volumes and flows and examine which reference values were used to report the predicted volumes and flows. The use of appropriate references is required not only for spirometry but also for measures of lung volumes and diffusion capacity.

Table 6-2. Grades of Impairment

Grade	FEV_1 or FVC % Predicted	$FEF_{25\%–75\%}$, % Predicted	FEV_1/FVC, Absolute Ratio
Normal	> 80	> 70	> 0.80
Mild	< 80–70	< 70–60	< 0.80–0.60
Moderate	< 70–55	< 60–40	< 0.60–0.40
Severe	< 55–30	< 40–15	< 40–0.25
Extreme	< 30	< 15	< .25

Table 6-3. Differences of Percent-Predicted Values on Spirometry for a 15-Year-Old Black Boy

Parameter	Results	Reference[a]	% Predicted[a]	Reference[b]	% Predicted[b]
FVC, L	2.69	4.18	64	4.83	56
FEV_1, L	2.29	3.59	64	3.98	57
FEV_1/FVC, absolute ratio	0.85	0.86	—	0.83	—
$FEF_{25\%–75\%}$, L/s	2.48	4.00	62	5.08	49

Abbreviations: $FEF_{25\%–75\%}$, forced expiratory flow between 25% and 75% of the FVC; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.
[a] National Health and Nutrition Examination Survey III; www.cdc.gov/nchs/nhanes.htm.
[b] European Community Respiratory Health Survey; www.ecrs.org.

Lung Volumes

When the FVC on a spirometry test is low (<80% of that predicted) and the FEV_1/FVC ratio is normal or elevated (>80%), a restrictive defect in pulmonary function is suggested. When the FVC is less than 80% and the ratio of FEV_1/FVC is less than 80%, an obstructive defect is suggested. To confirm a restrictive versus obstructive disease pattern, measure complete lung volumes, (ie, residual volume [RV], functional reserve capacity [FRC], and total lung capacity) (**Figure 6-6**). With spirometry, only lung volumes and flow rates within the FVC are measurable—the volume of air that is exhaled or inhaled from maximal inhalation to maximal exhalation, such as the FVC, FEV_1, and $FEF_{25\%–75\%}$. Because RV is the volume of air that cannot be exhaled from the lungs even after maximal exhalation, it must be measured indirectly. The most common methods for measuring lung volumes are helium dilution, nitrogen washout, and body plethysmography (the body box). In practice, the FRC is measured, and RV and TLC are calculated from the FRC by measuring the

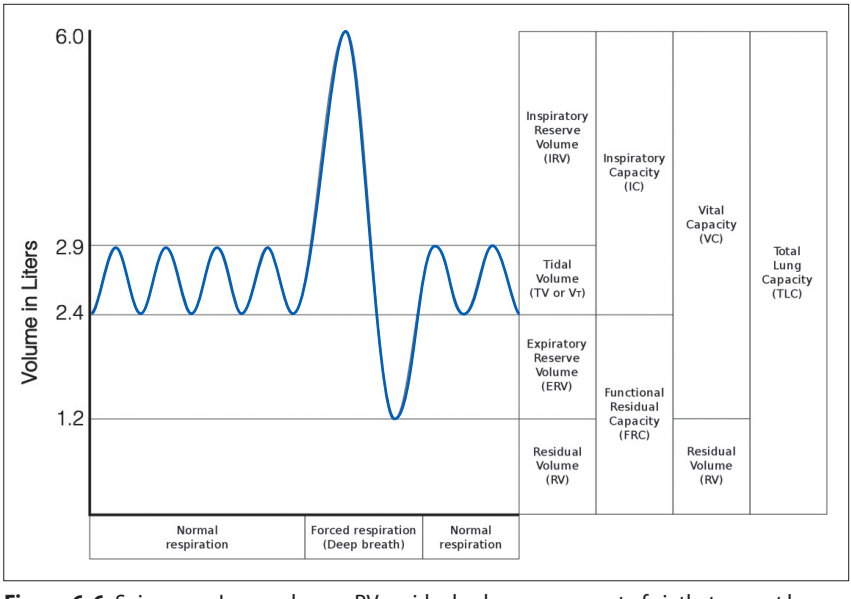


Figure 6-6. Spirogram. Lung volumes: RV, residual volume—amount of air that cannot be exhaled from the lung; ERV (expiratory reserve volume), volume that can be exhaled starting from FRC to RV; FRC, the volume of air in the lungs at the end of the tidal breath, and a combination of ERV and RV; TLC, the total volume of air in the lung on full inspiration.

From Whitmer KH. Assessment of pulmonary function: spirometry. In: *A Mixed Course-Based Research Approach to Human Physiology*. Iowa State University Digital Press. Accessed August 30, 2022. https://iastate.pressbooks.pub/curehumanphysiology/chapter/pulmonary-function/.

expiratory reserve volume and vital capacity. The helium dilution and nitrogen washout methods rely on the mixing of known concentrations of gas with the patient's lung volume at the start of the test, which by convention starts at FRC. If a patient has severe obstructive lung disease, this method is not very accurate because the gases mix too slowly to reflect accurate volumes or not at all in regions of the lung that have significant air trapping. In this case, use of the body box is more accurate. Almost all body boxes today are referred to as *pressure boxes*, in which pressure changes at the mouth with the patient inside a closed box permit calculation of FRC. The body box can provide useful information about air trapping (high FRC or RV) in patients with CF but cannot be used successfully if obesity prevents the patient from fitting in the closed box or the patient depends on supplemental oxygen.

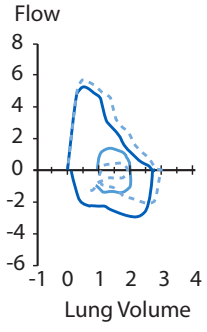
When a restrictive lung disease is suspected, such as a neuromuscular disorder or sickle cell disease, measuring lung volumes can provide more detail about the severity of the restrictive changes. These studies take more time than spirometry and usually can be performed only in a pulmonary function laboratory with standardized protocols that follow American Thoracic Society guidelines. These techniques require little or no effort on the part of the patient but depend greatly on the skill and experience of the technician.

Carbon Monoxide Diffusing Capacity

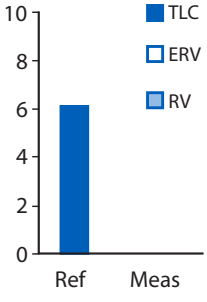
Diffusing capacity of the lung for carbon monoxide (D_{LCO}) is the measurement of carbon monoxide (CO) transfer from inspired gas into the pulmonary capillary. The transfer of CO into the blood depends on many variables, including alveolar capillary interface (thickness), capillary volume, hemoglobin concentration, and the reaction rates between CO and hemoglobin.[19] In patients with lung disease, the D_{LCO} correlates with disease severity and arterial blood oxygenation, particularly during exercise.[20] Measuring D_{LCO} over time may be useful for patients with the potential for progressive loss of alveolar surface area, such as those with sickle cell disease (**Figure 6-7**), those under-going chemotherapy or radiation therapy, and those who have undergone lung resection. The D_{LCO} is diminished in young adults with a history of being born preterm, regardless of whether they had a diagnosis of bronchopulmonary dysplasia.[21] This diminished D_{LCO} likely reflects inadequate or abnormal growth of the alveoli after preterm birth. Normative data for D_{LCO} are not as comprehensively available for different racial and ethnic groups and young ages as are data for spirometry[19]; but the new GLI reference ranges discussed earlier in spirometry are excellent.[14] Generally speaking, a D_{LCO} of 60% and up to the lower limits of normal for the reference population is considered mildly abnormal, 40% to 60% is considered moderately abnormal, and less than 40% is considered severely abnormal. The clinician can evaluate trends over time for an individual patient to determine whether

Age: 15	Height(in): 70	Race: Black	Gender: Male	Weight(lb): 127
Diagnosis: Sickle cell/asthma		Medication:		
Dyspnea Rest: No	Dyspnea Exercise: No		Cough: No	Productive(cc):
Persistent: No	Smoker: No		How Long(pk/yrs):	Stopped(yrs):
Cigarettes: No	Cigars: No		Temp: 22	PBar: 757

PULMONARY FUNCTION ANALYSIS



Spirometry		Ref	Pre Meas	Pre % Ref	Post Meas	Post % Ref	Post % Chg
FVC	Liters	4.83	2.69	56	2.89	60	7
FEV1	Liters	3.98	2.29	57	2.53	64	11
FEV1/FVC	%	89	85		87		
FEF25-75%	L/sec	5.08	2.48	49	3.02	60	22
PEF	L/sec	7.92	5.26	66	5.74	72	9
FET100%	Sec		5.67		6.41		13
FIVC	Liters	4.83	2.55	63	2.03	42	-21
FIF50%	L/sec		2.51		1.52		-35
MVV	L/min						



Lung Volumes					
VC	Liters	4.76	2.89	61	
TLC	Liters	6.04	3.96	65	
RV	Liters	1.26	1.06	65	
RV/TLC	%	23	27		
FRC N2	Liters	2.97	2.35	79	
ERV	Liters		0.55		

Diffusion					Hb: 8.8
DLCO	mL/mmHg/min	29.4	17.9	61	
DL Adj	mL/mmHg/min	35.1	22.2	61	
VA	Liters	7.14	3.76	53	
DLCO/VA	mL/mmHg/min/L	5.06	4.77	94	
DL/VA Adj	mL/mmHg/min/L	5.06	5.91	117	
IVC	Liters		2.35		

Figure 6-7. Example of pulmonary function test: sickle cell disease. Moderate restrictive defect shown with spirometry is suspected from decreased FVC and normal FEV/FEV_1 and confirmed with lung volumes with an FVC of 56% predicted and TLC of only 65% predicted. The DLCO is decreased to 61%, corrected for the patient's anemia (with a Hb level of 8.8). This patient has had multiple episodes of acute chest syndrome.

Abbreviations: Adj, adjusted; Chg, change; DL, lung diffusion; DLCO, carbon monoxide diffusing capacity; ERV, expiratory reserve volume; $FEF_{25-75\%}$, forced expiratory flow between 25% and 75% of the FVC; $FET_{100\%}$, forced expiratory time; FEV_1, forced expiratory volume in 1 second; $FIF_{50\%}$, forced inspiratory flow; FIVC, forced IVC; FRC, functional reserve capacity; FVC, forced vital capacity; FVL, flow-volume loop; Hb, hemoglobin; IVC, inspiratory vital capacity; Meas, measure; MVV, maximum voluntary ventilation; PEF, peak expiratory flow; Ref, reference; RV, residual volume; TLC, total lung capacity; VA, alveolar volume; VC, vital capacity.

there is progressive loss of alveolar or capillary surface area for gas exchange in certain disease states that require close monitoring, such as those in patients undergoing chemotherapy for cancer, patients with sickle cell hemoglobinopathy, and patients with interstitial lung disease. Whole-lung irradiation can lead to mild, moderate, and severe changes in D_{LCO},[22] so monitoring the effects of cancer therapy in children is very important.

Assessing Airway Reactivity

Children who have asthma or a history of early neonatal lung injury (eg, bronchopulmonary dysplasia, bronchiolitis, aspiration syndromes, prolonged mechanical ventilation) may have increased bronchial reactivity. In addition, children with symptoms of dyspnea or chest pain with normal physical findings and normal spirometry test results at rest may be evaluated by using tests of airway reactivity.[23]

Bronchodilator Testing

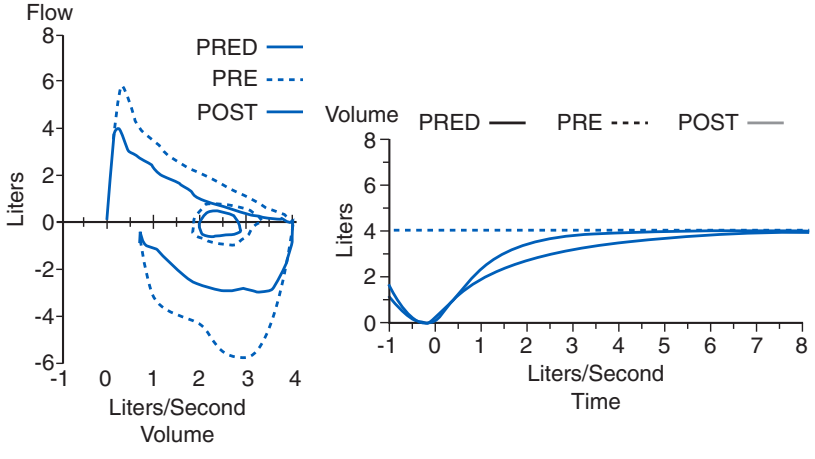
Spirometry before and after the use of an aerosolized bronchodilator can help evaluate the usefulness of bronchodilator therapy for a patient with known obstructive lung disease or who is suspected of having obstructive lung disease (**Figure 6-8**).[24] Asthma is the most common reversible obstructive airway disease, and if it is suspected as the cause of a patient's signs and symptoms, bronchodilator testing can help confirm the diagnosis. For patients with neuromuscular disease, the usefulness of bronchodilators can be assessed with spirometry before and after albuterol use. As shown in **Figure 6-9**, a 13-year-old boy with Duchenne muscular dystrophy had worse expiratory flows after albuterol use (17% worsening of FEV_1 and 67% worsening of $FEF_{25\%–75\%}$), showing that albuterol is not useful in his treatment. A lack of response to a bronchodilator in a patient with an obstructive pattern at spirometry may indicate long-standing airway inflammation and raise the question of other diagnoses, such as CF (**Figure 6-10**). Spirometry performed at rest can be repeated 10 to 15 minutes after a standard dose of an inhaled bronchodilator if the patient has not used any bronchodilators for at least 4 hours before testing. Albuterol administered with a metered-dose inhaler (2–4 puffs) with a spacer for adequate dose delivery or 2.5 to 5.0 mg of nebulized albuterol should be adequate for assessing bronchodilation. As a general rule, an increase in FVC or FEV_1 of 12% would be considered a significant bronchodilator response and compatible with a diagnosis of asthma regardless of whether the baseline spirometry test result demonstrated obstruction or was normal compared with reference values.

Hospital for Children

Pediatric Pulmonary Function Lab

Gender: Male
Age: 15 Race: Black
Height(in): 65 Weight(lb): 132
Diagnosis:

Spirometry		Ref	Pre	% Ref	Post	% Ref	% Chg
FVC	Liters	3.39	4.10	121	4.17	123	2
FEV1	Liters	2.96	2.02	68	2.68	91	33
FEV1/FVC	%	86	49		64		
FEF25-75%	L/sec	3.50	0.94	27	1.81	52	93
PEF	L/sec	6.98	4.37	63	6.52	94	49
Vol Extrap	Liters		0.01		0.04		600



Comments:

Interpretation:
Forced expiration demonstrates a moderate obstructive ventilatory defect. There is an immediate response to aerosolized bronchodilator. Spirogams plateau normally. Flow volume loops reveal decreased expiratory flow rates at low lung volumes consistent with airway obstruction.

Figure 6-8. Example of pulmonary function test: severe airflow obstruction attributable to asthma due to FEV_1/FVC % of only 49% before bronchodilator with improved but not quite normalized flows after bronchodilator response: FEV_1/FVC % of 64%.

Abbreviations: Chg, change; $FEF_{25-75\%}$, forced expiratory flow between 25% and 75% of the FVC; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; FVL, flow-volume loop; PEF, peak expiratory flow; Post, after bronchodilator; Pre, before bronchodilator; Pred, predicted; Ref, reference; Vol Extrap, extrapolated volume.

DUCHENNE MUSCULAR DYSTROPHY

Age:	13 years	?????TL3097134	
Sex/Race:	Male/Caucasian	Room: Out	
Height:	63 in 161 cm		
Weight:	142 lbs 65 kg		

			Pre-RX		Post-RX		
Spirometry	(BTPS)	PRED	BEST	%PRED	BEST	%PRED	%CHG
FVC	Liters	3.69	0.90	26	0.95	26	–1
FEV1	Liters	3.17	0.90	38	0.75	29	–17
FEV1/FVC	%		94		79		–16
FEF25-75%	L/Sec	3.33	2.00	38	0.66	19	–67
FEF25%	L/Ses		1.34		1.19		–53
FEF50%	L/Sec		2.18		0.72		–67
FEF75%	L/Sec		1.55		0.41		–47
PEF	L/Sec	2.26	2.73	38	1.48	18	–49
FIVC	Liters	?	0.99	27	0.98	41	1
PIF	L/Sec		2.24		2.63		0

Figure 6-9. Example of pulmonary function test: Duchenne muscular dystrophy. A severe restrictive pattern is shown, with FVC at only 0.90 L or 26% of that predicted, FEV_1 at 0.90 L or 28% of that predicted, and FEV_1/FVC at 94%, with worsening after use of a bronchodilator (FEV_1 decreased by 17%).

Abbreviations: CHG, change; BTPS, body temperature, ambient pressure, and gas saturated with water vapor; FEF, forced expiratory flow; FEV_1, forced expiratory volume in 1 second; FIVC, forced inspiratory vital capacity; FVC, forced vital capacity; PEF, peak expiratory flow; PIF, peak inspiratory flow; Post-Rx, after bronchodilator; Pred, predicted; Pre-Rx, before bronchodilator.

CYSTIC FIBROSIS

Age:	21 Years	
Sex/Race:	Female/Caucasian	
Height:	59 in	150 cm
Weight:	86 lbs	39 kg

				Pre-RX		Post-RX		
	Spirometry	(BTPS)	PRED	BEST	%PRED	BEST	%PRED	%CHG
FVC	Liters		3.31	1.45 #	44#	1.52 #	46#	5
FEV1	Liters		3.01	0.91 #	30#	0.94 #	31#	3
FEV1/FVC	%		91	63 #	69#	62 #	68#	–2
FEF25-75%	L/Sec		4.02	0.48 #	12#	0.46 #	11#	–4
FEF25%	L/Sec			1.48		1.63		10
FEF50%	L/Sec			0.54		0.56		4
FEF75%	L/Sec			0.20		0.16		–20
PEF	L/Sec			2.60		2.75		6
FIVC	Liters		3.31	1.33 #	40#	1.37 #	41#	3
PIF	L/Sec			2.38		2.64		11

= Outside 95% Confidence Interval # = Outside Normal Range

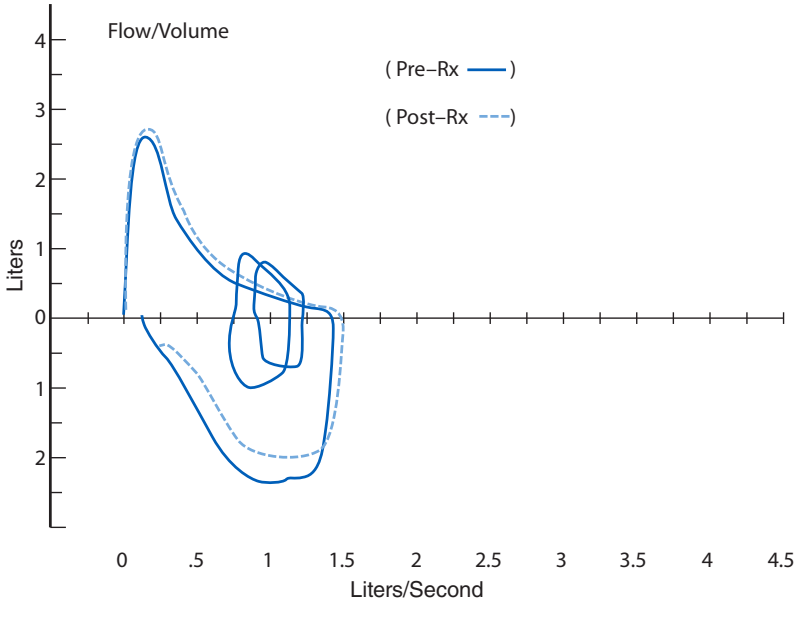


Figure 6-10. Example of pulmonary function test: cystic fibrosis. Shown are severe airflow obstruction (FEV_1 at 30% of that predicted) and a severe restrictive pattern (FVC at 44% of that predicted), with no improvement after bronchodilator administration. Flow limitation is worse with forced exhalation compared with tidal breathing at rest.

Abbreviations: CHG, change; BTPS, body temperature, ambient pressure, and gas saturated with water vapor; FEF, forced expiratory flow; FEV_1, forced expiratory volume in 1 second; FIVC, forced inspiratory vital capacity; FVC, forced vital capacity; PEF, peak expiratory flow; PIF, peak inspiratory flow; Post-Rx, after bronchodilator; Pred, predicted; Pre-Rx, before bronchodilator.

Bronchial Challenge Testing

For patients with a history or physical examination findings suggestive of asthma (eg, cough, dyspnea, chest pain, wheezing), it is not uncommon for a clinician to prescribe a trial of bronchodilator or an anti-inflammatory therapy. However, continued use of a therapy for an unconfirmed diagnosis of asthma can expose a child to unnecessary adverse effects. When an adolescent with unexplained dyspnea, chest pain, or cough has normal spirometric results and an unclear response to bronchodilators, bronchial challenge testing can be used to diagnose airway hyperreactivity. Airway hyperreactivity is a more sensitive objective marker of asthma in children than is PEFR or spirometry at rest or after bronchodilator use.[25]

Inhalation of methacholine is frequently used to determine whether airway hyperreactivity is present. Children with asthma will respond to methacholine with a pattern of airway obstruction at spirometry at a lower dose than do children who do not have asthma. In addition to asthma, factors that increase bronchial hyperresponsiveness include exposure to environmental antigens, occupational sensitizers, respiratory infections, air pollutants, cigarette smoke, and chemical irritants.[26] After baseline spirometry is measured, the patient inhales increasing doses of methacholine. A change in FEV_1 is the primary outcome measure for methacholine challenge testing. *Provocative concentration 20* (PC_{20}) is defined as the exact concentration of methacholine that causes a 20% decrease in FEV_1 from the baseline FEV_1. A positive test result is one in which the PC_{20} occurs at less than 4.0 mg/mL[22] (**Table 6-4**). A patient with a PC_{20} of less than 1.0 mg/mL has moderate to severe bronchial hyperreactivity. If doses of greater than 16 mg/mL methacholine do not cause a 20% decrease in FEV_1, then the patient's result is considered normal, and another cause for the reported symptoms should be sought. Approximately 30% of patients without asthma who have allergic rhinitis have a PC_{20} in the borderline range (4.0–16 mg/mL). Approximately 90% to 98% of patients with asthma are hyperreactive to methacholine or histamine, another inhalation challenge agent.[27] Methacholine challenge testing should be performed in a pulmonary function laboratory with experienced personnel because of the risk of serious airflow obstruction.

Table 6-4. Methacholine Challenge Interpretation of Bronchial Hyperresponsiveness

PC_{20}[a]	Interpretation
> 16 mg/mL	Normal
4–16 mg/mL	Borderline
1–4 mg/mL	Mild
< 1 mg/mL	Moderate to severe

[a] Provocative concentration of methacholine causing a 20% decrease in forced expiratory volume in 1 second.

Exercise Challenge Testing

Although a little less sensitive than methacholine testing, bronchial challenge testing can also be accomplished by using exercise on a treadmill or bicycle. The test may be particularly useful for a patient whose respiratory concerns occur primarily with exercise to confirm a suspected diagnosis of exercise-induced bronchospasm (EIB). Bronchial challenge can also be used to determine the ability of an adolescent to perform demanding or lifesaving work and to determine the effectiveness of therapy to prevent symptoms. As many as 95% of children and adolescents with asthma have EIB.[28,29] A child or adolescent suspected of having EIB whose respiratory symptoms are not prevented by treatment with an inhaled bronchodilator given 15 to 20 minutes before exercise and who has no other manifestations of asthma should be referred for exercise challenge testing to confirm the diagnosis.[23]

Patients are asked to walk or run on a treadmill to reproduce symptoms experienced with exercise. The standard is a minimum of 4 minutes at the target heart rate: heart rate is 80% to 90% of the predicted maximum, calculated as 220 minus age in years, or ventilation at 40% to 60% of the predicted maximum voluntary ventilation, estimated as $FEV_1 \times 35$.[26] For the bicycle ergometer to produce an adequate test, a target work rate to achieve the target ventilation must be sustained for at least 4 to 6 minutes. Only 50% to 70% of children demonstrate significant bronchoconstriction with cycling, so the treadmill is more likely to provide confirmation of airway hyperreactivity. As with methacholine challenge testing, the change in FEV_1 is the primary outcome variable. Repeated measures of spirometry are obtained immediately after exercise and then serially 5, 10, 15, and 20 minutes after completing the exercise. If the FEV_1 is not back to a baseline level by 20 minutes, then another measure at 30 minutes should be obtained. Response to a bronchodilator may be assessed if the patient experiences significant dyspnea or the FEV_1 has not returned to within 10% of baseline at 30 minutes. A 10% decrease from the baseline FEV_1 is generally accepted as abnormal,[29,30] although a decrease of 15% is considered by some to be more diagnostic of EIB.[23,31]

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing (CPET) involves assessing cardiac and pulmonary function during incremental exercise and includes measuring gas exchange (oxygen consumption, CO production, minute ventilation), performing electrocardiography, and measuring blood pressure.[32] The clinician requests CPET for patients who report shortness of breath, dyspnea on exertion, or exercise intolerance without a clear cause or response to therapeutic trials. It may also be used to assess cardiopulmonary fitness. If the patient has chest pain or symptoms suggestive of cardiovascular disease, a cardiologist should perform a cardiac stress test. Exercise challenge testing

is more appropriate if the patient complains of chest tightness and wheezing during or after exercise (see Exercise Challenge Testing). Cardiopulmonary exercise testing is useful for a child or adolescent who feels limited by exercise. Limitation can be attributable to impaired lung function; impaired cardiac, pulmonary, or peripheral circulation; or poor conditioning. Patients with asthma, chronic lung disease, or sickle cell disease may have limitations to their oxygenation or ventilatory responses to exercise. See **Box 6-3** for indications for CPET.

Box 6-3

Indications for Cardiopulmonary Exercise Testing

- **To determine exercise capacity or the cause of any exercise impairment**
- **To identify abnormal responses to exercise**
- **To stratify risk and exercise response for training and rehabilitation**
- **To evaluate results of treatment**
- **For preoperative assessment**
- **To evaluate impairment or disability**
- **To evaluate unexplained dyspnea**

Pulse Oximetry

Pulse oximetry is a convenient, in vivo, noninvasive technique for measuring oxygen saturation. Oxygen saturation is determined by the ratio of oxyhemoglobin to the sum of oxyhemoglobin and reduced hemoglobin. Pulse oximeters perform optical measurements across a pulsating arterial bed (on the finger or ear) at only 2 wavelengths of light to discriminate oxygenated and deoxygenated hemoglobin. Carboxyhemoglobin and methemoglobin also absorb light at the wavelengths measured by the pulse oximeter and, if abundant, can affect the accuracy of the pulse oximeter. These devices are calibrated by means of healthy volunteers with insignificant amounts of dysfunctional hemoglobins.[33]

Pulse oximetry is used widely to assess arterial oxygenation and provides a useful estimate of hypoxia. Oxygen saturations of less than 93% predict a partial pressure of oxygen of less than 70 mm Hg. The pulse oximeter has been validated in various cohorts of patients with presumably normal hemoglobin levels, such as neonates, and in patients with cyanotic heart disease[34]; however, a retrospective review of simultaneous pulse oximetry and arterial blood gas analysis data obtained in patients with sickle cell disease in the ED suggested that the pulse oximeter did not predict hypoxemia well.[35] Results from a prospective study in children and adolescents with sickle cell hemoglobin demonstrated that pulse oximetry led to overestimation of the number of children with hypoxia and could have led to inappropriate treatment with

supplemental oxygen.[36] Pulse oximetry may be less sensitive to hypoxemia in patients with more darkly pigmented skin.

One cannot rely on the pulse oximeter for assessing oxygenation in an adolescent or young adult with potential smoke inhalation. Carbon monoxide bound to hemoglobin has wavelength-absorption characteristics similar to those of oxygenated hemoglobin, and patients with smoke inhalation will have a falsely normal pulse oximetry value. In the evaluation of a patient with potential smoke exposure, measuring carboxyhemoglobin directly from an arterial blood sample is essential. Methemoglobin causes the pulse oximeter readout to tend toward 85%. If the clinician is aware of the presence of dyshemoglobins in a patient's blood, correlation of an arterial blood sample with pulse oximetry is advisable. Normal oxygen saturation of the blood does not ensure adequate oxygen delivery to the tissues, especially in patients with anemia, patients in heart failure, or patients in shock.

Arterial Blood Gas

Arterial blood gas measurements are used to assess oxygenation and ventilation. This subject is covered in Chapter 2, Pulmonary Physiology.

When to Refer

- Spirometry should be used to confirm a suspected diagnosis of asthma (reversible airways obstruction) and periodically used to monitor progression of the disease and its response to therapy. If a primary care office does not have access to spirometry, children and adolescents who have asthma or other chronic pulmonary disease should be referred to a pediatric pulmonologist for evaluation at some point in their course.
- If spirometry is performed, referral to a pediatric pulmonologist or to a pediatric pulmonary function laboratory should be considered if there is:
  - Any suggestion of restriction
  - Severe degree of obstruction
  - Nonresponsiveness or ambiguous response to bronchodilators
  - Unexplained inability to perform acceptable or reproducible forced expiratory maneuvers
  - Clinical history inconsistent with pulmonary function findings.

key points

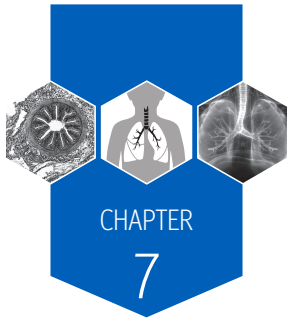
- Spirometry is useful to distinguish restrictive from obstructive lung disease to develop a differential diagnosis in children with chronic respiratory symptoms.
- Using PFTs can provide objective evidence of the severity of pulmonary disease, changes over time, and response to therapies (eg, in disorders such as asthma, CF, sickle cell disease, and muscular dystrophy).
- Although some children can perform spirometry as young as age 3 years, consistent results are more likely after the age of 6 years.
- Measurement of RV requires more sophisticated testing than simple spirometry and should be performed in a pulmonary function laboratory with experience testing in children.
- Pulmonary function testing may be useful in the primary care office, but oversight and interpretation by the pediatric pulmonologist is helpful and using appropriate normative data for comparison is essential.
- If the primary care office performs PFTs, it is important that there is a mechanism in place to ensure that studies are performed to American Thoracic Society guidelines, which implies that there is a medical director responsible for oversight of the testing.
- Exercise challenge should be used for evaluating exercise-related symptoms, particularly if lung function measures are normal at rest and there is little or no response to therapy.
- Cardiopulmonary exercise testing can be used to evaluate fitness or the cause of exercise limitations.
- Pulse oximetry is a useful, noninvasive test to measure arterial oxygen saturation, but it has limitations (eg, normal adult hemoglobin is assumed).

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CHAPTER 7

Pulmonary Imaging

Michael J. Light, MD
Julieta M. Oneto, MD
Ricardo Restrepo, MD

Radiation Exposure in Children

A clinician ordering an imaging test must be familiar with the indications and contraindications of multiple imaging modalities and their alternatives, taking into consideration factors such as radiation exposure, cost, and goal of imaging. A major concern with imaging in children is the child's exposure to ionizing radiation. Pediatric radiologists modify imaging parameters to minimize radiation by following standard protocols, particularly for computed tomography (CT) scans. Pediatric radiologists keep in mind the concept of *as low as reasonably achievable* in terms of a child's exposure to radiation during imaging. The Image Gently campaign[1] is an initiative of the Alliance for Radiation Safety in Pediatric Imaging. The campaign goal is to change practice by increasing the awareness of the opportunities to lower radiation dose while performing imaging in children.

Ionizing radiation is used in plain radiography, fluoroscopy, and CT scanning. The effective dose is a calculated age- and sex-averaged value that is used as a measure of the potential risk of cancer and hereditary effects due to exposure to ionizing radiation by comparing that value with those of other sources of exposure such as background radiation or air travel.

The biological effect of ionizing radiation is represented in the unit of Sieverts, which is the product of the absorbed dose and a weighting factor. The weighting factor is a function of the type of radiation and the tissue involved.[2]

Ionizing radiation has the potential to alter DNA directly or by generating free radicals. In the extreme, ionizing radiation causes cell death. In addition, high doses of ionizing radiation are carcinogenic. Medical imaging accounts for an increasing amount of radiation exposure to the general population. In the United States, imaging accounts for about 50% of the total radiation exposure; of this amount, 50% is accounted for by CT scanning. Children are 2 to 10 times more susceptible to radiation of all kinds than are adults.

The risk of cancer from radiation has not been defined, and clinical studies have not been performed to define the risk-versus-benefit ratio. The theoretical risk of radiation exposure from medical imaging has been suggested from the studies of cancer incidence in survivors of the Hiroshima atomic bomb. Moderate or severe exposure (> 100–150 mSv) is clearly a cancer risk, but lower levels are less obvious. The difference in effect on the body between acute and chronic exposure is not fully understood, but it is clear that exposures over a lifetime are cumulative.

The dose of a single chest radiograph is approximately 0.1 mSv, which is equivalent to the natural background radiation that the population is exposed to in 10 days. In an effort to decrease radiation, pediatric radiologists have developed a low-dose protocol that can reduce the radiation dose in children.[2,3] Recently, ultralow-dose protocols have been developed for patients with chronic conditions, such as cystic fibrosis (CF), that require continuous follow-up. Such ultralow-dose protocols can have an effective dose as low as 0.14 mSv.[4] Children with chronic conditions have a longer life expectancy than in the recent past, and their exposure to medical imaging is higher as well.

Imaging Approach

Several modalities are available to evaluate the chest and its structures in children. In general, chest radiography is the initial imaging approach when a chest anomaly is suspected. General suggestions on choosing an imaging technique are found in **Table 7-1.**

Table 7-1. Imaging Approach According to Condition or Suspected Condition

Indication	Imaging Modality
Suspected foreign body	Expiratory radiography, or bilateral lateral decubitus if patient cannot breathe on command (due to age or developmental delay)
Suspected pneumothorax	Lateral radiography with suspected side up Ultrasonography
Suspected fluid in pleural space	Lateral decubitus and radiography Ultrasonography
Visualized structural anomalies (chest wall, vascular, tracheobronchial tree, lung parenchyma)	MDCT scanning, with or without contrast material
Anomalies of the tracheobronchial tree, evaluate lumen and pulmonary infiltrates that fail to resolve in 10 to 14 days	CT virtual bronchoscopy
Chronic unexplained respiratory symptoms with low suspicion for foreign body	CT virtual bronchoscopy
Pleural effusion	Ultrasonography

Table 7-1. Imaging Approach According to Condition or Suspected Condition *(continued)*

Indication	Imaging Modality
Lung abscess	CT scanning
Suspected vascular rings	Swallow study or CT angiography
Visualized vascular rings	MRI
Characterized vasculature of developmental lung malformations	MRI
Chronic interstitial process	HRCT scanning
Airspace disease	CT scanning
Bronchiectasis	HRCT scanning
Asthma complications	CT or HRCT scanning
Measuring airway thickness	MDCT scanning
Uncomplicated pneumonia	No imaging is required
Complicated pneumonia	Chest radiography as an initial step; CT scanning as clinically indicated
Anterior or middle mediastinal mass	CT scanning, PET scanning for lymphoma
Posterior mediastinal mass	MRI

Abbreviations: CT, computed tomography; HRCT, high-resolution CT; MDCT, multidetector CT; MRI, magnetic resonance imaging; PET, positron emission tomography.

Chest Radiography

The posteroanterior (PA) and lateral views are the standard order for chest radiography. Although a single view saves cost, it has not been shown to be useful because the diaphragm obscures much of the lung field in the PA view, particularly the bases. The radiograph is obtained at full inspiration, which may be difficult to time in the young child. Full inspiration typically results in the diaphragm being at the level of the eighth to tenth posterior rib or the fifth to sixth anterior rib. Whenever possible, the patient should undergo imaging in the upright position. On occasion—for example, in evaluating for a foreign body or pneumothorax—an expiratory radiograph may be ordered. The anteroposterior (AP) portable radiograph, obtained with the patient in bed, may not present as clear an image as that taken in the radiology department, but it is of great value in imaging patients who are critically ill. A lateral decubitus radiograph may be ordered to evaluate layering of fluid in the pleural space; however, this radiograph has been largely replaced by ultrasonography because ultrasonography does not involve radiation, can be performed at the bedside, and allows evaluation of the pleural effusion's characteristics. The dependent lung in the lateral decubitus radiograph should show increase in density because atelectasis results from the weight of the mediastinum. Failure to show increased density suggests that there is air trapping, which is useful to know if a foreign body is suspected. A lordotic view is obtained to view the apices of the lungs.

Multidetector CT Scanning

Multidetector CT (MDCT) scanning is considered the best modality to characterize in detail the chest wall, vascular structures, tracheobronchial tree, and lung parenchyma. The different postprocessing techniques, 2- and 3-dimensional reformations, virtual bronchoscopy (VB), and maximum intensity projections allow detailed characterization of structural anomalies (**Figure 7-1**). Computed tomography provides accurate information about the location and extent of involvement, as well as anatomical landmarks and relationship to the abnormality in question.



Figure 7-1. A, Computed tomography scan of the neck showing laryngeal papillomatosis (arrow).

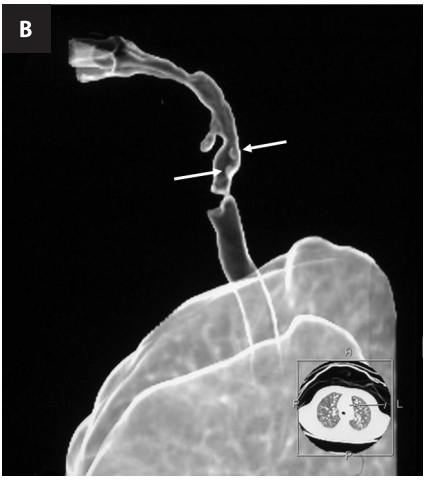


Figure 7-1. B, Three-dimensional volume rendered image, also known as virtual bronchoscopy, showing laryngeal papillomatosis (arrows).

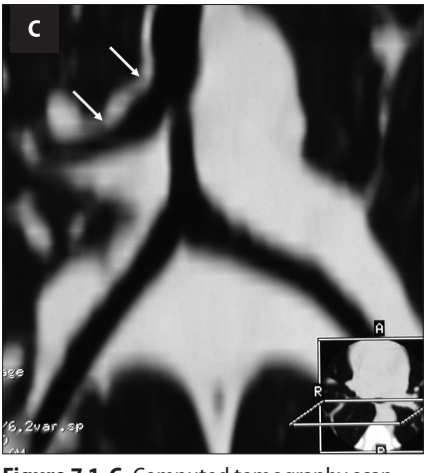


Figure 7-1. C, Computed tomography scan showing the tracheal bronchus (arrows).

Virtual bronchoscopy is a relatively new technique that provides an internal rendering of the tracheobronchial walls and lumen.[5] Despite the use of a low-tube-current technique and rapid table speed, the major disadvantage of CT scanning and VB is radiation exposure. Indications for VB include pulmonary infiltrates that fail to resolve in the usual time (10–14 days) and chronic, unexplained respiratory symptoms in a patient who has a low suspicion for foreign body aspiration and normal or nonspecific chest radiographic results. The advantages of VB are the ability to evaluate tortuous structures and segmental and subsegmental bronchi, which are hard to evaluate with conventional bronchoscopy given the small size of airways in children. Virtual bronchoscopy also allows evaluation distal to the obstruction and proper visualization of upper lobe bronchi that arise at an acute angle from the major bronchi.[6,7]

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is appropriate in certain circumstances; however, the evaluation of the lung parenchyma with this technique is limited. Magnetic resonance imaging may help characterize the vasculature of developmental lung malformations or vascular rings. A magnetic resonance (MR) angiogram provides a very detailed map of the vasculature (**Figure 7-2**).[3]

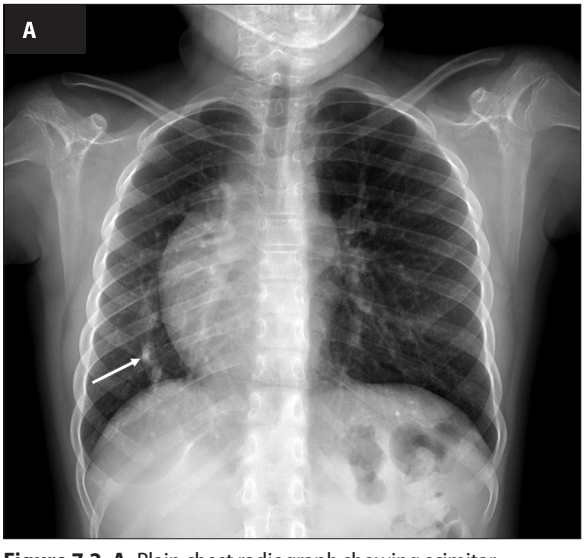


Figure 7-2. A, Plain chest radiograph showing scimitar syndrome, also known as hypogenetic lung syndrome. The arrow shows the vein that drains into the inferior vena cava.

Magnetic resonance imaging is accurate in evaluating chest wall masses and depicting intraspinal extension of neurogenic lesions in the posterior mediastinum, a feature that helps in the differential diagnosis and treatment. Disadvantages of MRI include its availability and the length of the studies that in some cases require sedation.[8]



Figure 7-2. B, Magnetic resonance image showing scimitar syndrome. The thick arrows show the pulmonary vein draining into the inferior vena cava (IVC).

Abbreviation: RLPV, right lower pulmonary vein (thin arrow).

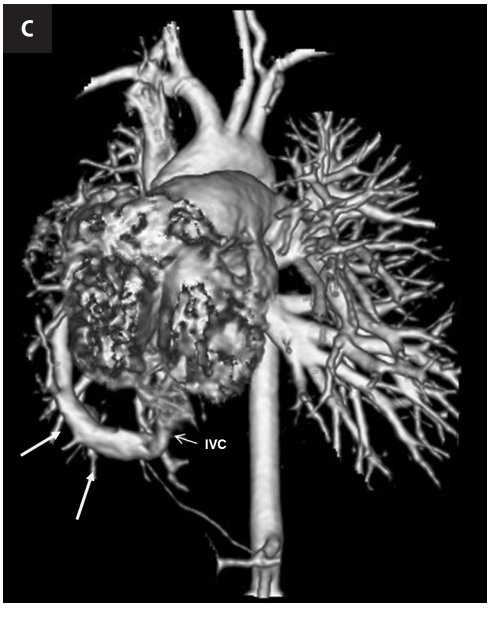


Figure 7-2. C, Three-dimensional reconstruction of Figure 7-2B. The long arrows show the pulmonary vein draining into the inferior vena cava (IVC; short arrow).

Ultrasonography

Although ultrasonography has not replaced the stethoscope, it is increasingly used to evaluate the lungs (and heart) in the emergency department and intensive care unit. For imaging the fetus, ultrasonography is of particular value when bronchopulmonary foregut malformations or diaphragmatic hernias are suspected. Ultrasonography is very helpful in evaluating pleural effusions, providing the best detail of the fluid consistency and demonstrating septations, solid components, or debris that cannot be well characterized on radiographs or CT scans (**Figure 7-3**).[9] Assessing mediastinal vascular structures and the thymus is possible with ultrasonography by using the correct acoustic window. For superficial chest wall lesions, ultrasonography also can provide information regarding the cystic or solid nature of a mass, the presence of fat or calcification, and the margins and size of a lesion if confined to the superficial tissues, which helps narrow the differential diagnosis and provides guidance regarding a therapeutic approach. The advantages of ultrasonography include no need for sedation, cost savings when compared with CT scanning, portability, and lack of radiation.[10]

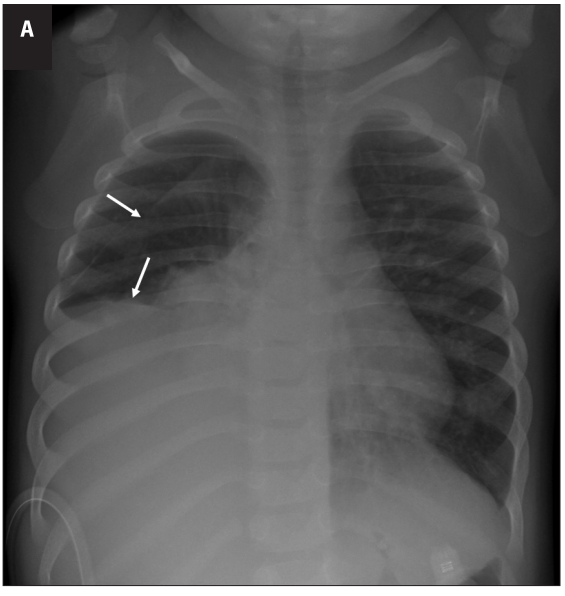


Figure 7-3. A, Radiograph showing hydropneumothorax. Note the central trachea. The upper arrow shows the lung margin, and the lower arrow shows the air-fluid interface.

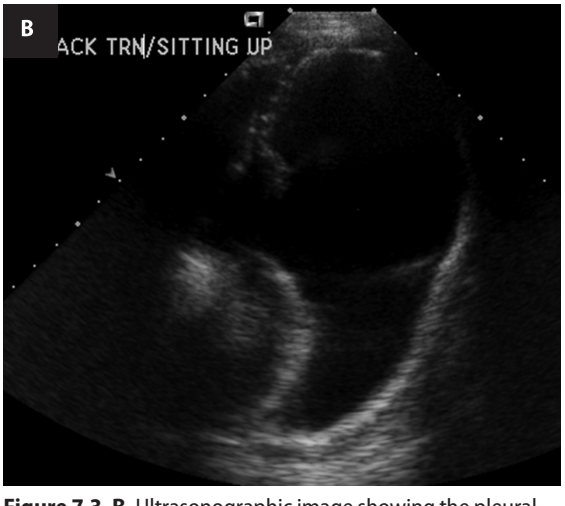


Figure 7-3. B, Ultrasonographic image showing the pleural effusion in Figure 7.3A.

Angiography

Traditionally, angiography was the technique of choice for imaging vascular anomalies, particularly when vascular rings, pulmonary sequestration, or hypogenetic lung syndrome is suspected and surgical treatment is considered. Currently, MDCT scanning has replaced conventional angiography because of its exquisite spatial resolution, noninvasiveness, and multiplanar reformation capabilities allowing the characterization of other tissues (**Figure 7-4**).



Figure 7-4. A, Multidetector computed tomography scan showing a vessel (arrow) supplying sequestration.



Figure 7-4. B, Computed tomography reconstruction of Figure 7-4A. The arrows show the vessel supplying the sequestered lobe.

Ventilation/Perfusion Scanning

Ventilation/perfusion scanning indicates the degree of vascular perfusion of different lobes of the lung and the distribution of ventilation. Ventilation scanning is performed as the child inhales xenon through a mask. The perfusion study is performed by injecting nuclear particles that produce microemboli in the parenchyma of the lung, which can indicate the degree of vascular perfusion of the different lobes of the lung. The results are expressed as percentages of ventilation and perfusion.

Chest Radiograph Report

The radiology report is a consultation between the radiologist and the physician who orders the study. It is helpful for the ordering physician to view the images rather than rely only on the written or oral report. It is not only a good exercise but also a good practice because the referring physician has knowledge of the entire clinical history and may aid in the final diagnosis. If necessary, the radiologist can be contacted in person or by phone to explain the findings in greater detail. The written report is part of the medical record and, as such, may be written in language that requires interpretation. It may be useful to discuss the findings with the radiologist, who may provide additional information that is not in the report. A good example is the statement, "these findings are consistent with the diagnosis of pneumonia," which may mean that this is likely a case of pneumonia or alternatively that pneumonia is in the differential diagnosis. Two different radiologists might report the same radiograph as "pneumonia in the right lower lobe" and "there is an infiltrate in the right lower lobe." It is good practice for radiologists to describe the findings and in the conclusion to include a brief summary followed by a differential diagnosis in descending order of possibility. The radiologist should be able to provide insight to help refine the physician's decision for treatment or perhaps recommend additional imaging.

Reading the Chest Radiograph

The first step in evaluating the radiograph is to identify the name and the date of birth or medical record number and note the date of the radiograph, although the widespread use of picture archiving and communication systems obviates this step. If prior studies are available, comparison of the findings with previous radiographs helps to identify acute versus chronic abnormalities and change over time.

Radiologists are trained to evaluate the quality and the technique of the study. An appropriate depth of penetration is important for a good radiograph. The thoracic spine should be visible on the PA radiograph above the carina and almost invisible behind the heart. The position of the chest is also important. If there is rotation, the lucency of the 2 lungs will be unequal and will need

to be differentiated from alterations in aeration of the lungs. Also in a rotated radiograph, one pulmonary hilum is more exposed and may be misinterpreted as a perihilar opacity. The degree of rotation is assessed by looking for symmetry of the ribs and the position of the ends of the clavicles.

Landmarks and Structures

The chest radiograph is a 2-dimensional picture, so objects outside the chest may be superimposed, including monitor leads, jewelry, hair plaits, and other objects that may confuse the picture. An initial broad view should be taken to include the mediastinum and the position of the trachea and the great vessels. The cardiothoracic ratio should be less than 50% in the upright PA view, but the heart will appear larger than in the PA view if the image was obtained with a supine or AP view or by using portable radiography. These factors must be considered before making a diagnosis of cardiomegaly, particularly from an AP radiograph. The physician should review the lung fields from the apices to the costophrenic angles while comparing the right lung to the left lung. The right diaphragm is typically higher than the left diaphragm, and the outline should be clear and continuous. The costophrenic angles should be sharp; if they are blunted, it may indicate a pleural effusion or sometimes pleural thickening. When a pleural effusion is small, it may be obscured by the overlying lung in an upright radiograph. When a pleural effusion is large enough and free-floating, a meniscus sign typically is visible. On a supine radiograph, a free-floating pleural effusion will layer, and the involved hemithorax will appear diffusely hazy.

A deviation or shifting of the position of the heart and mediastinum toward one side of the chest may suggest volume loss on that side. If the mediastinum shifts away from the lesion, this suggests a space-occupying lesion or pleural effusion. A large tension pneumothorax will shift the mediastinum toward the other side of the chest.

If the hilum is enlarged, it may be because of enlarged pulmonary vessels, enlarged lymph nodes, or a mass in the area. Peribronchial thickening (or cuffing) is caused by inflammation or edema of the airways and is a common finding in children with reactive airway disease, especially in preschoolers or in patients with viral lower respiratory infections. Pulmonary edema is also a cause of peribronchial cuffing.

Silhouette Sign

The silhouette sign was first described by Dr Ben Felson and is useful to locate the anatomical position of an abnormality.[11] The silhouette sign is the elimination of the lung and soft-tissue interface and is caused by fluid or a mass in the lung. The most common example of this sign is the presence of

a right middle lobe opacity that obscures the border of the right side of the heart. If the opacity was in the right lower lobe, the border of the right side of the heart would be visible (**Figure 7-5**). Another example of the silhouette sign is the lingular opacity overlying and obscuring the border of the left side of the heart. The silhouette sign is applicable to the heart, aorta, chest wall, and diaphragm.

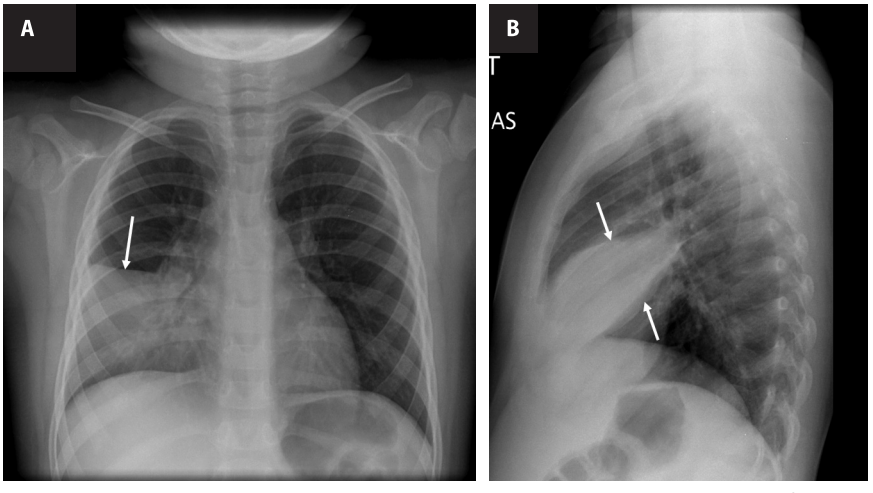


Figure 7-5. Radiographs showing right middle lobe pneumonia obscuring the border of the right side of the heart and demonstrating a positive silhouette sign. **(A)** Arrow shows the horizontal fissure. **(B)** The upper arrow shows the horizontal fissure, and the lower arrow shows the oblique fissure.

Fluoroscopy

Fluoroscopy is used for dynamic airway assessment to evaluate the following:

- Diaphragmatic motion
- Tracheomalacia and laryngomalacia
- Airway obstruction in suspected foreign bodies

Fluoroscopy is also used for a swallow function study.

- Generally performed by a radiologist with an experienced speech pathologist
- Performed to evaluate the mechanics and efficiency of swallowing
- Can be used to identify aspiration during ingestion of liquids or solids

Other Specific Findings

The following terms are words radiologists commonly use to describe findings to reach a differential diagnosis. The Fleischner Society unified this thoracic imaging terminology most recently in 2008.[12]

A *bronchogram* refers to the outline of the airway made visible by filling the alveoli with cells or fluid. The air bronchogram is seen in the following situations:

- Any condition causing lung consolidation, most commonly pneumonia
- Atelectasis
- Neonatal respiratory distress syndrome
- Acute lung injury (adult respiratory distress syndrome)
- Some neoplasms
- Normal expiration

Atelectasis is collapse or incomplete expansion of the lung or part of the lung and is described in Chapter 25, Atelectasis. It can be lobar, segmental, or subsegmental, depending on the extension, and passive or postprogressive according to the pathophysiological characteristics. Atelectasis appears as an increased density on the chest radiograph and is in the differential diagnosis of a parenchymal consolidation.

Infiltrate is a term formerly used to describe an ill-defined opacity in the lung field that almost by definition is not diagnostic of any specific abnormality and should be interpreted with caution. Even though some radiologists still frequently use the term to refer to pneumonia, it is not synonymous with this condition. The use of the term *infiltrate* is currently discouraged; the correct term to be used is *opacity* or *airspace disease*.

A *consolidation* is characteristic of lobar pneumonia, and the area may increase in size. If the involved area is airless and decreased in size, it is described as collapse. Areas of consolidation may be seen with pulmonary hemorrhage and vasculitic disorders in addition to the diagnosis of pneumonia. Lobar consolidation is classically seen in pneumococcal pneumonia.

Interstitial as a descriptor has fallen out of favor. By definition, the interstitium is a continuum of connective tissue throughout the lung, including the bronchovascular, the parenchymal and acinar, and the subpleural connective tissue. The correct terms to be used are *reticular pattern* and *reticulonodular pattern*. A reticular pattern usually indicates interstitial lung disease (ILD). Interstitial pneumonia is more commonly seen with atypical organisms or viral pneumonia. A nodular pattern is characterized on chest radiographs by the presence of myriad tiny round opacities ranging from 2 to 10 mm that are

usually widespread. When a reticular pattern is combined with a nodular pattern, it is known as a *reticulonodular pattern*. Recognition of these patterns is critical because each is associated with a subset of diseases that is useful when generating a differential diagnosis.

An *opacity* should be characterized by noting the size and shape, the number and location, the margins, and the homogeneity. Comparison with a previous radiograph is important. *Ground-glass opacities* are partially filled airspaces (with fluid or cells) and interstitial thickening. At CT scanning, this finding is seen as hazy lung parenchyma that is not opaque enough to obscure the adjacent interstitial prominence, as opposed to a consolidation. Ground-glass opacities are seen in patients with pulmonary edema, pulmonary hemorrhage, pneumocystis pneumonia, and alveolar proteinosis, among many other entities (**Figure 7-6**). They are also seen in those with chronic ILDs and even as an incidental finding in the dependent portion of the lungs as the result of blood flow redistribution in the horizontal position. In cases of ILD, they are considered a marker of active disease and suggest inflammation or alveolitis, which are potentially treatable.[13]

A *micronodule* is a discrete opacity in the lung measuring less than 3 mm, whereas nodules are rounded opacities, well- or ill-defined, measuring up to 3 cm in diameter, without regard for contour, border, or intensity. The term *mass* implies a solid or partially solid lesion that may be caused by infection, by a granuloma such as tuberculosis (TB), or by a tumor (benign or malignant). Vascular anomalies may have the appearance of a nodule and may be caused by arteriovenous malformation and lung infarct, Wegener granulomatosis, or rheumatoid arthritis.

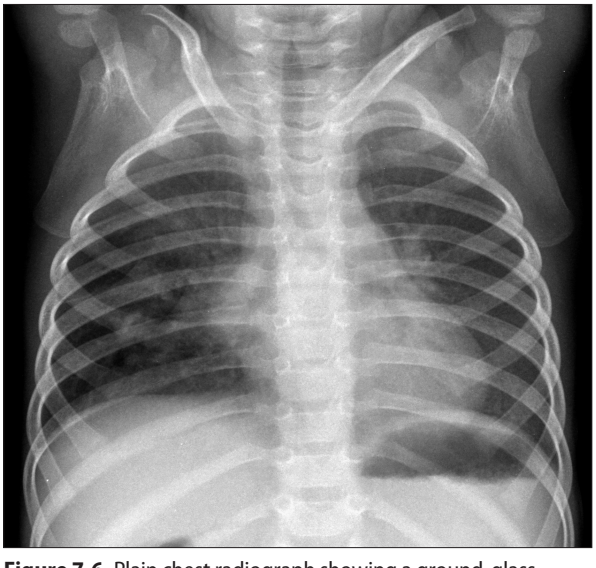


Figure 7-6. Plain chest radiograph showing a ground-glass appearance.

The rate of a nodule's enlargement is helpful in diagnosis. If the lesion doubles in size within a month, the diagnosis is likely infection, vascular lesion, or infarction. If the doubling time is 6 to 18 months, it is likely a benign tumor or malignant granuloma; if the doubling time is more than 24 months, then a benign nodule is likely. The presence of multiple nodules may indicate various causes, as shown in **Box 7-1.**

Box 7-1

Causes of Multiple Nodules

- **Infection: tuberculosis, fungal infection**
- **Neoplasm: lymphoma, hamartoma, metastatic lesions**
- **Rheumatoid: Wegener granulomatosis**
- **Granuloma: systemic lupus erythematosus**

A *cavity* is essentially a hole in the lung caused by destruction of lung parenchyma. The most common cause in children is infection, known as *necrotizing pneumonia*. Pneumococcus is the most common cause of necrotizing pneumonia. Other microorganisms potentially causing cavitation include *Staphylococcus aureus, Mycobacterium tuberculosis,* gram-negative bacteria (especially *Klebsiella*), group A *Streptococcus*, anaerobic bacteria, and fungi. It is also seen in nontuberculous mycobacteria in children with CF. Cavitation also can occur in those with septic emboli or vasculitis, such as Wegener granulomatosis.

Cystic changes in the lung are seen in the late stages of pulmonary fibrosis, also known as *honeycomb lung*. Cysts are also seen with bronchiectasis, especially saccular bronchiectasis.

A *pneumatocele* is an air-filled, thin-walled space that is most commonly associated with prior history of pneumonia or trauma. The pathophysiological mechanism is unclear but is believed to be due to either focal overinflation or parenchymal necrosis, with a check valve mechanism that may allow it to grow. In most cases, it resolves spontaneously.[14]

A *bleb* is a small gas-containing space smaller than 1 cm within the visceral pleura or subpleural lung, and a *bulla* is 1 cm or larger; however, the distinction is of little clinical significance. They can be associated with other signs of pulmonary emphysema. The cause of blebs and bullae is not known, but they are still meaningful because the possibility of rupture or air leakage may result in pneumothorax.

A *cyst* is a gas-filled round space, which also may be fluid filled or solid, surrounded by a thin wall (<2 mm) and without evidence of emphysema. Cysts are seen in patients with Langerhans cell histiocytosis or in

lymphangioleiomyomatosis. Thicker-walled cysts are seen in the development of end-stage fibrosis (honeycomb lung).

Bronchiectasis is usually considered irreversible localized or diffuse bronchial dilatation secondary to bronchial wall destruction. Three types are described: cystic, cylindrical, and saccular. Cases of reversible or temporary bronchiectasis are related to the re-expansion of a lung that has been collapsed due to infection or atelectasis,[15] as well as in cases of acute pneumonia, bronchitis, and allergic bronchopulmonary aspergillosis (ABPA). Its distribution is also important in narrowing the cause. Upper lobe bronchiectasis is more common in patients with CF and chronic mycotic and mycobacterial infections, the lower lobes are more commonly involved in idiopathic cases, and perihilar or central bronchiectasis is frequently seen in those with ABPA.[16]

Reading the CT Scan

In CT scanning, the scan is axial and is reconstructed so that 3 planes—coronal, sagittal, and oblique—can be viewed. The usual chest CT scan is viewed as a cross-section, which implies a horizontal section from the neck to the abdomen if someone is standing. The standard CT scan of the chest provides continuous images of sections of the lung, whereas a high-resolution CT (HRCT) scan has thin sections with skipped areas between the sections. The parameters used at HRCT scanning are meant to optimize spatial resolution to assess fine parenchymal patterns. The images obtained will be representative of the overall lung parenchyma but only cover skipped areas and may not reveal small isolated findings (eg, isolated cavity or nodule, consolidation). It is best used to evaluate diffuse parenchymal disease. Examples of diseases well assessed with HRCT scanning are bronchiectasis, CF, immotile cilia syndrome, asthma, Langerhans cell histiocytosis, interstitial pneumonias, ABPA, recurrent aspiration, and pulmonary infections.[17]

The range of normal findings has considerable overlap with disease, and care must be taken to avoid overinterpretation, particularly for the ground-glass appearance.[5] Computed tomography scanning has become very sophisticated and provides images that are not overlaid by tissues, as occurs with 2-dimensional radiography, and results in much clearer CT images. Instant reformation in different planes allows the review of the examination on the axial and coronal planes and can help sort out findings that are merely normal structures. The mediastinal structures, especially the vessels, can be evaluated only with intravenous contrast material. The indications for using intravenous contrast material are many, but in general it is administered to evaluate neoplasms in the mediastinum, lung, and chest wall; pulmonary and chest wall abscesses; pleural effusions; congenital developmental lung malformations; and adenopathy.

Ground-glass attenuation is a hazy attenuation of the lung parenchyma and is caused by alveolar filling, interstitial thickening, or both.[18] The appearance is visible on chest radiographs but is more obvious on CT scans.
It is seen with infant respiratory distress syndrome, pulmonary edema, interstitial pneumonitis, idiopathic pulmonary fibrosis, and alveolar proteinosis (**Figure 7-7**). The *tree-in-bud* pattern, seen on thin-section CT scans, is the finding of linear branching opacities of similar caliber connecting to small centrilobular nodules of soft tissue and indicating bronchiolar luminal impaction with mucus, pus, or fluid, which makes the normally invisible peripheral airways visible (**Figure 7-8**). A tree-in-bud pattern is not visible on the chest radiograph. It is indicative of inflammation and is nonspecific, although certain conditions are associated with the finding. Originally, it was used as an indicator of endobronchial spread of TB, but any infectious organism—bacterial, viral, fungal, or parasitic—may cause the pattern.[6] It has also been noted in bronchogenic dissemination of atypical mycobacteria and is seen in conditions that result in bronchiectasis, including CF and primary ciliary dyskinesia. The tree-in-bud finding is also seen in ABPA and connective tissue disorders. Less commonly, certain malignancies, including gastric, breast, and renal cancer, can produce this pattern.[19]

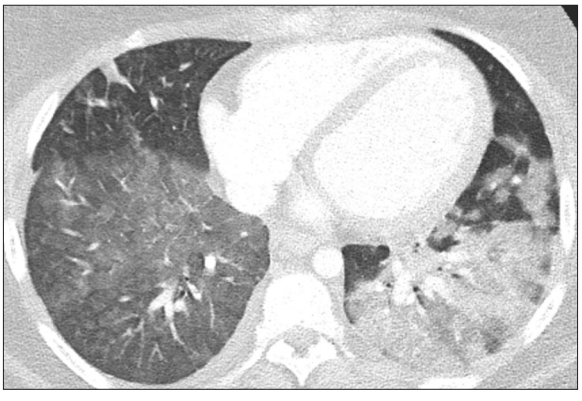


Figure 7-7. Axial computed tomography images in lung window show ground-glass airspace opacities within the right lower lobe. Consolidation of the left lower lobe is also noted.

Courtesy of Mariangeles Medina Perez, MD.

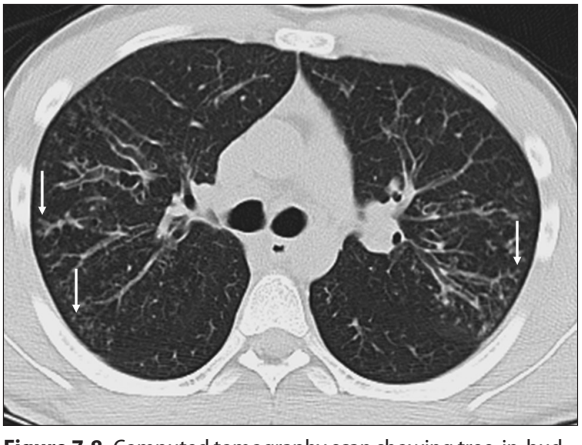


Figure 7-8. Computed tomography scan showing tree-in-bud appearance at the arrows and elsewhere.

Imaging for Specific Conditions

Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis usually manifests in children with long-standing asthma or CF. Aspergillosis infection can be divided into 5 categories according to manifestation: (1) saprophytic aspergillosis (aspergilloma in a preexisting cavity), (2) semi-invasive (chronic necrotizing consolidations), (3) hypersensitivity reaction (ABPA), (4) airway-invasive aspergillosis (tracheobronchitis, bronchopneumonia), and (5) angioinvasive aspergillosis. Radiologically, ABPA may manifest with a normal chest radiograph or mild hyperinflation. The earlier changes typically are single or multiple ill-defined opacities and tubular finger-in-glove areas of increased density in a bronchial distribution in the upper lobes. The later stages include bronchiectasis with fibrotic changes.

In children with debilitating chronic illness, aspergillosis may manifest in a semi-invasive form with segmental unilateral or bilateral consolidations with or without cavitation; however, the course of the disease takes years and is most commonly seen in adulthood. Airway-invasive and angioinvasive aspergillosis are more common in patients who are immunocompromised. Airway-invasive disease manifests as acute tracheobronchitis with bronchiolitis (tree-in-bud pattern on CT scans) and bronchopneumonia in a peribronchial distribution. Angioinvasive disease manifests as nodules surrounded by a halo of ground-glass attenuation (*halo sign*).[20]

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis, also called *extrinsic allergic alveolitis*, is the immunologic response to allergens from organic dust of plant or animal origin or chemicals. Acute hypersensitivity pneumonitis may manifest with a normal chest radiograph or as airspace consolidations. The subacute form also may manifest with a normal chest radiograph, but ground-glass opacities and nodules, and sometimes air trapping, can be observed on HRCT scans. The chronic manifestation is fibrosis that mostly spares the lung bases, as opposed to other causes of fibrosis (idiopathic pulmonary fibrosis, interstitial pneumonias), with other associated findings from the acute or subacute form.[21,22]

Eosinophilic Pneumonia

Acute eosinophilic pneumonia results in diffuse alveolar or alveolar-interstitial opacities with chest radiography. Computed tomography scanning shows bilateral patchy areas of ground-glass opacity with septal thickening. There may be additional areas of consolidation or ill-defined nodules.[23,24] The appearance may be similar to that of hydrostatic pulmonary edema without cardiomegaly. Chronic eosinophilic pneumonia has CT findings of airspace opacities predominantly in the upper lobes and peripheral lung fields ranging

from ground-glass opacities to consolidations with air bronchograms. The most distinctive radiographic feature is the *photographic negative* of pulmonary edema, which is infrequent and not specific.[25]

Asthma

Most patients can have asthma diagnosed clinically by means of medical history and physical examination and tend to respond rapidly to bronchodilator therapy. Therefore, chest radiography is not needed for the diagnosis in most children. The value of chest radiography is in diagnosing complications, establishing a precipitating cause for the asthma episode, and excluding alternate diagnoses that resemble asthma (**Box 7-2**).

Hyperinflation is the most common abnormality and is identified radiographically as hyperexpansion, flattening of the diaphragms, increased retrosternal lucency, anterior bowing of the sternum, and bulging of the intercostal rib spaces. There is poor correlation between the degree of hyperinflation and the severity of the asthma attack or the patient's responsiveness to therapy. Hyperinflation can persist even after symptoms resolve in up to 15% of patients.

The finding of hypoinflation at chest radiography significantly correlates with hospital admission for children aged 6 to 17 years (but not younger children); thus, hypoinflation is a poor prognostic sign and may indicate the need for more aggressive therapy.[26] Hypoinflation may result in clinically significant hypoxemia, possibly because children with asthma exacerbations may begin to lose their respiratory drive or may exhaust their accessory muscles of respiration. Bronchial wall thickening is usually transient and is more common in patients with asthma and superimposed acute viral infections and in those with persistent asthma.

Box 7-2

Indications for Chest Radiography in Children With Asthma

- **Severe respiratory distress**
- **Unequal breath sounds (to exclude pneumothorax)**
- **Fever (to exclude pneumonia)**
- **Detection of complications such as atelectasis or pneumomediastinum**
- **No response to routine treatment**
- **When other causes of wheezing are suspected, such as a foreign body, endobronchial lesion, vascular ring, or cystic fibrosis**

Atelectasis secondary to thickened airway secretions is common and may be lobar, segmental, or subsegmental. The next most common finding in children with complicated asthma is pneumonia. The reported radiographic incidence of pneumonia ranges from 0% to 30%.

Pneumothorax is an uncommon complication in children with asthma, with a reported incidence of 0% to 3%.[27] It is an important complication of mechanical ventilation in children with asthma and should be suspected if there is acute deterioration. The reported incidence of pneumomediastinum in children with asthma ranges from 0% to 15% and may be underreported. There is a bimodal distribution, peaking at ages 4 to 6 and 13 to 18 years. The extent of the pneumomediastinum involved correlates with the severity of the attack. The diagnosis requires a high level of suspicion because up to 30% of cases may be missed initially with radiography.[28]

High-resolution CT scanning in children with asthma provides additional information about lung disease, including bronchial wall thickening, narrowing of the bronchial lumen, regions of decreased attenuation and vascularity on inspiratory scans and air trapping on expiratory scans, bronchiectasis, emphysema, atelectasis, pneumonia, and mucus impaction. A combination of inspiratory and expiratory CT scans reveals the major physiological consequences of small airway diseases. Advanced findings include bronchiectasis, bronchial wall thickening (because this is caused by inflammation or remodeling rather than only bronchoconstriction), fibrotic reactions, and emphysema.[29]

Airway remodeling refers to the thickening of the airway walls because of the hypertrophy of smooth muscle, infiltration with inflammatory cells, and mucous gland hyperplasia. Airway wall thickening has been related to the severity of the disease and airflow obstruction. Airway thickness can be measured with HRCT scanning; therefore, the effects of various stimuli and treatments on remodeling can be monitored longitudinally.[30]

Bronchiolitis

Although chest radiography is not indicated for children with acute respiratory syncytial virus bronchiolitis, the most typical findings are hyperinflation with flattened diaphragms, increased AP diameter of the chest, and increased lucency in the anterior clear space. There may be prominent peribronchial markings and small opacities, particularly in the lower lobes (**Figure 7-9**). Pleural effusion does not occur. Changing atelectasis, especially of the right upper lobe, may result from inflammation of the airway.

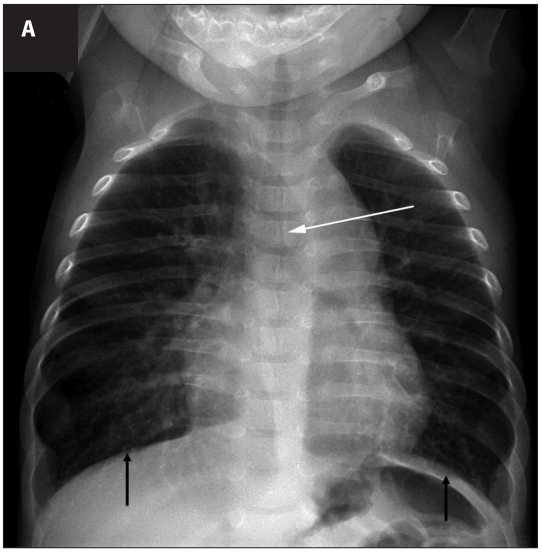


Figure 7-9. A, Plain radiograph showing bronchiolitis and flattened diaphragms (black arrows). There is peribronchial thickening. Note the herniation of the right lung into the anterior mediastinum (white arrow).

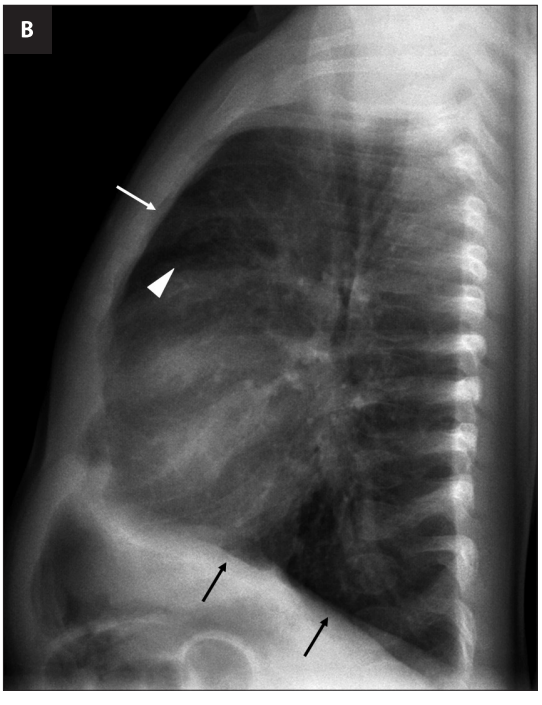


Figure 7-9. B, Lateral view of **Figure 7-9A** showing flat diaphragms (black arrows) and lung in the anterior mediastinum (white arrow). Arrowhead shows air trapping.

Bronchiectasis

The finding of parallel lines ("tram tracks") radiating from the hilum is the hallmark of bronchiectasis on the chest radiograph. The CT scan provides significantly improved images of the degree and extent of bronchiectasis. Ring shadows indicate enlarged thickened airways, which may extend well into the lung parenchyma. Cystic bronchiectasis is often accompanied by mucus-filled cysts, which may have air-fluid levels. Multiple nodular densities represent mucous plugging of the peripheral airways.

There are 3 patterns of bronchiectasis that can be identified on CT scan. Cylindrical bronchiectasis is the earliest change, with dilatation of the airway and mucous plugging. Varicose bronchiectasis involves increased dilatation, with ballooning of the airway and reduction of the number of branching airways to the sixth or seventh generation. The most severe form of bronchiectasis is cystic or saccular bronchiectasis. Clusters of cysts may be seen, and on occasion there is a honeycomb appearance.

Congenital Anomalies

Airway Compression Caused by Vascular Anomalies

Vascular rings are congenital anomalies that encircle the esophagus and trachea and typically compress these structures. They are classified as true rings (anatomically complete) or partial rings, though both can have similar clinical manifestations. Types of complete vascular rings include the double aortic arch and right aortic arch with aberrant left subclavian and left ligamentum arteriosum. Incomplete rings include innominate artery compression and pulmonary artery sling.[31]

A double aortic arch is the most common symptomatic vascular ring. It causes respiratory symptoms earlier in life more frequently than do other vascular rings. The second most common vascular ring is the right-sided aortic arch with aberrant left subclavian artery and left-sided ligamentum arteriosum. Other less commonly encountered rings include a right aortic arch with mirror image branching and left-sided ligamentum arteriosum, left aortic arch with aberrant right subclavian artery and right-sided ligamentum arteriosum, and circumflex aorta (the descending aorta crosses behind the esophagus to the opposite side of the arch) with a ligamentum arteriosum on the contralateral side of the arch. The pulmonary artery sling is the anomalous origin of the left pulmonary artery from the right pulmonary artery coursing between the trachea and esophagus to reach the left pulmonary hilum. Pulmonary slings are associated with complete O-shaped tracheal rings in 40% to 50% of cases, which narrow the trachea. Other airway abnormalities include the bridging bronchus and tracheal bronchus. Multidetector CT angiography as well as MR angiography offer exquisite detail of the vascular anatomy. Association with ipsilateral lung agenesis has been reported.

Posteroanterior and lateral chest radiographs may be useful for screening for vascular rings. Right-sided or double aortic arch, tracheal narrowing, anterior bowing, and increased retrotracheal soft tissues are the most common findings. At least 1 of these findings is reported in more than 95% of cases. Therefore, the importance of frontal and lateral chest radiographs cannot be underestimated because a normal chest radiograph significantly decreases the likelihood of finding a vascular ring in a patient with symptoms.

Barium esophagography was previously considered the most useful study to confirm the diagnosis of a vascular ring. A posterior indentation suggests an aberrant subclavian artery. Bilateral indentation on the AP view suggests a double arch. Anterior pulsatile indentation of the esophagus is virtually pathognomonic of pulmonary artery sling.

Computed tomography and MR angiography are now preferred for confirmation of the vascular ring.[32] Multidetector CT scanning has advantages in that it is widely available and has a short scanning time that can obviate sedation. Computed tomography can be used to evaluate the tracheobronchial tree and lung parenchyma. Magnetic resonance imaging is advantageous in that its multiplanar capabilities depict precisely the vascular anatomy.

Lung Malformations

Congenital developmental lung malformations have been described as a spectrum of disease from lung parenchymal abnormalities with relatively normal vascularity at one end of the spectrum to vascular abnormalities with relatively preserved parenchyma at the other end.[33,34]

Computed tomography angiography provides the more comprehensive approach because some of these lesions may have arterial, parenchymal, and tracheobronchial tree abnormalities. Characterizing these structures is important not only for establishing the diagnosis but also for surgical planning and evaluation of complications, such as superimposed infections.

Pulmonary Agenesis or Hypoplasia

Radiographically, pulmonary agenesis mimics pneumonectomy. There is hyperinflation of the remaining lung, mediastinal shift, diaphragmatic elevation, and sometimes chest wall deformity.

Bronchial Atresia

Bronchial atresia is thought to be due to intrauterine interruption of bronchial arterial supply. The distal branches can develop normally.

Congenital Lobar Hyperinflation

In children with congenital lobar hyperinflation, previously known as *congenital lobar emphysema*, the left upper and right middle lobes are the most commonly affected. Radiographically, this manifests as overinflation with air trapping during expiration (**Figure 7-10**).

Congenital Pulmonary Airway Malformation

Congenital pulmonary airway malformation, previously known as *congenital cystic adenomatoid malformation*, makes up 25% of all congenital lung anomalies. It consists of adenomatoid proliferation of bronchioles that form cysts instead of normal alveoli. There are 3 most commonly described types: Type 1 cysts are the most common and measure 2 to 10 cm, type 2 cysts are 0.5 to 2 cm, and type 3 solid-appearing lesions are formed by microscopic cysts (**Figure 7-11**).

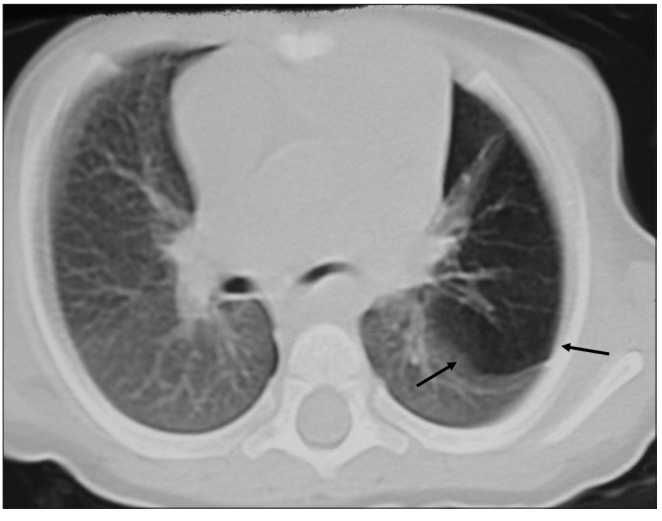


Figure 7-10. Axial computed tomography scan showing lobar emphysema (arrows).

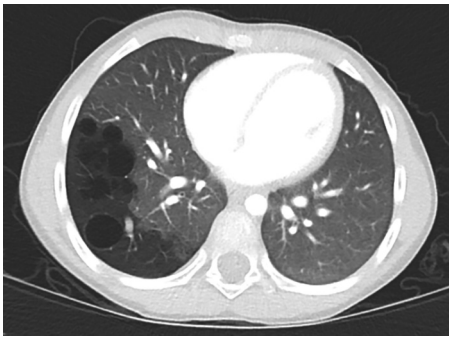


Figure 7-11. Axial computed tomography image in lung window demonstrating a multicystic lucent lesion within the right lower lobe with macrocyts and microcysts.

Courtesy of Mariangeles Medina Perez, MD..

Bronchogenic Cysts

A bronchogenic cyst is usually an incidental finding on a chest radiograph and is in the differential diagnosis of a mediastinal mass. Both CT scanning and MRI help to differentiate, but the MRI is more specific. The cyst contains fluid of water density, but, on occasion, the mass is of soft-tissue density, which makes differentiation from lymph nodes or other solid lesions more difficult. The cyst is derived from the foregut and is typically in the aortopulmonary window. More than 65% are mediastinal; when located in the lung parenchyma, they are usually in the lower lobes. Bronchogenic cysts can be asymptomatic or manifest because of superimposed infection simulating a lung abscess.

Pulmonary Sequestration

Pulmonary sequestration is defined as a segment of lung tissue that is separate from the tracheobronchial tree and receives its blood supply from a systemic artery rather than from the pulmonary artery.[35,36] There are 2 types of pulmonary sequestration: intralobar and extralobar (**Table 7-2**).

Because pulmonary sequestration may manifest as a consolidation, a history of repeated pneumonias in the same location should raise the suspicion of possible intralobar sequestration. Computed tomography is a useful method for measuring the volume of pulmonary sequestration.

Table 7-2. Characteristics of Intralobar and Extralobar Pulmonary Sequestration

Characteristic	Intralobar	Extralobar
Frequency	**~75%**	**~25%**
Location	Posterior basal Left > right—2:1	Between lower lobe and diaphragm, also within the diaphragm, lung, hilum, mediastinum, retroperitoneum, upper abdomen, etc Left > right
Arterial supply	Descending thoracic aorta, upper abdominal aorta, splenic or celiac arteries	Aorta, less commonly from splenic, gastric subclavian, intercostal or pulmonary arteries
Venous drainage	> 80% to left atrium	Systemic
Chest radiograph	Normal Postobstructive hyperinflation (ventilation by collateral channels) Mucoid impaction surrounded by hyperinflated lung Solid mass, if infected	Usually manifests as a solid mass because it rarely connects to bronchi
Visceral pleura	Within the lobe	Separated visceral pleura
Bronchial communication	Often present	Sometimes present

Dysmorphic Lung Syndrome

Dysmorphic lung syndrome, which includes scimitar syndrome, is characterized by arrested development of either a whole lung (lung agenesis-hypoplasia complex) or a lobe (lobar agenesis-aplasia complex). Absence of a lobe may be associated with other abnormalities.

Three forms of lobar agenesis have been described: pulmonary agenesis, aplasia, and hypoplasia. Although complete agenesis of a lung has been reported to be twice as common on the left side as it is on the right, in general, hypogenetic lung is considered to be almost exclusively on the right (**Figure 7-12**). Hypogenetic lung is part of the congenital pulmonary venolobar syndrome. The major components include hypogenetic lung, partial anomalous pulmonary venous return, absence of a pulmonary artery, pulmonary sequestration, systemic arterialization of the lung, absence of the inferior vena cava, and accessory diaphragm.[37]

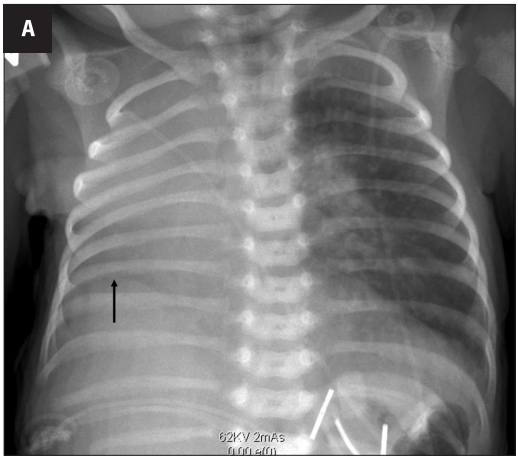


Figure 7-12. A, Radiograph showing the right lung volume loss with the mediastinal shift to the right and crowded ribs. The arrow points to the hemidiaphragm, which is still visible due to some aerated lung at the base.



Figure 7-12. B, Computed tomography scan showing hypoplastic right lung posterior to the heart.

Absence of Main Pulmonary Artery

In a child with absence of the main pulmonary artery, the peripheral pulmonary arteries are usually intact and supplied by systemic collateral circulation, which most often arises from the bronchial arteries. It is more common on the right side. At imaging, the lung and hilum are small; the pulmonary vascularity is decreased, rendering a radiolucent lung. Serrated pleural thickening with subpleural bands may indicate the systemic collateral vessels.

Pulmonary Arteriovenous Malformation

Pulmonary arteriovenous malformations can be solitary or multiple, as in children with hereditary hemorrhagic telangiectasia or Osler-Weber-Rendu

disease. The lesions tend to be recognized with increased age because time is needed for the flow effects to manifest.

Pneumonia

Chest radiography should not be performed routinely in the outpatient treatment of children suspected of having pneumonia. Radiological findings are accepted as the reference standard for defining pneumonia, but it is not clear to what extent chest radiographs alter the outcome of childhood pneumonia even though they frequently are used to confirm the presence, site, and extent of pulmonary infiltrates.[38] Swingler et al[39] observed that undergoing chest radiography significantly increased the likelihood of being prescribed antibiotics. Accepted clinical indications for chest radiography are severe disease and confirmation of nonspecific clinical findings, as well as assessment of complications and exclusion of other thoracic causes of respiratory symptoms.[40]

Computed tomography is not indicated in uncomplicated pneumonia. Computed tomography scans provide more information than do plain radiographs for complicated pneumonias and for assessment before procedures. In patients who are immunocompromised and hospitalized, CT scanning has a higher accuracy than plain radiography in detecting early fungal and *Pneumocystis jirovecii* pneumonia.

Ultrasonography has an advantage over CT scanning in the identification of, characterization of, and management decisions about complicated effusions. Ultrasonography also has an established role in the imaging-guided drainage of pleural fluid. The decision of whether a fluid collection needs to be drained is clinical and is indicated if the collections are increasing in size or respiratory function is compromised.[41] If thrombolytic therapy is contemplated, CT scanning should be considered if a bronchopleural fistula is suspected because a fistula is a contraindication to thrombolytic therapy.

Round Pneumonia

Round pneumonia occurs in children younger than 8 years because young children have poorly developed pathways of collateral ventilation (eg, pores of Kohn, canals of Lambert), more closely apposed connective tissue septa, and smaller alveoli than do adolescents and adults[42] (**Figure 7-13**). Round pneumonias clinically manifest with cough, tachypnea, and malaise followed by an acute febrile illness. Round pneumonias on chest radiographs characteristically are located posteriorly in the lower lobes and touching the pleura or a fissure. Satellite lesions are not seen in children, whereas satellite lesions are found in more than 50% of round pneumonias in adults.[43] In a child younger than 8 years with the typical clinical findings of pneumonia and a typical

radiographic appearance, the diagnosis is almost always round pneumonia. Round pneumonias are diagnosed on radiographs and, if all the criteria are met, all that is needed is follow-up chest radiography to ensure resolution.

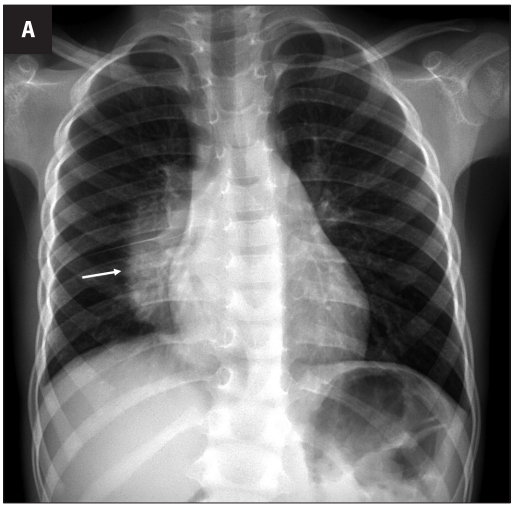


Figure 7-13. A, Radiograph showing round pneumonia (arrow) in the right lower lobe. Note the negative silhouette sign (border of the right side of the heart is visible) and horizontal fissure parallel to the arrow.

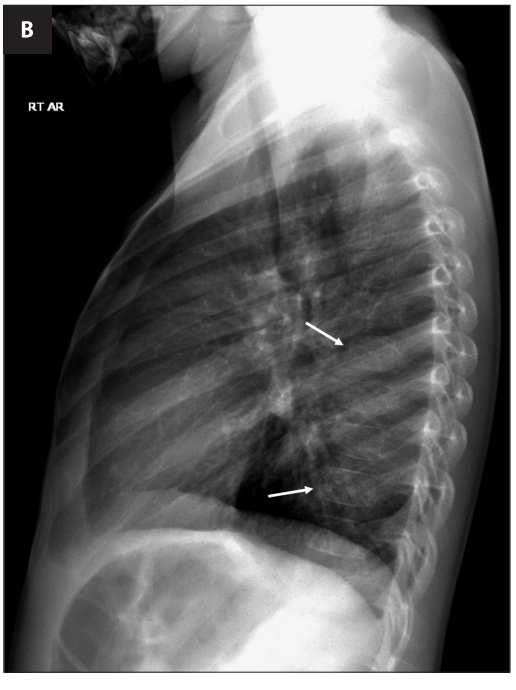


Figure 7-13. B, The arrows delineate the edges of the round pneumonia.

Aspiration

Aspiration is of great concern in children because of the frequency with which they place foreign objects in their mouths or noses and the frequency with which young children choke on food items. The most common organic aspirated foreign bodies include peanuts, seeds, and nuts; blades of grass; and bone fragments. The most common inorganic bodies are plastic objects (toy fragments, pen caps, dental prostheses) or metal objects (hairpins, pins, steel filaments). Chest radiography is the first imaging study performed when aspiration is suspected.[44] Because less than 10% of aspirated foreign bodies are radiopaque, the inhaled object is usually not visible, but indirect findings may assist in supporting the diagnosis. Radiological findings in the event of an acute aspiration include hyperinflation, air trapping, regional oligemia, atelectasis, or consolidation. The airway is usually either unobstructed or partially obstructed during inspiration but completely obstructed during expiration because the physiological expiratory decrease in bronchial diameter results in air trapping. To improve the accuracy of radiographs, the physician may order inspiratory and expiratory views in cooperative children and lateral decubitus radiographs in younger children (**Figures 7–14**).[44] However, radiographs are still negative in up to 30% of cases of aspiration.

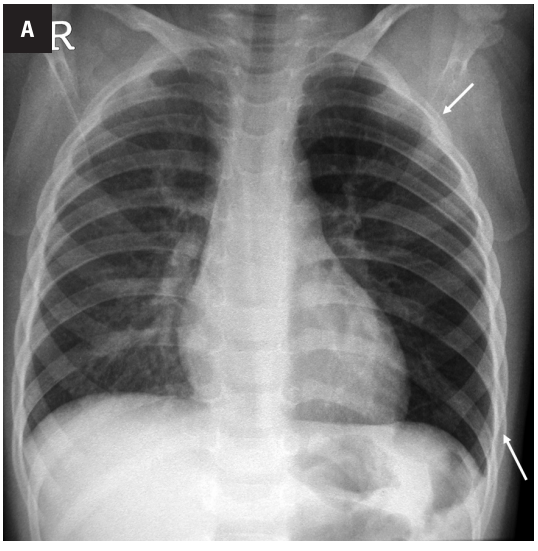


Figure 7-14. A, Radiographs showing aspirated foreign body. **B**, The left lateral decubitus view shows persistent expansion of the left lung (white arrows).

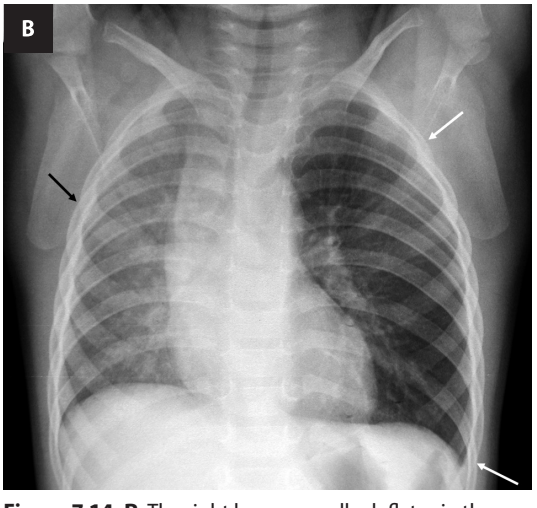


Figure 7-14. B, The right lung normally deflates in the right lateral decubitus position (black arrow).

Multidetector CT scanning is more accurate than chest radiography in the detection of radiolucent foreign bodies, and it is suggested in patients with a low clinical suspicion of foreign body aspiration in whom chest radiography results are negative.[45] Multidetector CT scanning, as opposed to single-section CT scanning, allows rapid acquisition of volumetric data sets, essential to reduce radiation exposure in children and to avoid sedation. Multidetector CT scanning also can be helpful in children after bronchoscopy when residual foreign bodies are suspected. Although this is a relatively uncommon complication, retained foreign bodies are described in 1% to 18% of cases. Computed tomography in these children can offer a description of the pattern of residual obstruction, which would help in future decisions as to whether repeat bronchoscopy is indicated.[45]

Complications of Pneumonia

Pleural Effusion

The chest radiograph may show pneumonia before the effusion is evident. The earliest sign is blunting of the costophrenic angle, which will be evident on a radiograph obtained with the patient in an erect position but not on a radiograph obtained with the patient in a supine position. A radiograph obtained with the patient in a lateral decubitus position with the affected side down may be helpful in showing small amounts of fluid. If the fluid does not shift with the lateral decubitus position, it implies loculation of the fluid. If there is an air-fluid level, there is both an effusion and pneumothorax, which is called *hydropneumothorax*. The presence of hydropneumothorax in the absence of a recent intervention is suggestive of a bronchopleural fistula. Empyemas on chest radiographs, because of the intrapleural location, tend to have obtuse angles superiorly and inferiorly on the frontal view. On the lateral view, a distinguishing feature of pulmonary abscess is the decrease in diameter when compared with the frontal view. Lung abscesses tend to have the same AP and transverse diameter on both frontal and lateral views.

Ultrasonography is the best imaging modality to characterize pleural fluid. It can depict fluid before it is evident on a chest radiograph and can easily help distinguish between free and loculated fluid. Pleural effusions at ultrasonography are classified as simple or complex. Simple effusions are anechoic or black and in most cases indicate a transudate. Complex effusions indicate an exudate. Features that make an effusion complex include internal septations, debris, honeycombing, and pleural thickening, all of which are easily depicted at ultrasonography.[9] Ultrasonography may also be helpful in defining the best site for thoracentesis and the need for intrapleural fibrinolysis or video-assisted thoracoscopic surgery (**Figure 7-15A–B**). Computed tomography scanning is not more helpful than ultrasonography in defining a pleural effusion but does have a place in detecting abnormalities in the lung parenchyma.

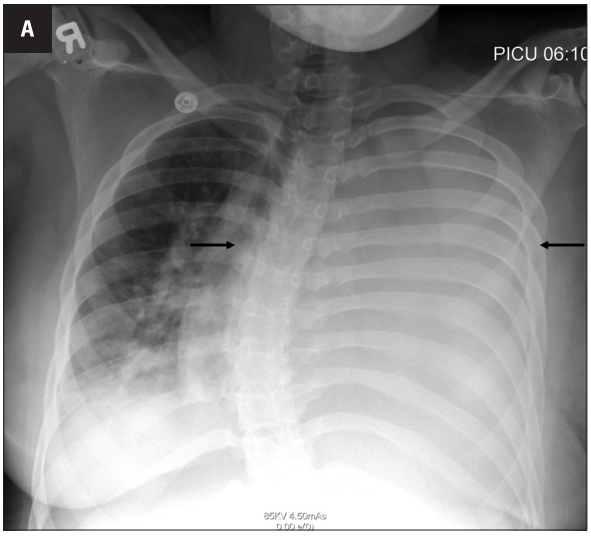


Figure 7-15. A, Radiograph showing a complicated effusion. The left arrow shows the displaced trachea. The right arrow shows whiteout of left thorax.

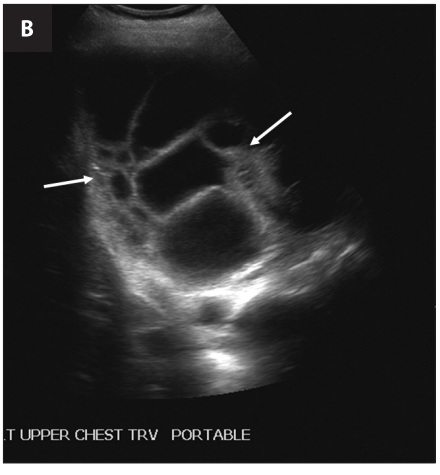


Figure 7-15. B, Ultrasonographic image showing septations (arrows) in an effusion.

Lung Abscess

A lung abscess is a thick-walled cavity that contains purulent material as a result of a pulmonary infection that has led to suppurative necrosis of the involved lung parenchyma. Lung abscesses in the early stages manifest as consolidation; however, unlike necrotizing pneumonia, abscesses tend to be spherical and well-defined, and the diagnosis is more obvious when there is a connection between the abscess and a draining bronchus because an air-fluid level will be present. The air-fluid level will be evident only on a radiograph obtained with the patient in a lateral decubitus or erect position.[46] The presence of an air-fluid level is not pathognomonic of an abscess, given that an air-fluid level can be seen in developmental lung malformations or pneumatoceles with

superimposed infection, cavitary pneumonia, cavitary septic emboli, Wegener granulomatosis, and other conditions. For distinguishing a lung abscess from other conditions, contrast-enhanced CT scanning of the chest is the imaging modality of choice (**Figure 7-16**).[47] Lung abscess caused by aspiration typically is located in the posterior segments of the upper lobes or superior segments of the lower lobes. When in a subpleural location, lung abscesses and any consolidation can be identified at ultrasonography. In this location, ultrasonography can be used as a guiding tool for percutaneous drainage.



Figure 7-16. Computed tomography scan showing a lung abscess with an air-fluid level (arrow).

Necrotizing Pneumonia

Necrotizing pneumonia is a complication of severe pneumonia that produces cavities by means of tissue necrosis in the area of pneumonic consolidation. The chest radiograph may show the cavities, but a significant number of children who have CT findings of cavities have no evidence of necrosis on plain radiographs. If the cavity contains air, the chest radiograph may show the cavity, but if it is fluid filled, the plain radiograph may show only consolidation. Unlike a pulmonary abscess, the cavities of necrotizing pneumonia tend to be multiple, tubular or round, and more irregular. In addition, the borders of the consolidation are less distinct. Air bronchograms can be present (**Figure 7-17**).



Figure 7-17. A, Coronal computed tomography scan showing necrotizing pneumonia. The arrowheads show pleural effusion, and the arrows point to cavities.

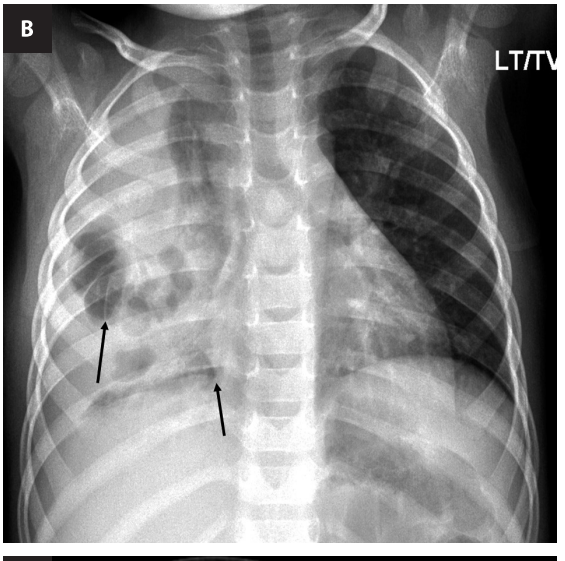


Figure 7-17. B, Plain radiograph showing necrotizing pneumonia, suggestive of bronchopleural fistula. The arrows point to cavitation necrosis.

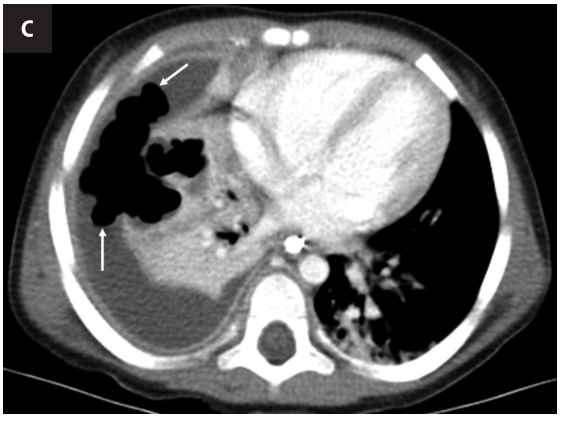


Figure 7-17. C, Computed tomography scan showing necrotizing pneumonia and bronchopleural fistula. The arrows point to cavitation necrosis.

Tuberculosis

Primary Pulmonary TB

The radiographic findings in primary TB are nonspecific. The plain radiograph may be normal, but more commonly there is an area of segmental or lobar consolidation with hilar adenopathy in the adjacent area. Hilar adenopathy is an important finding because it is unusual to see lymphadenopathy in postprimary TB. The lung opacity of primary TB tends to become smaller over time, calcify, and be apparent as a calcified granuloma.

Airway involvement is common in primary TB, and airway compression by the lymphadenopathy may result in atelectasis, which may result in consolidation of the right upper or middle lobe. One of the life-threatening manifestations of TB is miliary TB, most common in infants and toddlers. It manifests as small nodules (usually <2 mm) with uniform distribution in the lungs.

Postprimary Pulmonary TB

Pleural effusion is an important manifestation of postprimary TB in adolescents. Miliary TB results from hematogenous spread so that there are diffuse, small (1–2 mm) nodules scattered throughout the lung fields. The characteristic finding of postprimary TB is upper lobe consolidation with cavitation. The findings are usually evident at chest radiography, but CT scanning is useful to define the extent of disease, in particular the degree of cavitation.

Pulmonary Nontuberculous Mycobacteria

The radiological findings of nontuberculous mycobacteria are nonspecific and similar to those of TB, fungal infections, and other granulomatous processes. The typical imaging features are as follows:

- Multiple small nodules
- Multilobe bronchiectasis
- Tree-in-bud pattern (see Reading the CT Scan, earlier in this chapter)
- Progressive fibrosis

Most children with pulmonary nontuberculous mycobacteria are those with HIV infection or CF.

Systemic Lupus Erythematosus

Pleural effusion is the most common pulmonary manifestation of systemic lupus erythematosus, and the effusions are typically small. There may be an associated pericardial effusion. The greatest pulmonary imaging challenge in children with systemic lupus erythematosus is differentiating pneumonia, pulmonary hemorrhage, and lupus pneumonitis. Computed tomography findings with lung disease, either pneumonia or lupus pneumonitis, include

patchy consolidation, especially in the lower lobes, often with a pleural effusion. Lupus pneumonitis has the potential to develop into chronic interstitial pneumonitis with irreversible lung disease and pulmonary fibrosis. Acute alveolitis, recognized by a ground-glass appearance, has the potential to be improved by steroids and should be treated promptly to prevent chronic changes.

Interstitial Lung Disease

Chest radiography is the usual imaging modality to diagnose ILD in children. It is not specific and therefore usually requires additional imaging studies, especially HRCT scanning. The plain chest radiograph may reveal characteristic patterns, including ground-glass opacities, reticular or nodular opacities, and honeycombing. Ground-glass opacities are seen with active alveolitis, and honeycombing is seen with advanced disease. The findings are often described as interstitial even though the disease is primarily alveolar.

High-resolution CT scanning is better than chest radiography for defining the extent of pulmonary disease, and tree-in-bud patterns and patterns of differential aeration may be evident.

Cystic Fibrosis

Chest radiography is not important in diagnosing CF but does allow longitudinal assessment of the progression of pulmonary disease. The findings of CF clearly overlap with those of other disorders of chronic lung disease; nevertheless, bronchiectasis of unknown cause is an indication to evaluate for CF. The usefulness of the chest radiograph during an exacerbation of CF is unclear. In this situation, the advantage of the chest radiograph is to exclude a pneumothorax, pneumonia, or atelectasis.

More recently, the use of CT scanning to evaluate inflammation and early lung damage has been confirmed. High-resolution CT scanning allows demonstration of mucous plugging and bronchiectasis to the fifth or sixth generation of bronchi.

Bronchial arteriography is the preferred technique to evaluate major hemoptysis, and the technique is to view all of the bronchial vessels in preparation for embolization. The vessels that are bleeding may not be identified; therefore, all vessels should be embolized, because if only the bleeding vessels are embolized, other nonembolized vessels will likely bleed at a later date.

The most widely used CF scoring system in the United States is the Brasfield scoring system, also called the *Birmingham system*, which was developed in 1979.[48] Five elements are evaluated as shown in **Table 7-3.**

Several additional scoring systems have been reviewed and attempts made to provide radiological and clinical correlation. One of the reasons for deriving scores is to reduce interobserver differences and permit longitudinal following of the clinical course.

Computed tomography findings of CF include air trapping, early evidence of airway inflammation, or bronchiectasis. Mucous plugging, centrilobular nodules, and peribronchial thickening are potentially reversible findings in patients with symptoms. Because children are more sensitive to radiation-induced cancer than are adults, special care should be taken, particularly when multiple radiological examinations in a lifetime will be needed. Computed tomography scanning is used to assess the following conditions:

- ABPA
- Atypical mycobacterial infection
- Unexplained clinical deterioration
- Pulmonary embolism
- Severe hemoptysis
- Sinus disease

Table 7-3. Components of the Brasfield Scoring System

Category	Definition	Scoring
I. Air trapping	Generalized pulmonary overdistension as sternal bowing, depression of the diaphragm, and/or thoracic kyphosis	0 = absent; 1–4 for increasing severity (4, most severe)
II. Linear markings	Line densities due to prominence of bronchi as parallel line densities, sometimes branching, or as end-on circular densities with thickening of bronchial wall	0 = absent; 1–4 for increasing severity (4, most severe)
III. Nodular cystic lesions	Multiple, discrete, small, rounded densities, ≥ 0.5 cm, with either radiopaque or radiolucent centers (does not refer to irregular linear markings); confluent nodules not classified as large lesions	0 = absent; 1, 2, 3, or 4 for involvement of 1, 2, 3, or 4 quadrants
IV. Large lesions	Segmental or lobar atelectasis or consolidation; includes acute pneumonia	0 = absent; 3 if segmental or lobar; 5 if large
V. General severity	Impression of overall severity of changes on radiographs	0 = normal; 1–4 for increasing severity of abnormalities; only cardiac enlargement or pneumothorax require 5

Points are subtracted from a total possible score of 25, so that 25 is without abnormality and 3 is the most severe.

From Brasfield D, Hicks G, Soong S, Tiller RE. The chest roentgenogram in cystic fibrosis: a new scoring system. *Pediatrics*. 1979;63(1):24–29.

Mediastinal Masses

The location of mediastinal masses in children is shown in **Box 7-3.**

Box 7-3

Location and Types of Mediastinal Masses

Anterior mediastinum (about 40%)
- Thymus
- Lymphoma
- Germ cell tumors

Middle mediastinum (about 20%)
- Bronchogenic cyst
- Enteric and neurenteric cysts
- Mediastinal lymphadenopathy
- Pericardial cyst

Posterior mediastinum (34%)
- Neurogenic mass: neuroblastoma
- Ganglioneuroblastoma, ganglioneuroma
- Schwannoma, neurofibroma

Anterior Mediastinal Masses

More than 40% of mediastinal masses are anterior mediastinal masses, with most of them arising from the thymus or mediastinal lymph nodes.

Thymus

There is extensive variability in the configuration and radiographic appearance of thymic tissue, including the possibility of manifesting in an ectopic location. It can usually be recognized at chest radiography—microlobulated borders, ability to see the normal pulmonary architecture through it, and absence of mass effect. If the diagnosis remains uncertain, CT scanning or MRI can aid in its recognition.

The thymus can change in shape and size within hours. An external stimulus, commonly seen in patients who are hospitalized, can dramatically reduce the size of the thymus. Likewise, thymic rebound is the enlargement or hyperplasia of the thymus in response to withdrawal of myelosuppressive therapy. It typically occurs 6 to 12 months after suspension of therapy but cases as early as 1 week after suspension of therapy have been described.[49]

Lymphoma

Lymphoma (Hodgkin and non-Hodgkin) is the most common true anterior mediastinal mass in children. Mediastinal lymphoma appears as a hypoattenuating lobulated, nonhomogeneous, mediastinal, soft-tissue mass. Hilar lymphadenopathy is associated with Hodgkin lymphoma. In Hodgkin lymphoma, bulky mediastinal disease has a worse prognosis than in cases in which there is a small tumor volume. In non-Hodgkin lymphoma, tumor bulk does not appear to influence outcome.

Positron emission tomography (PET)/CT scanning is a valuable tool to use for the initial staging, to monitor interim treatment response, and to assess complete response to treatment. Substantial evidence supports that the addition of PET scanning to current staging investigations in lymphoma increases the accuracy of staging and results in change in management.

An International Harmonization Project released consensus recommendations[50] in 2007 to standardize clinical trial parameters for the use of PET scanning. At initial staging, CT scanning should be performed either alone or in combination with PET scanning. Most commonly, the combination is preferred to reduce the amount of radiation delivered. If hepatic or splenic disease is also present, then intravenous contrast material should be administered to improve the assessment.

Germ Cell Tumors

Germ cell tumors account for up to 20% of anterior mediastinal masses in children. Germ cell tumor can be diagnosed definitely when the characteristic CT scanning or MRI findings of a complex mass with cystic and solid areas containing fat and irregular calcifications are observed.

Middle Mediastinal Masses

Middle mediastinal masses account for about 20% of mediastinal masses. Foregut duplication cysts include bronchogenic, enteric, and neurenteric cysts, which are developmental malformations of the embryonic foregut. Computed tomography or MRI can be used to confirm the diagnosis and characterize the mass. These masses are relatively well marginated, round, or oval with homogeneous water or soft-tissue attenuation or signal intensity (because of proteinaceous material) without internal contrast enhancement.[49]

The extension of lymphoma into the middle mediastinum is common. Other causes of lymphadenopathy include metastatic disease, infection or inflammation from granulomatous diseases, or Langerhans cell histiocytosis.

Posterior Mediastinal Masses

Posterior mediastinal masses account for 34% of mediastinal masses, and most (~90%) are neurogenic in origin.[49] Most neurogenic masses, including neuroblastoma, ganglioneuroblastoma, and ganglioneuroma, arise from ganglion cells in the paravertebral sympathetic chain. The remaining masses are nerve sheath tumors, such as schwannoma and neurofibroma. Chest radiographic findings include a well-circumscribed posterior mediastinal mass with calcifications or adjacent bone erosion (**Figure 7-18**). Imaging does not allow differentiation among the tumor types, so biopsy is needed. Evaluation of the extent of disease, particularly looking for intraspinal extension, should be performed, and MRI is the modality of choice (**Figure 7-19**).

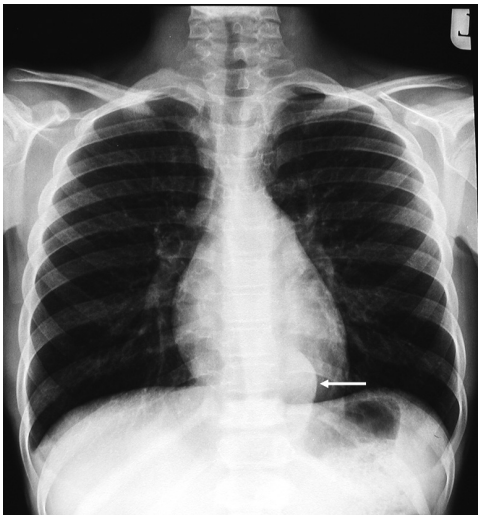


Figure 7-18. Radiograph showing a posterior mediastinal mass (arrow), with the diaphragm and border of the right side of the heart visible.

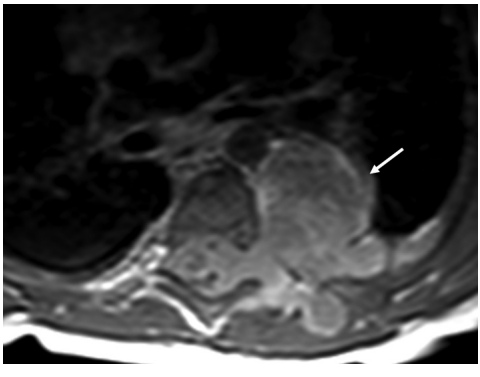


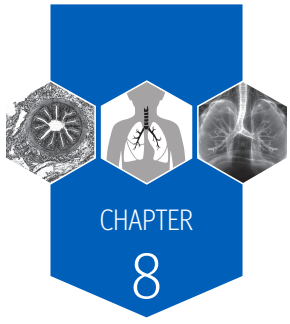
Figure 7-19. Magnetic resonance image showing ganglioneuroma (arrow).

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Bronchoscopy

Pi Chun Cheng, MD, MS
Samuel B. Goldfarb, MD

CASE REPORT 8-1

A 6-month-old infant had vibratory inspiratory stridor since the age of 1 month. He fed poorly and had gasping respiration, neck hyperextension, and intermittent upper airway obstruction during sleep. Results of flexible bronchoscopy with the patient under light sedation and with his head in a neutral position demonstrated foreshortening of the aryepiglottic folds and prolapse of the arytenoid cartilages during inspiration, causing almost complete obstruction of the glottis. The dynamic airway events correlated with the infant's stridor and clinical airway obstruction. Evaluation results for the rest of the airway to the level of the segmental bronchi were normal. Severe laryngomalacia was diagnosed. The infant was referred to an otolaryngologist who performed an aryepiglottoplasty, removing some redundant tissue from the arytenoid cartilages. The infant's stridor and obstructive sleep apnea markedly improved, as did his growth. By the age of 12 months, his stridor had resolved completely, and both growth and development were normal.

Introduction

Until relatively recently, direct evaluation of a young child's airway required the skills of a surgeon versed in rigid (open tube) bronchoscopy, with the child under general anesthesia. Flexible bronchoscopy became routinely available in the United States in 1969, but use of the technique was restricted in children because of the instruments' size limitations. By 1980, a commercially available scope that was 3.5 mm in diameter with an integral suction channel and a tip that could be directed was being used to evaluate newborns.[1] With improvements in fiberoptic technology, thinner (eg, 2.8 mm) bronchoscopes could be made without sacrificing functionality or image quality. More recently, digital technology has been applied to bronchoscopic images, and a 2.8-mm or 3.8-mm pediatric bronchoscope with a video chip in the tip provides high- resolution digital images in an instrument that can be used in

most newborns through adolescents. There are also ultrathin scopes ranging from 1.8 to 2.2 mm, but these have neither suction channels nor angulation capabilities, so their use
is limited to evaluation of the trachea and proximal main bronchi in children with established artificial airways (endotracheal or tracheostomy tubes).

Choosing Between Flexible and Rigid Bronchoscopy

General Considerations

The flexible bronchoscope complements, but does not replace, the rigid bronchoscope. Each has strengths and weaknesses that must be considered when deciding on the approach to a particular patient. **Table 8-1** lists some of the relative advantages of each type of procedure. Flexible bronchoscopy is usually performed via a transnasal approach. This approach allows the patient's head to be kept in a neutral position, and there is no distortion of upper airway structures as the bronchoscope follows the normal contour of the nasopharynx, oropharynx, and hypopharynx. Thus, dynamic events that occur in this part of the airway can be observed without altering tissue relationships. In contrast, direct laryngoscopy with a rigid bronchoscope or laryngoscope requires hyperextension of the neck and suspension of the base of the tongue for optimal visualization. In this situation, structures that cause noisy breathing could be elevated and the cause of airway obstruction missed.

The transnasal approach, however, causes the flexible bronchoscope to be angulated anteriorly as it approaches the glottis. Although anterior structures of the glottis are easily examined, it is more difficult to obtain a thorough evaluation of the intra-arytenoid portion of the glottis, and posterior lesions might be missed. Thus, if a lesion like a laryngoesophageal cleft is being considered, rigid bronchoscopy is the preferred technique. Similarly, the subglottic space is better evaluated using a rigid scope than a flexible scope.

The flexible bronchoscope can be advanced more distally in the tracheobronchial tree, allowing for better peripheral evaluation of the airway. The diagnostic capabilities of flexible bronchoscopy are broadened when combined with techniques like bronchoalveolar lavage (BAL), bronchial brushing, and, in select circumstances, transbronchial biopsy. All of these techniques are better accomplished with a flexible scope than a rigid scope.

Table 8-1. Relative Advantages of Flexible and Rigid Bronchoscopy

Site or Procedure	Flexible	Rigid
Nasopharynx	++	–/+
Hypopharynx	++	+
Larynx	++	++
Laryngeal function	++	–
Subglottis	+/–	++
Trachea	++	++
Main bronchi	++	++
Lobar bronchi	++	+
Segmental and subsegmental bronchi	++	+/–
Foreign body	–	++
Bronchoalveolar lavage	++	+
Control of bleeding	–	++
Mucosal biopsy	++	++
Transbronchial biopsy	++	+

Abbreviations: ++, most likely to provide optimal diagnostic and therapeutic outcome; +, likely to provide optimal diagnostic and therapeutic outcome; +/-, uncertain diagnostic and therapeutic value; -, unlikely to provide diagnostic and therapeutic outcome.

Foreign Body

When a retained foreign body in the airway is suspected, the procedure of choice is rigid bronchoscopy with the patient under general anesthesia. The rigid bronchoscope has a larger working channel than does the flexible scope, allowing for a wide range of instruments specially designed for the safe retrieval of a foreign body. Furthermore, the child's airway and ventilation are carefully monitored and controlled, maximizing the safety of the procedure. Continual communication with the anesthesiologist is critical to ensure adequate depth of anesthesia and patient stability. A combined approach with flexible bronchoscopy is often taken to allow exploration of the distal airway for further debris. Although there are reports of retrieving a foreign body from the respiratory tract of young children by means of flexible bronchoscopy,[2] this approach should be performed by a skilled bronchoscopist with the option for a rigid scope should flexible bronchoscopy not be successful. The greatest risk of using flexible bronchoscopy to remove a foreign body is the accidental lodging of the foreign body in the larynx with total occlusion of the airway. However, if the presence of a retained foreign body is considered as a differential diagnosis but not the most probable diagnosis, it is reasonable to perform flexible bronchoscopy as an initial procedure.[3] If a foreign body is in fact present, either flexible or rigid bronchoscopy can subsequently be used to remove it.

Hemoptysis and Pulmonary Hemorrhage

Bronchoscopy is occasionally performed in the evaluation and treatment of hemoptysis and pulmonary hemorrhage. When conducted as part of the evaluation of pulmonary bleeding, the procedure should occur after acute bleeding has subsided to maximize the diagnostic yield. If no bleeding site is immediately obvious, or if the diagnosis of pulmonary hemorrhage is uncertain, BAL can be performed to look for hemosiderin-laden macrophages. However, if bronchoscopy is being entertained to help manage an episode of massive hemoptysis, the procedure of choice is rigid bronchoscopy. In this situation, control of the airway is paramount, and bleeding may be so brisk that visualization will be impaired unless large amounts of blood can be suctioned quickly. Depending on the size of the patient, larger scopes with a 2.0- to 2.3-mm working channel may allow for better removal of blood and identification of the source of bleeding. Smaller children who cannot accommodate a larger scope may require a rigid scope that would better facilitate clearance of the airway, but the 1.2-mm channel of the pediatric bronchoscope cannot. If the area of bleeding can be identified, a solution of cold saline or topical epinephrine can be used to achieve hemostasis. In addition, a balloon-tipped catheter can be placed under direct visualization in the airway from which blood is emanating to isolate the source and protect other regions of the lung from being soiled.[4]

Indications for Flexible Bronchoscopy

Flexible bronchoscopy is used for diagnostic, therapeutic, and research purposes (**Box 8-1**).[5–7] It is commonly chosen to evaluate chronic stridor or wheezing and chronic or recurrent pulmonary opacities seen on radiographs

Box 8-1

Indications for Flexible Bronchoscopy

- Noisy breathing
  - Stridor
  - Chronic wheezing (especially homophonous)
  - Voice disturbance (hoarse, decreased amplitude)
- Persistent moist cough
- Persistent radiographic abnormality
- Congenital anomaly
- Recurrent pneumonia
- Atelectasis
- Retained foreign body
- Hemoptysis
- Interstitial lung disease
- Pneumonia in an immunocompromised host
- Tracheostomy evaluation
- Post–lung transplant evaluation
- Examination of lungs to determine suitability for donation for lung transplant

in children or to determine the cause of pneumonia in children with compromised immune function. The procedure is also used to evaluate hemoptysis, recurrent aspiration, and chronic cough, and it can be used to examine the airways in children with tracheostomies.

The most common indications for bronchoscopy are stridor or noisy breathing, followed in no particular order by chronic wheezing, atelectasis, and recurrent radiographic opacities.[8–12] The frequency and distribution of indications vary with the characteristics of the programs that use bronchoscopy. For example, a program involved in lung transplantation will frequently evaluate patients for airway stenosis at the anastomosis site and perform transbronchial biopsies to assess for signs of rejection, whereas programs associated with large cardiac centers would commonly evaluate patients for airway compression associated with cardiac or pulmonary vascular enlargement.

When the decision to use flexible bronchoscopy as a diagnostic modality is made, the yield is quite good but varies depending on the indication for the procedure. For instance, Wood[12] found that an abnormality relevant to the primary indication for the procedure was present in 97% of subjects with stridor but in only 46% of those with chronic or recurrent pneumonia. When considering all indications for the procedure, findings related to the primary indication were present in 76% of the 1,000 procedures reviewed. Godfrey et al[10] found the diagnostic yield of bronchoscopy in children younger than 18 years to be 67% of the 200 consecutive procedures reviewed. The groups most likely to have relevant findings included those with noisy breathing (96.2%) and atelectasis (76%). The ability to determine a diagnosis related to the indication for bronchoscopy can be enhanced with the addition of BAL or biopsy. When cytological examination and bacterial or fungal culture results were added to findings on inspection, the incidence of clinically meaningful findings increased to 90.5%.[10]

Flexible bronchoscopy can be used therapeutically to remove mucous plugs that cause atelectasis (**Figure 8-1**) or to instill agents directly into the airway, like deoxyribonuclease in patients with cystic fibrosis who have a high-DNA mucous burden.[13] Relief of atelectasis is more likely to occur when no air bronchograms are visible in the atelectatic region, suggesting the presence of a central mucous plug (**Figure 8-2**). In contrast, if air bronchograms are present (**Figure 8-3)**, it is likely that there are multiple distal mucous plugs that will not be easy to retrieve via bronchoscopy.

Bronchoscopy with BAL has been used as a research tool for evaluating early changes in the lungs in infants with cystic fibrosis.[14] Similarly, results from BAL and endobronchial biopsies are shedding new light on the pathophysiological characteristics of bronchiolitis, asthma, and childhood interstitial lung disease in the pediatric population.[15,16]



Figure 8-1. Plastic bronchitis cast of the right lower lobe bronchi removed from a patient with congenital heart disease and respiratory compromise. The cast was a mixed formation of fibrin, mucin, and cells.

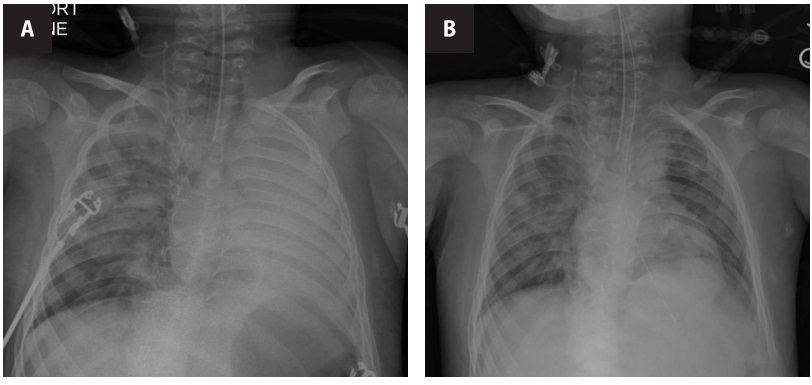


Figure 8-2. A, Chest radiograph in a girl with VACTERL association and acute respiratory failure from adenovirus pneumonia. Note the abrupt ending of an air bronchogram in the distal left main bronchus, together with left lung atelectasis. **B**, The same patient 24 hours after bronchoscopic removal of a mucous plug from the left main bronchus.

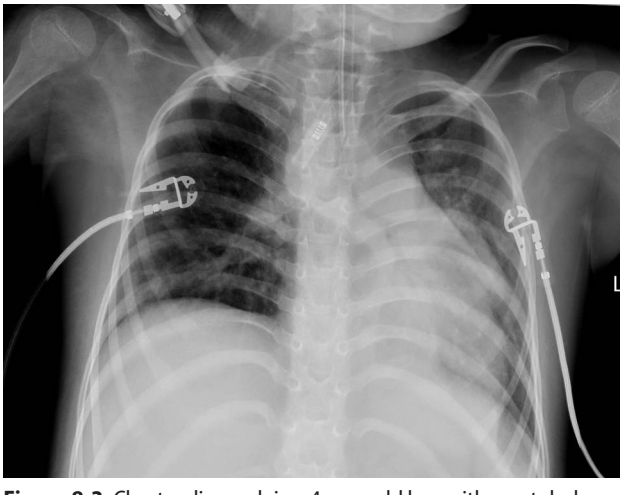


Figure 8-3. Chest radiograph in a 4-year-old boy with myotubular myopathy and left lower lobe atelectasis. Note the air bronchograms within the area of atelectasis, reflecting multiple distal sites of airway obstruction rather than a central mucous plug.

Contraindications for Bronchoscopy

It has been said that the only time bronchoscopy is truly contraindicated is when the information or therapeutic objective can be obtained in a less invasive fashion.[11] There are, however, relative contraindications for which the risk of the procedure must be balanced against the information or therapeutic benefit to be derived. Generally, an uncorrected bleeding diathesis like thrombocytopenia or clotting dysfunction, profound hypoxemia before the procedure, moderate or severe pulmonary hypertension, or severe airway obstruction all should be carefully weighed so that the added risk of the procedure is worth the anticipated outcome to the patient. Occasionally, these very conditions are the reason to perform bronchoscopy (eg, if hypoxemia is the result of massive atelectasis or if removing a mucous plug can potentially reverse a condition).[11]

Pathophysiological and Clinical Features in Diagnostic Bronchoscopy

When diagnostic bronchoscopy is performed to evaluate abnormal noises, the diagnostic yield is enhanced if the child creates the noise during the procedure, which may require the examiner to reproduce the situation in which the noise occurs. Thus, if the noise is heard mostly when the child sleeps, as in cases of obstructive sleep apnea, examining the child during sedated quiet sleep is more likely to recreate the airway obstruction and enable the examiner to determine its origin than if the child were minimally sedated. Alternatively, if the noise occurs with increased breathing effort, the child should be only lightly sedated to accentuate breathing effort. Having the patient emerge from anesthesia with the bronchoscope positioned in the nasopharynx often is used to assess the upper airway dynamics at the end of the procedure.

CASE REPORT 8-2

A young athlete was evaluated for possible exercise-related vocal cord dysfunction. To recreate the situation, he was told to hyperventilate with a bronchoscope in place, but this did not reveal any abnormalities. The only time he reported symptoms, however, was during indoor swimming practice and competitions. The examination was repeated while he smelled chlorine bleach, and he quickly demonstrated paradoxical vocal fold motion within a few breaths.

Extrathoracic Airway

Intraluminal airway pressure is subatmospheric during inspiration, giving structures in the extrathoracic airway the propensity to collapse. Thus, any dynamic lesion will be louder during inspiration. Fixed lesions (ie, those that do not result in a respiratory phase–dependent change in airway caliber, like

subglottic stenosis) can cause biphasic noise. The noise created by dynamic lesions depends on the magnitude of the intraluminal pressure decrease and the tone or stiffness (compliance) of the airway structures. It may also be positional, as neck hyperextension places longitudinal traction on the extrathoracic airway and can stiffen it to some degree.

Flexible bronchoscopy offers the advantages of examining the extrathoracic airway from the nostril onward, so that any structure in the extrathoracic airway that might cause obstruction or airway vibration should be visible. Furthermore, the patient is examined while the head is in a neutral position. Because the flexible scope follows the contours of the nasopharynx, it does not distort the anatomy of the airway.[17] Sedation can be made lighter or deeper so that the conditions under which the noise or obstruction is usually present can be replicated.

Extrathoracic lesions that cause noisy breathing or obstruction are identified in most children who undergo bronchoscopy.[10,12] When stridor is the indication for evaluation, in the absence of a known history of prolonged airway intubation, the cause is usually a congenital lesion.[7,10,17] Of these, laryngomalacia is the most common condition, followed by vocal cord paralysis.[7,12,17] The finding of laryngomalacia during laryngoscopy does not obviate the need to look below the vocal cords: 15% to 21% of patients will have a second airway abnormality noted during more distal evaluation of the airways.[12,17] Severe stenosis should generally not be examined below the lesion with flexible bronchoscopy because of the risk of worsening swelling and edema; it is better accomplished with a combined procedure.

Excessive sedation or breathing effort can lead to erroneous diagnoses. The presence of large airway collapse in an infant making heroic efforts to breathe because of inadequate sedation may be mistaken for tracheomalacia or bronchomalacia. Excessive sedation or the application of lidocaine to the larynx[18] can result in dynamic collapse of laryngeal structures and be mistaken for true laryngomalacia. If there is no preprocedure history of wheezing in the former case or stridor in the latter case, such findings are likely artifactual. A list of common lesions that lead to noisy breathing is shown in **Box 8-2.**

Box 8-2

Lesions Associated With Noisy Breathing

Stridor
- Laryngomalacia
- Subglottic stenosis
- Vocal cord paralysis
- Hemangioma
- Vocal cord dysfunction

Wheezing
- Tracheomalacia or bronchomalacia
- Tracheal stenosis
- Airway compression
  - Vascular
  - Lymph nodes
  - Mediastinal mass
- Bronchitis
- Endobronchial tumor

Not all children with noisy breathing, however, require airway evaluation. Bronchoscopy should be reserved for children whose noisy breathing is progressive, leads to episodes of apnea, and is associated with feeding difficulty and poor growth or sleep disruption and impaired development, or when the history and physical examination results raise the possibility of a lesion other than congenital laryngomalacia.[7] Bronchoscopy might also be considered in an infant with laryngomalacia when parental anxiety regarding the noise is so great that confirmation of the diagnosis is necessary to allow for reassurance regarding the natural history of the disorder.

Intrathoracic Airway

Diagnostic bronchoscopy is performed to evaluate chronic wheezing or cough unresponsive to medical therapy, persistent or recurrent radiographic opacities in the lung, atelectasis, localized hyperinflation, hemoptysis, suspected recurrent aspiration, or possible retained foreign body. When bronchoscopy is combined with techniques like BAL or transbronchial biopsy, information can also be gleaned about processes in small airways and alveolar spaces. In addition, biopsies of the airway wall can yield disease-specific information (eg, ciliary ultrastructure and function or the type of inflammatory cells and presence of rejection after lung transplant).

Evaluating Intrathoracic Airway Collapse

As with evaluation of the extrathoracic airway, the degree of respiratory effort must be considered when evaluating intrathoracic airway collapse. In contrast to extrathoracic obstruction, the forces acting across intrathoracic airway walls favor their narrowing during exhalation. Excessive expiratory effort will cause invagination of the posterior membrane of the trachea and main bronchi; oversedation or paralysis will minimize the collapsing pressures exerted across the airway wall. This situation makes the diagnosis of primary intrathoracic tracheomalacia or bronchomalacia exceedingly difficult because all patients can demonstrate some degree of airway collapse with excessive expiratory effort or cough. Furthermore, visual estimates of airway narrowing are highly subjective, and no universally agreed-on definition based on magnitude of airway narrowing exists.[19] When tracheomalacia occurs secondary to another condition, like tracheoesophageal fistula, there is often a larger than normal ratio of posterior membrane to anterior cartilage; this is not necessarily true in primary tracheomalacia or tracheomalacia acquired after prolonged mechanical ventilation.

Evaluating Narrowed Intrathoracic Airway

When an intrathoracic airway is narrowed, the endoscopist must determine (1) if the obstruction is dynamic or fixed, (2) if the lesion is intrinsic (web, tumor, mucosal lesion, etc) or if the narrowing is from extrinsic compression, and (3) whether the compression is pulsatile. Location of the narrowing often is an important clue in determining extrinsic compression; the left pulmonary

artery crosses over the left main bronchus and proceeds behind the left lower lobe and left upper lobe bronchi, and the right pulmonary artery crosses over the bronchus intermedius (because the right upper lobe bronchus is superior to its attendant pulmonary artery, it is never compressed by it). The aorta will cause a pulsatile compression of the left anterior tracheal wall on its ascent, and the descending aorta can compress the left main bronchus posteriorly.[20] Enlarged lymph nodes encircling the right middle lobe bronchus can narrow the bronchus intermedius; bronchogenic cysts, which are often subcarinal, can cause compression of the main bronchi or widening of the main carina.

Interpreting Other Intrathoracic Bronchoscopic Findings

Often, when bronchoscopy is undertaken for evaluation and treatment of atelectasis, there are no secretions for removal. Absence of such a finding still may be critical for care decisions (**Figure 8-4**). Similarly, absence of a suspected retained foreign body is as important as finding one. It may be difficult to interpret BAL findings when that modality is used to determine the cause of infection in children with chronic or recurrent radiographic opacities or with a compromised immune system. The bronchoscope is passed through the nose and mouth, compromising the sterility of the samples. Efforts to avoid suctioning the airway until the scope is below the vocal cords can reduce, but not eliminate, the risk of contaminating the specimens. Combining the visual findings from bronchoscopic examination (presence or absence of airway inflammation and secretions) with cell count, cytological examination, and *quantitative* bacterial culture will strengthen the interpretation of the findings (see Diagnostic Procedures, later in this chapter). If the proportion of squamous cells is high, or if cultures return showing polymicrobial flora, upper airway contamination of the specimen is likely. If the central airways are inflamed and there are large amounts of secretions in those airways, however, the cells and bacteria may be there because the child chronically aspirates oral secretions.

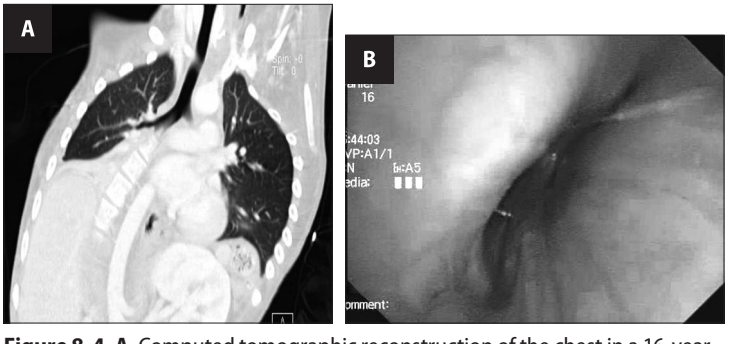


Figure 8-4. A, Computed tomographic reconstruction of the chest in a 16-year-old boy with Duchenne muscular dystrophy and chronic right lower lobe atelectasis. The air bronchogram ends abruptly, suggesting a mucous plug. **B**, Bronchoscopic evaluation demonstrates airway narrowing and distortion resulting from the patient's severe scoliosis and chest wall deformity but no mucous plug.

Airway Management and Examination

There are several different ways to examine the pediatric airway by using flexible bronchoscopy. These methods include transnasally or transorally or via face mask, laryngeal mask airway, endotracheal tube, or tracheostomy tube. The mode of airway entry should take into account the clinical context and the reason for the procedure (**Table 8-2**).[9]

Table 8-2. Advantages and Disadvantages of Different Airway Entry Techniques

Technique	Advantages	Disadvantages
Natural airway (transnasal or transoral approach)	• Inspect entire airway • Assess airway dynamics • May allow for the use of a larger bronchoscope • Allows for airway evaluation with a rigid scope	• More difficult to monitor ventilation • Laryngospasm
Face mask	• Inspect entire airway • Assess airway dynamics • Does not limit size of bronchoscope	• More difficult to monitor ventilation • Laryngospasm • May limit movement of bronchoscope
Laryngeal mask airway	• Is easy to place • Is a relatively secure airway • Can assist ventilation with positive pressure	• Cannot assess upper airway • Cannot accurately assess vocal cord movement • May limit size of bronchoscope • May hinder passage of bronchoscope • Requires deeper sedation than natural airway • Can mask lower airway dynamics • Does not completely protect airway if vomiting occurs during the procedure
Endotracheal or tracheostomy tube	• Is easy to place • Secures the airway • Is easy and quick to reinsert bronchoscope if needed • Enables positive pressure ventilation • Prevents contamination of lower airway specimens by upper airway secretions	• Cannot assess upper airway • Cannot assess vocal cord anatomy and movement • Cannot assess airway dynamics • May limit size of bronchoscope • Requires deeper sedation than natural airway

Diagnostic Procedures

Bronchoalveolar Lavage Testing

Bronchoalveolar lavage is used to sample the alveoli for different cell types, including migrated leukocytes and macrophages, invading bacteria, and other infectious pathogens. Analysis can also be performed to evaluate acellular components, including viral particles, cytokines, and proteins. The flexible bronchoscope is advanced into progressively more distal airways until it is wedged or unable to be advanced further. The lavage is performed first by instilling normal saline through the working channel of the bronchoscope into the distal airways and airspaces and then by withdrawing it by means of suction. The amount of saline used for a lavage varies from center to center, from 0.5 to 3.0 mL/kg per aliquot with a maximum of 4 aliquots taken at 1 procedure. Typically, a protocol is used to limit the total amount of saline that is instilled. In many centers, the first sample is discarded because it is believed not to represent alveolar sampling, but rather sampling of bronchial cells. A return of at least 30% to 40% of the aliquot used in the lavage is considered a good sample.[7,9,21] Bronchoalveolar lavage is performed in the most affected area as determined with radiographic imaging or direct visualization with the bronchoscope. If there is no identified affected area, the lavage is performed in the right middle lobe or lingula in children, and the lavage is performed in the right lower lobe in infants to optimize fluid recovery.[9,21]

Normal Cell Types

Bronchoalveolar lavage is a diagnostic tool used to evaluate cellular counts of the lavage fluid (**Table 8-3**). The absolute number of nucleated cells and red blood cells can be detected, and the different types of white blood cells can also be analyzed. In healthy lungs, alveolar macrophages make up roughly 80% to 90% of the cells in the BAL fluid, and lymphocytes and neutrophils make up roughly 2% to 12% and 0% to 5% of the BAL fluid, respectively.[22] There are subtle age-dependent differences in the BAL fluid. A slight increase in the number of neutrophils is observed in patients younger than 12 months when compared with those in children aged 12 to 36 months. Younger children also can have a greater number of total cells when compared with those in the adult population.[23] Squamous epithelial cells, when detected in BAL, suggest either contamination by oropharyngeal secretions because of poor technique in performing the BAL or aspiration of upper airway secretions by the patient.

Table 8-3. Cell Types in Bronchoalveolar Lavage Fluid

Cell Types	Normal Percentage in Healthy Patients	Disease Associated With Abnormal Cell Type or Number
Alveolar macrophages	80%–90%	**Lipid-laden macrophages:** aspiration, gastroesophageal reflux
		Hemosiderin-laden macrophages: idiopathic pulmonary hemosiderosis, vasculitis and collagen vascular disease, infections, pulmonary vascular disease, drug-associated increase
Lymphocytes	2%–12%	**Increased CD4+ cells:** sarcoidosis, Crohn disease
		Increased CD8+ cells: hypersensitivity pneumonia, histiocytosis X, drug-induced pneumonitis, ILD, bronchiolitis obliterans organizing pneumonia
Eosinophils	0%–1%	**Increased eosinophils:** asthma, ILD, drug-associated increase
		Idiopathic increases: Churg-Strauss syndrome, eosinophilic lung disease
Neutrophils	0%–5%	**Increased neutrophils:** ILD, infection, asthma, chronic bronchitis

Abbreviations: CD4+, cluster of differentiation 4 positive; CD8+, cluster of differentiation 8 positive; ILD, interstitial lung disease.

Abnormal Cell Differentials

The BAL fluid can be examined for pathological cell types to enhance diagnostic yield. The number of different abnormal cell types and analysis of the ratio of different cell types can be informative. For example, elevated numbers of lipid-laden macrophages, in the proper clinical context, may be associated with aspiration from swallowing dysfunction or from gastroesophageal reflux disease (GERD). Similarly, hemosiderin-laden macrophages reflect a history of pulmonary bleeding. The presence of increased numbers of normal cell types is often nonspecific but can guide further investigation. Thus, increased numbers of eosinophils in the BAL can be associated with multiple disorders, including eosinophilic lung diseases, asthma, Churg-Strauss syndrome, drug reaction, allergic bronchopulmonary aspergillosis, and interstitial lung disease. Increased numbers of neutrophils can be found in infections, asthma, and some interstitial lung diseases. In contrast, an increase in absolute numbers of lymphocytes and variation in T-cell subpopulation ratios (particularly the CD4:CD8 ratio, which is elevated in sarcoidosis and Crohn disease) can help to identify specific diseases. An increase in CD8 lymphocyte populations is associated with hypersensitivity pneumonitis, histiocytosis X, drug-induced pneumonitis, interstitial lung disease associated with collagen vasculitis, and cryptogenic organizing pneumonia (**Table 8-3**).[21,22]

In addition to cultures and cell types, BAL fluid can be analyzed for other contents. For example, markers that suggest GERD with microaspiration can

be detected in BAL fluid. Investigators in several studies have attempted to correlate the presence of pepsin and bile acids in BAL fluid with lung disease from GERD. In patients with lung transplants, detection of either marker has been an important finding because an elevation of either of these indexes correlates with the onset of bronchiolitis obliterans.[24] Bronchoalveolar lavage fluid can also be analyzed for cytokines. Although such measurements currently are largely relegated to research investigations, they can help to assess the effect of different pharmacological therapies on various lung diseases, particularly inflammatory disease of either infectious or noninfectious origins. For example, a reduction in measured cytokines in BAL fluid from patients with asthma or cystic fibrosis might be demonstrated after a pharmacological intervention.[25,26] Investigators in some studies have measured immunoglobulin levels in the BAL fluid. Patients with chronic disease had higher levels of immunoglobulin G than did healthy control subjects.[27] Although measurements of cytokines or immunoglobulins are not routinely performed in the pediatric patient population, their analysis underscores the importance of the BAL fluid and its usefulness in both research and clinical care.

Microbiology

Testing for bacteria should include direct visualization of the BAL fluid specimen by using the Gram stain. Such screening provides not only a rapid clue to the type of bacteria that might be present but also some qualitative assessment of the adequacy of the specimen. Fluid that contains large numbers of squamous cells, for instance, is likely to indicate contamination by mouth flora. In contrast, the presence of large numbers of neutrophils supports a diagnosis of acute infection. On the basis of a patient's clinical history, BAL fluid can be cultured for bacteria, acid-fast bacilli, fungi, and molds. Quantitative cultures that yield greater than 10^5 colony-forming units per milliliter offer insight into predominant strains of bacteria present in the lavage fluid and help to eliminate contaminated samples.

Screening for viruses can also be performed. Polymerase chain reaction detection to augment antigen detection and viral cultures has increased the sensitivity of discovering viruses in the lower airways. As an adjunct to these techniques, or if polymerase chain reaction or rapid antigen detection techniques are not available, cytological examination of the BAL fluid can also help identify viral infection of the lung.[9] Inclusion bodies in the cytoplasm or nucleus, balloon cells, syncytial cells, and smudge cells are pathognomonic for agents like herpesvirus, cytomegalovirus, varicella, respiratory syncytial virus, or adenovirus. In addition to using the Gram stain to detect gram-positive or gram-negative organisms, other special stains can be used to find specific pathogens. The Gomori methenamine silver stain is used to detect fungal organisms and *Pneumocystis jirovecii,* and the Ziehl-Neelsen stain is used to detect acid-fast bacilli.

The keys to effective anaerobic bacterial cultures include collecting a contaminant-free specimen and protecting it from oxygen exposure. Bronchoalveolar lavage fluid is aspirated using a sterile syringe that is then tightly capped to prevent entry of air. The specimens should be plated as rapidly as possible onto specially prepared anaerobic culture media. Cultures should be placed in an environment that is free of oxygen at 35° C (95° F) for at least 48 hours before the plates are examined for growth.

Special Studies

Transbronchial Biopsy

Transbronchial biopsies are used in select pediatric populations. By far the largest experience is in the population with lung transplants. Transbronchial biopsy is the gold standard for the diagnosis of acute cellular rejection, a common complication in the first 12 months after lung transplant. The procedure is performed under fluoroscopic guidance by using 1.2-mm or 2.0-mm forceps that are passed though the working channel of the bronchoscope. Six to 12 samples are taken for evaluation. These samples can be examined histologically to evaluate for different cell types to establish a diagnosis.[28] Samples can also be cultured if infection is being considered.

Ciliary Biopsy

Ciliary biopsy is an important diagnostic tool for evaluating for primary ciliary dyskinesia.[29] To diagnose primary ciliary dyskinesia, the physician can take samples from the upper and lower airways. Sampling from the upper airway through nasal brushing often yields false-positive findings secondary to inflammation from respiratory infections, exposure to tobacco smoke, and allergic rhinitis. Sampling from the lower airway will improve overall yield by eliminating these secondary changes. Bronchoscopic sampling in the lower airway is performed by using a cytology brush and sampling the bronchial membrane at the main carina or in close proximity to it. Samples are fixed in glutaraldehyde and sent for evaluation with electron microscopy to assess ciliary ultrastructure. Some centers will also grow or culture cilia samples or take samples for direct microscopic evaluation of ciliary motion. Examination of ciliary ultrastructure with electron microscopy requires a pathologist experienced in this area.

Therapeutic Bronchoscopy

Medication can be administered via a flexible bronchoscope. Epinephrine can be instilled topically to help control bleeding in patients with pulmonary hemorrhage.[4] Although the drug is often administered blindly through an endotracheal tube, localized deposition to a specific area of concern offers a more directed therapeutic intervention. Dornase alfa also can be administered via flexible bronchoscope. This mucolytic agent has been used in patients with

cystic fibrosis to target the DNA polymer network in the airway. It can improve mucous clearance and pulmonary function in patients with cystic fibrosis.[13]

Mechanical removal of mucous plugs can also be achieved bronchoscopically. In some instances, particularly in the intensive care unit setting, frequent bronchoscopy can be used for airway clearance. This technique is useful to clear proximal airways, if a chest radiograph shows an abrupt ending of an air bronchogram (**Figure 8-2**). The technique is not an effective method of airway clearance for processes in which air bronchograms are seen throughout an area of atelectasis or consolidation (**Figure 8-3**), as discussed previously. Simple saline washes of the airway through the bronchoscope can also help remove tenacious, thick mucous plugs.

Removal of other foreign bodies is traditionally accomplished with rigid bronchoscopes. Although some investigators have described foreign body removal with a flexible bronchoscope, the general consensus is that rigid bronchoscopy is a safer and more efficient mode for removing foreign bodies from the airway, with decreased risk of airway obstruction when removing the foreign body.[2]

Therapeutic Lavage

Pulmonary alveolar proteinosis is a disease for which whole lung lavage is a therapeutic treatment option. This rare disease that occurs in both children and adults is the result of an abnormality in surfactant homeostasis and metabolism, resulting in abnormal accumulation of surfactant in the alveoli, which in turn leads to abnormal gas exchange. Whole lung lavage, whereby each lung sequentially undergoes lavage in a controlled manner to remove the proteinaceous material filling the airspaces, is a treatment option generally effective at ameliorating symptoms, and it is used along with other therapies in this patient population.[30]

Endoscopic Intubation

Endoscopic intubation, in which an endotracheal tube is passed over the flexible bronchoscope to guide its placement under direct visualization, can be used when the standard approach to visualizing the larynx is not feasible or possible. Thus, patients with cervical injuries, craniofacial abnormalities, temporomandibular joint limitation, or known previous difficult airway intubations can benefit from this approach.[31]

Stent Placement

Endobronchial stents can be positioned bronchoscopically in the central airways, as distal as the lobar bronchi. There is limited indication for airway stent placement in the pediatric population, typically involving severe cases of airway narrowing that are not candidates for surgical intervention. Patients

with severe tracheomalacia, bronchomalacia, or stenosis can benefit from airway stent placement when there is clinically significant respiratory compromise. Children with lung transplants are the population in which stent placement has been used most commonly. This cohort can benefit from temporary placement of stents when there is stenosis or malacia at the anastomosis site while it is healing. It is theorized that the temporary placement of a stent can help reshape the area of concern.[32] Limitations of the procedure in the pediatric population include stent sizing and complications from the stent placement. Some stents may be easily dislodged with coughing, and others are difficult to remove because of clinically significant growth of granulation tissue.[32,33] Another concern is poor airway clearance of secretions in the area of the stent.

Balloon Dilation of the Airway

Balloon dilation is performed with special balloon catheters. They can be introduced into the affected region through the working channel of the bronchoscope, after which the balloon is inflated under pressure to expand the area. Balloon catheters come in a variety of dimensions and levels of rigidity and can be used in patients with either congenital or acquired airway stenosis. Often this procedure needs to be repeated at regular intervals to maintain airway patency.[33]

Laser Therapy and Electrosurgery

Laser bronchoscopy uses laser energy delivered via standard bronchoscopes to treat endobronchial disorders. Laser therapy is a tool widely used in adults, in whom the incidence of endobronchial lesions is greater because of a higher prevalence of carcinomas.[34] However, in the pediatric population, this technique is helpful in the treatment of bronchial lesions, such as hemangiomas and papillomas, or for the removal of granulation tissue. Another method of treating these obstructions is endobronchial electrosurgery (also known as *electrocautery* or *diathermy*), which uses high-frequency electrical current through a probe to coagulate or vaporize tissue.

Endobronchial Ultrasonography

Endobronchial ultrasonography is a diagnostic technique for visualizing the tracheobronchial wall and the immediate surrounding structures. Ultrasound waves are transmitted to anatomical structures, and the reflected echoes are transformed into electrical signals, which are converted to a visual image on the monitoring screen. Endobronchial ultrasonography with ultrasound-guided biopsy is used in the adult population, particularly in diagnosing tumors.[35] In 2020, endobronchial ultrasonography was reported to be safely and successfully performed in more than 20 pediatric patients with reported increased yield in diagnosis compared with that at standard bronchoscopy. The youngest patient in this cohort was aged 2.5 years.[36]

Electromagnetic Navigational Bronchoscopy

Electromagnetic navigational bronchoscopy is a navigational system using electromagnetic technology to guide a bronchoscope through the airways for accurate targeting of lesions for biopsy that were previously inaccessible. Using a virtual, 3-dimensional bronchial map from a computed tomography scan of the chest and a catheter with a sensor probe, bronchoscopists are able to navigate to a desired location for diagnostic biopsy and therapeutic treatment.[37] These techniques are currently limited to adult pulmonary centers with expertise. This technology has the potential to expand the scope of pediatric bronchoscopy in the future.

Complications of Flexible Bronchoscopy

Flexible bronchoscopy is a safe procedure in practiced hands, but some complications occur with low frequency.[9] Direct trauma to airway mucosa can result in epistaxis or bronchial bleeding; these are typically minor and self-limited problems. Crying, coughing, or phonating while the bronchoscope is positioned between the vocal cords can lead to hoarseness or stridor that is also mild and self-limited, and inadequate topical laryngeal anesthesia can cause laryngospasm. Airway obstruction by the bronchoscope and sedation can impair gas exchange, leading to hypoxemia and hypercapnia.[9] Administration of supplemental oxygen during the procedure usually prevents significant hypoxemia, allowing the procedure to be completed safely, and the bronchoscope can be withdrawn quickly from a narrowed airway if its presence causes critical obstruction. Airway instrumentation can elicit vagal responses and cause bradycardia, but this problem is easily avoided by using a topical application of lidocaine. Passage of the scope through an infected upper airway (ie, if the procedure is performed when the patient has an acute upper respiratory infection) can predispose a child to lower respiratory infection; similarly, meticulous cleaning of equipment is mandatory between procedures to prevent a contaminated scope from infecting other patients. Fever commonly occurs after flexible bronchoscopy, but it is usually transient and resolves after a single dose of an antipyretic. Its persistence may indicate significant infection.

Some complications are more likely when procedures like BAL or transbronchial biopsy are also performed. Persistent fever after BAL, especially in the setting of bronchitis, may reflect transient bacteremia or local extension of infection. Sepsis after bronchoscopy, however, is a rare complication. The risk of pneumothorax is increased when transbronchial biopsy is performed; therefore, any patient undergoing the procedure must be monitored for several hours for the complication.

key points

- Fiberoptic bronchoscopy can be used at any age as a diagnostic or therapeutic procedure.
- Foreign body removal usually requires rigid bronchoscopy.
- The most common indication for fiberoptic bronchoscopy is evaluation of noisy breathing.
- Bronchoalveolar lavage is useful to define lower airway microbiological and cytological characteristics.
- Extensive experience has demonstrated that flexible bronchoscopy is safe in the hands of experienced bronchoscopists.
- The usefulness of diagnostic and therapeutic flexible bronchoscopy continues to expand in parallel with technological advances.

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PART 2

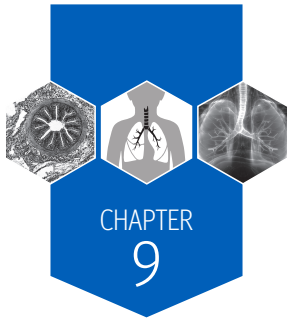
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CHAPTER 9

Allergic Bronchopulmonary Aspergillosis

Richard M. Kravitz, MD, FAAP

Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is a T-helper 2 (Th2 cell) and immunoglobulin E (IgE)–mediated allergic reaction to the mold *Aspergillus fumigatus.* This ubiquitous mold is usually of little consequence in the immunocompetent host. In patients with an immunodeficiency, however, this mold can infect the lung, leading to an overwhelming infection. Patients with asthma and cystic fibrosis (CF) can become colonized with this organism, and while no actual infection is present, the body's immune system mounts a Th2 inflammatory response marked by increased expression of interleukin (IL) 5 (IL-5) and IL-13, leading to eosinophil recruitment to the lung and increased production of IgE. This can lead to asthma that is difficult to control, and, in patients with CF, increased pulmonary exacerbations and worsened bronchiectasis. Failure to recognize this condition can lead to progressive lung disease with significantly decreased pulmonary function and, ultimately, bronchiectasis and pulmonary fibrosis.

The *Aspergillus* species represents a family of molds often found in soil and decaying plant matter.[1–3] More than 300 species have been described, with *A fumigatus* the most common in human infections.[3] Transmission via inhalation is the most common method of inoculation. No human-to-human spread occurs.[1,2] The conidia (spore) form is infectious, while the hyphae form is what is seen in invasive disease.[4]

Aspergillus infections can take on 1 of 5 forms, 3 of which predominate: allergic, saprophytic, and invasive (with allergic sinusitis and chronic pulmonary aspergillosis less commonly seen).[1,5] Allergic forms include ABPA, hypersensitivity pneumonitis, and severe asthma with *Aspergillus* colonization in immunocompetent hosts. The saprophytic form includes aspergillomas, a situation in which the mold grows within preexisting pulmonary cysts or cavities. This represents a nonallergic situation in an immunocompetent host. Finally, the invasive form of the disease is the most severe and life-threatening. These cases are seen in immunocompromised

hosts, such as those with prolonged neutropenia (ie, patients with cancer or those undergoing transplantation; graft-versus-host disease) or impaired phagocytosis (eg, chronic granulomatous disease).

Etiology

The immunologic cause of ABPA is complicated and not fully elucidated. While several animal models are available to study this allergic-mediated disease, they do not exactly mimic what is seen in humans. Many patients with asthma and CF are sensitized to *A fumigatus*. Approximately 20% to 25% of patients with asthma and up to 60% of patients with CF are skin test positive.[6–8] Up to 80% of patients with CF have immunoglobulin G (IgG) antibodies to Aspf14, and 60% to 80% may at one time grow *A fumigatus* in their sputum culture.[4,7,9] Despite this, not all of these patients develop ABPA.

Allergic bronchopulmonary aspergillosis is thought to be a Th2-mediated disease, with IL-4, IL-5, IL-13, and IgE being important mediators of disease progression.[4,6,8] The working disease model for ABPA is outlined here[1,2,4,6,10–12] and in **Figure 9-1**.[10]

1. *Aspergillus fumigatus* spores are inhaled. The spores become trapped in the airway surface mucus and eventually germinate.
2. Airway clearance is compromised by the underlying disease (asthma or CF).
3. *Aspergillus fumigatus* releases virulence factors, allergens (especially Af1), and proteases in genetically susceptible patients, which
   - disrupt and break down airway epithelial barriers.
   - impair fungicidal proteins and complement.
   - inhibit phagocytotic killing cells (macrophages and neutrophils).
4. The immune system is activated.
   - Cytokines recruit CD4+ Th2 cells.
   - Interleukin-5 production increases and IL-10 production decreases with subsequent eosinophil infiltration.
   - Interleukin-8 production increases with subsequent neutrophil infiltration.
5. A specific humoral adaptive response occurs with elevation of IgG, immunoglobulin A (IgA), and IgE to *A fumigatus* as well as IL-4 production and nonspecific IgE elevation.

Aspergillus fumigatus spores demonstrate increased binding to inflammatory proteins. In particular, the *Aspergillus* antigens cross-link with the IgE on the mast cells, releasing mediators such as histamine, leukotrienes, and platelet-activating factor, which increase vascular permeability and cause smooth muscle constriction. Mast cell cytokines are chemoattractants for eosinophils.

Thus, a cycle of antigen-mediated stimulation and inflammation is created, ultimately leading to the development of bronchiectasis.

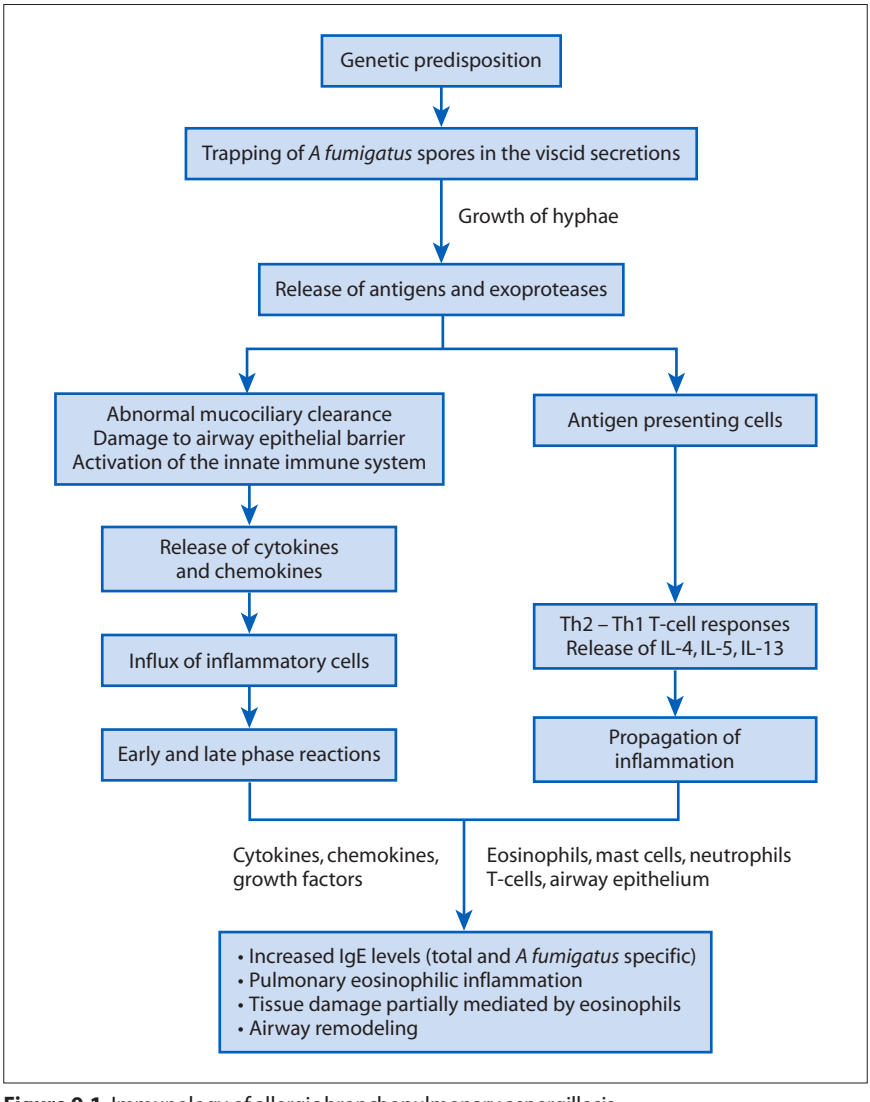


Figure 9-1. Immunology of allergic bronchopulmonary aspergillosis.

Abbreviations: *A fumigatus, Aspergillus fumigatus;* IgE, immunoglobulin E; IL, interleukin.

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Risk Factors

Certain genetic factors may increase a patient's risk from merely possessing *A fumigatus* sensitivity to developing ABPA. In particular, the presence of HLA-DR2 and DR5 restrictions, IL-4Rα single nucleotide polymorphisms, and IL-10 promoter mutations is associated with the development of ABPA.[5] In a small case series, patients with asthma who were heterozygous for *CFTR* mutations had a higher risk for the development of ABPA, suggesting that this gene has some effect on the organism's immunogenicity.[6,8,11,13]

There are several other factors that put one at risk for the development of ABPA. In patients with CF, the acquisition of *Pseudomonas aeruginosa* has been associated with a higher incidence of ABPA.[9] *Pseudomonas aeruginosa* is thought to heighten the Th2 response to *A fumigatus* antigens. Airway acquisition of *P aeruginosa* often precedes the sensitization with *A fumigatus*.[9]

Atopy is also associated with a higher risk of developing ABPA. Approximately 22% of patients with CF and atopy have ABPA, while 2% of patients with CF who do not also have atopy develop ABPA.[6,11] *Aspergillus fumigatus* colonization is greater in patients with ABPA than in those with just atopy.[6] Sensitization to *A fumigatus* is a key factor in the development of ABPA. In patients sensitized to *A fumigatus,* the B cells of those with ABPA release more IgE than the B cells of patients without ABPA. Different *Aspergillus* antigens are associated with different clinical effects. Patients with ABPA develop IgE to antigens Asp2, Asp4, or Asp6, while atopic patients develop IgE to antigens Asp1 or Asp3.[6,14]

High levels of *Aspergillus* antibodies are thought to be produced because the *Aspergillus* proteases disrupt the epithelial lining, exposing bronchoalveolar lymph tissue to *Aspergillus* antigens, thus generating a potent immune response.[12] In those with CF, the abnormal mucus traps the spores more effectively, further increasing the antigenic load.

Epidemiology

The prevalence of ABPA is difficult to determine because studies use varying criteria to determine the diagnosis. The rate for patients with asthma is about 1% to 2%.[10,11] It is much more common in people with CF, with prevalence varying between 2% and 15%.[4,6,10,11] Several large epidemiologic studies in those with CF have further attempted to define the prevalence. In a report from the Epidemiologic Study of Cystic Fibrosis published in 1999, the prevalence of ABPA among 14,210 patients in the United States and Canada was 2%,[7] similar to a rate of 2.2% reported in a Cystic Fibrosis Foundation Patient Registry analysis published in 1995[15] and the Registry analysis published in

2020,[16] with a rate of 2.2% in patients younger than 18 years (though the rate for older patients was higher at 7.4%, with an overall rate of 5%). In the United States, there appears to be regional variation in the CF population, with the highest rate in the West (4.0%) and the lowest rate in the Southwest (0.9%).[7] Different criteria used to assign the diagnosis of ABPA, and the extent to which this diagnosis was sought, may explain these regional variations, as well as the lower prevalence rates when compared with other studies. Other confounding features, such as environmental factors, could also not be ruled out. The European Registry of Cystic Fibrosis, published in 2000, covered 9 European countries and 12,447 patients and reported an ABPA prevalence of 7.8%.[17] This prevalence varied by country, with the highest rate (13.6%) found in Belgium and the lowest rate (2.1%) found in Sweden. All 3 of these studies demonstrated higher rates of ABPA in patients older than 5 to 6 years with lower FEV_1 values (<70% of predicted), *Pseudomonas* colonization, and a history of wheezing.

Clinical Presentation

The classic presentation of ABPA is a triad of reversible airway obstruction, recurrent pulmonary infiltrates, and central bronchiectasis. Common symptoms seen in patients with ABPA include wheezing, coughing, and increased mucus production.[5] Other symptoms that may be present include anorexia, malaise, fever, and the expectoration of mucus with brown to black plugs.[5,10] Hemoptysis has also been reported. In patients with asthma, their asthma frequently becomes more difficult to control, while those with CF usually have an increased number of pulmonary exacerbations and experience a significant deterioration in pulmonary function. Weight loss is often reported. Allergic bronchopulmonary aspergillosis may be easily confused with an exacerbation of the patient's underlying disease process; thus, a high degree of suspicion is required to avoid missing the diagnosis of ABPA.

The results of the physical examination are typical for an exacerbation of the patient's underlying illness. Wheezing and a productive cough are often found.[5,11] Clubbing (reports up to 16%) can be seen in patients with ABPA.[5,10] The chest wall can be hyperinflated.[5]

The differential diagnosis of ABPA is broad and includes illnesses that are similar to both asthma and CF.[5,10] These illnesses include acute processes such as pneumonia (viral or bacterial) or a retained foreign body in the airways. Allergy or inflammatory-mediated illnesses include eosinophilic pneumonia, pulmonary infiltrates with eosinophilia, hypersensitivity pneumonitis, Churg-Strauss syndrome, and sarcoidosis. The differential diagnosis also includes chronic infectious tuberculosis, as well as disorders associated with bronchiectasis, such as ciliary dyskinesia.

Evaluation

No single test can definitively establish the diagnosis of ABPA. Several tests may return abnormal results in patients with ABPA; however, each of these studies is insufficient to establish the diagnosis. To further complicate matters, in select patients, many of these test results may actually be normal despite clear evidence that the patient has ABPA. Accordingly, the diagnosis is ultimately established through a combination of history, physical examination findings, select laboratory study findings, and clinical judgment. Various diagnostic algorithms have been proposed, and these are discussed in Diagnostic Criteria later in this chapter. Microscopic identification of the mold can be accomplished with 10% potassium hydroxide on a wet mount. For pathologic examination of tissue, silver staining (using Gomori-methenamine or periodic acid–Schiff stains) is helpful but may be negative in cases of ABPA. Affected tissue may demonstrate black staining with dichotomously branching (at a 45-degree angle) hyphae.[1,3] In the airways of patients with ABPA, large mucus plugs (plastic bronchitis[3]) are often found. On examination of these plugs, one can see a variety of inflammatory cells or their breakdown products, including fibrin, Curschmann spirals, Charcot-Leyden crystals, eosinophils, other inflammatory cells, and mold hyphae.[2,10] Examination of the airway tissue itself demonstrates infiltration of the bronchial walls with eosinophils, lymphocytes, and plasma cells.[5] In more severe or chronic cases, proximal bronchiectasis, especially of the upper lobes, will be evident.[5]

Skin Testing

Because ABPA features an exaggerated IgE-mediated immune response to the presence of *A fumigatus,* a positive immediate skin test result (type 1 reaction) is seen as essential for diagnosis in all patients. Various studies consider a positive skin test finding to be a wheal 4 mm or larger, while others accept a wheal of 3 mm or larger.[6] This disagreement over the appropriate wheal size likely contributes to regional differences in reported ABPA prevalence. When the skin test is properly performed in patients with ABPA, an immediate wheal and erythema begins within 1 minute, reaches a maximal size in 10 to 20 minutes, and then resolves within 1 to 2 hours.[5,10] A delayed reaction (type 3) can also be seen 4 to 8 hours later and can occur in 33% of patients.[5,10] As with any type of skin testing, precautions need to be taken to ensure accurate testing, such as avoidance of antihistamines and steroids, which could lead to a diminished wheal and flare reaction, prior to testing. As stated earlier, *A fumigatus* is a ubiquitous organism, and many people have been sensitized to it. Approximately 20% to 25% of people with asthma are skin test positive to this mold,[6,7,18] as are 60% of patients with CF.[6–9,18]

Consequently, a positive skin test result by itself is insufficient to establish the diagnosis. On the other hand, a properly performed skin test with negative results makes the diagnosis highly unlikely.[5]

Serologic Testing

Serum IgE is a key marker of ABPA, both in helping to make the diagnosis as well as assessing for exacerbations. Total serum IgE is markedly elevated in cases of ABPA, with levels often greater than 1,000 IU/mL in untreated individuals. Lower levels (200–500 IU/mL) in patients with CF can be suggestive of ABPA, and the test should be repeated in 1 to 3 months to assess for persistent elevation. Repeated testing of serum IgE levels ideally should be performed while the patient is not being treated with steroids.[6] Decreasing IgE levels are a good indication of effective therapy, with levels dropping 35% to 50% within several days of instituting therapy.[10] Doubling of baseline levels is seen in relapses of ABPA. While most patients with ABPA have elevated IgE levels, a small subset may have normal IgE levels despite obvious ABPA. This is thought to be secondary to IgE isotype switching.[9]

IgE and IgG antibodies specific to *Aspergillus* are also useful diagnostic tests. In particular, IgE-specific antibodies are very sensitive markers for ABPA.[14] IgG-precipitating antibodies to *Aspergillus* antigens, although a less sensitive test and highly dependent on the antigens used in the assay, are also useful if positive (although a negative study finding does not eliminate the diagnosis).[10]

Eosinophilia is another nonspecific blood test finding used in making the diagnosis of ABPA. Patients with ABPA often have an elevated eosinophil count of greater than 1,000 cells/µL.

Culture

Allergic bronchopulmonary aspergillosis represents a hypersensitivity reaction to *A fumigatus,* which colonizes the airways of affected patients. Accordingly, a sputum sample can often yield *A fumigatus* on culture. Because colonization does not always lead to hypersensitivity, a positive sputum culture is not diagnostic for ABPA.[14]

Radiologic Studies

Abnormalities on chest radiographs are often seen in active cases of ABPA.[5,10] Transient or fixed pulmonary infiltrates are the classic finding. Central bronchiectasis may also be detected. Large bronchial mucus plugs are a pathologic finding of ABPA and manifest themselves on chest radiographs as “finger in glove” opacities or “toothpaste shadows.” Tram lines (fine parallel lines radiating from the hila) are another common radiologic finding of ABPA. These infiltrates often improve or resolve with appropriate therapy.[6,19]

Chest computed tomographic (CT) scans provide more detail than plain radiographs, but this extra detail is not always needed for diagnosis. Computed tomographic scans demonstrate the central bronchiectasis of ABPA, which can be varicose, cylindrical, or cystic in nature, with the varicose and cystic forms typically seen in ABPA.[14] Mucoid impaction can be seen as high-attenuation mucus plugs. The sine qua non of ABPA on CT scans is central bronchiectasis and peripheral tapering of the bronchi.[10,19] Other findings include centrilobular nodules and tree-in-bud opacities.

Pulmonary Function Testing

Pulmonary function testing demonstrates obstructive airway disease.[10] This is a nonspecific finding, however, because asthma and CF by themselves manifest as obstructive airway disease on pulmonary function tests; however, a significant decline in pulmonary function should raise concern of ABPA, particularly if usual interventions are not effective.

Diagnostic Criteria

Because there is no single diagnostic test for ABPA, various authors use different criteria to determine the diagnosis. This makes for difficulty in conducting epidemiologic studies as well as comparing various treatment regimens. In 2003, a consensus statement was created to guide the physician in diagnosing ABPA.[6] Algorithms were created for diagnosis (**Figure 9-2**) and determining the occurrence of an exacerbation.[10]

The criteria for diagnosing classic ABPA are listed in **Box 9-1**. The first 5 criteria should be present.[6,11,19]

In patients with CF, 5 criteria are present in classic cases (**Box 9-2**).[4,6,11] Because all 5 criteria are not always present, minimum criteria for diagnosing ABPA in patients with CF have been established (**Box 9-2**).[6] In assessing for these criteria, the physician must make sure that ABPA is the cause of the problem rather than the symptoms representing an exacerbation of the underlying asthma or CF. This can be quite challenging because of the large degree of overlap in these conditions. Confusion can arise both when determining the initial diagnosis and when determining if an exacerbation of ABPA (vs asthma or CF) is occurring. Therefore, referral to a pulmonary or allergy specialist should be considered when the diagnosis of ABPA is suspected.

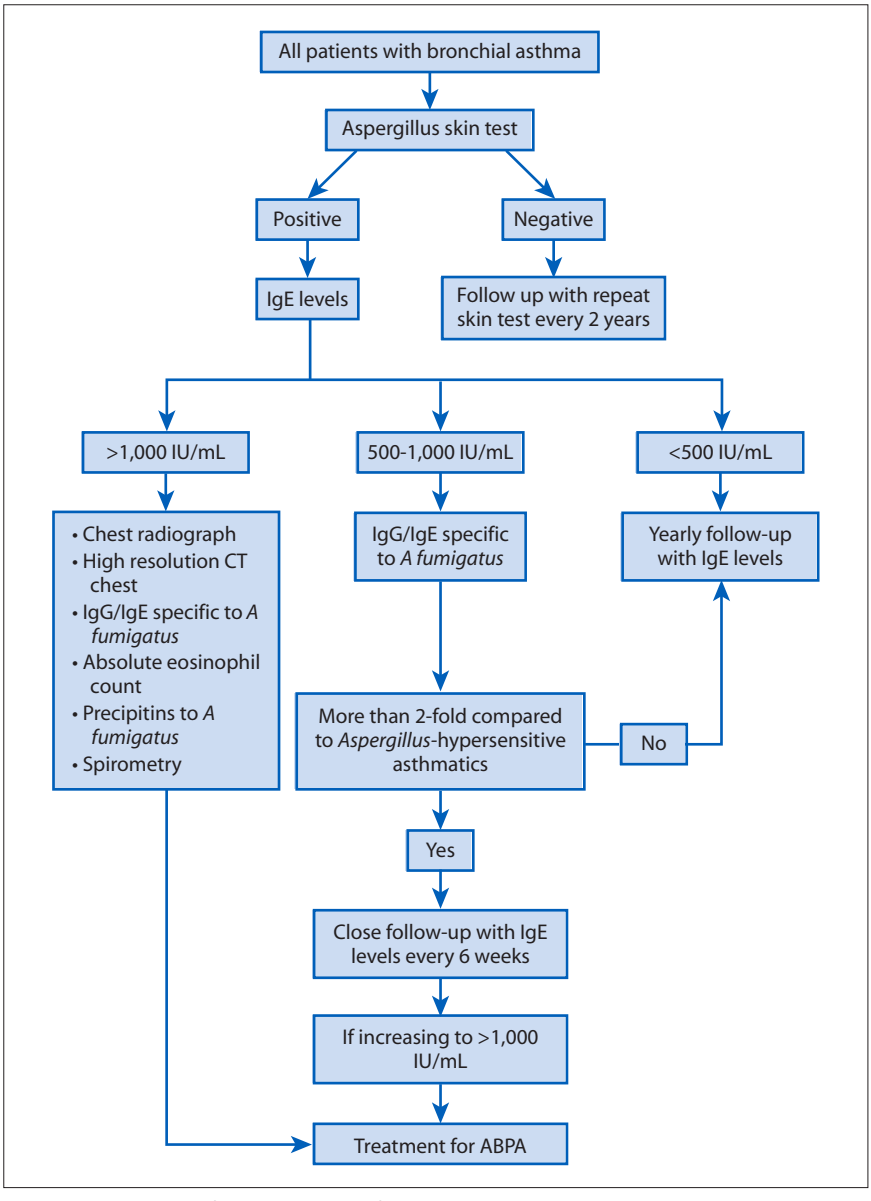


Figure 9-2. Algorithm for the diagnosis of allergic bronchopulmonary aspergillosis (ABPA).

Abbreviations: CT, computed tomography; Ig, immunoglobulin.

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Box 9-1

Criteria for Diagnosing Classic Allergic Bronchopulmonary Aspergillosis in Patients With Asthma[a]

1. **Underlying diagnosis of asthma**
2. **Proximal (central) bronchiectasis**
3. **Positive skin test to *Aspergillus fumigatus***
4. **Elevated total immunoglobulin (Ig) E (>417 IU/mL or >1,000 ng/mL)[b]**
5. **Elevated IgE and/or IgG to *A fumigatus***
6. **Infiltrates on chest radiograph**
7. **Positive precipitins to *A fumigatus***
8. **Eosinophilia**
9. **Sputum containing *A fumigatus***

[a]The first 5 criteria should be present.

[b]Other literature suggests >1,000 IU/mL or 2,400 ng/mL.[10]

Staging of ABPA has been developed and can be used in patients with asthma,[10,11,20] though it is not used in patients with CF.[6] Of note, one does not need to pass from stage 1 through stage 5 directly; rather, there can be transitioning back and forth between stages 1 through 3. Staging is summarized in **Table 9-1**.[19]

To help determine if ABPA is developing or if an exacerbation is occurring, serial monitoring of IgE levels is advisable, especially in patients with CF. Annual measurement of IgE levels should be performed. In patients with no history of ABPA, if the IgE level is greater than 500 IU/mL, a more formal evaluation for ABPA should be undertaken, including skin testing or IgE-specific testing for *Aspergillus*.[6,11] If the test results are positive, a diagnosis of ABPA can be considered using the minimal criteria outlined in **Box 9-2**. If IgE levels are lower (200–500 IU/mL) and a diagnosis of ABPA or a flare-up is still being entertained, further diagnostic tests (skin testing for *Aspergillus,* IgE and/or IgG specific for *Aspergillus,* precipitins, chest radiographs) should be considered.

Box 9-2

Diagnostic Criteria for Allergic Bronchopulmonary Aspergillosis (ABPA) in Patients With Cystic Fibrosis (CF)

Classic Diagnostic Criteria

1. Acute or subacute clinical deterioration (cough, wheeze, and other pulmonary symptoms) not explained by another etiology
2. Serum total immunoglobulin (Ig) E levels >1,000 IU/mL
3. Immediate cutaneous reactivity to *Aspergillus* or presence of serum IgE antibody to *Aspergillus fumigatus*
4. Precipitating antibodies to *A fumigatus* or serum IgG antibody to *A fumigatus*
5. New or recent abnormalities on chest radiograph or chest computed tomographic (CT) scan that have not cleared with antibiotics and standard physiotherapy

Minimal Diagnostic Criteria

1. Acute or subacute clinical deterioration (cough, wheeze, and other pulmonary symptoms) not explained by another etiology
2. Total serum IgE levels >500 IU/mL (if total IgE level is 200–500 IU/mL, repeat testing in 1 to 3 months is recommended)
3. Immediate cutaneous reactivity to *Aspergillus* or presence of serum IgE antibody to *A fumigatus*
4. One of the following: (1) precipitins to *A fumigatus* or demonstration of IgG antibody to *A fumigatus* or (2) new or recent abnormalities on chest radiograph or chest CT scan that have not cleared with antibiotics and standard physiotherapy

Screening for ABPA in Patients With CF

1. Maintain a high level of suspicion for ABPA in patients with CF.
2. Determine the total serum IgE levels annually. If the total serum IgE level is >500 IU/mL, perform *A fumigatus* skin test or use an IgE antibody to *A fumigatus*. If results are positive, consider diagnosis based on minimal criteria.
3. If the total serum IgE level is 200 to 500 IU/mL, repeat the measurement if there is increased suspicion for ABPA and perform further diagnostic tests (immediate skin test reactivity to *A fumigatus,* IgE antibody to *A fumigatus, A fumigatus* precipitins, or serum IgG antibody to *A fumigatus* and chest radiography).

Adapted from Stevens DA, Moss RB, Kurup VP, et al. Allergic bronchopulmonary aspergillosis in cystic fibrosis—state of the art: Cystic Fibrosis Foundation Consensus Conference. *Clin Infect Dis.* 2003;37(suppl 3):S225–S264, by permission of the Infectious Diseases Society of America.

Table 9-1. Staging of Allergic Bronchopulmonary Aspergillosis

Stage	Description	Radiographic Infiltrates	Total Serum IgE
I	Acute	Upper lobes or middle lobe	Sharply elevated
II	Remission	No infiltrate and patient off prednisone for >6 months	Elevated or normal
III	Exacerbation	Upper lobes or middle lobe	Sharply elevated
IV	Corticosteroid-dependent asthma	Often without infiltrates, but intermittent infiltrates might occur	Elevated or normal
V	End stage	Fibrotic, bullous, or cavitary lesions	Might be normal

Abbreviations: CT, computed tomography; IgE, immunoglobulin E; PFT, pulmonary function test.

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Therapy

Treatment for ABPA is directed at modulating the Th2-mediated immune response to *A fumigatus.* While several treatment modalities have been used, steroids appear to be the most effective at downregulating the hyperimmune reaction. Steroids are thought to work by inhibiting phospholipase A2 activity and arachidonic acid metabolism, thus diminishing chemotaxis and tissue infiltration of inflammatory cells. This results in a decrease in IgE levels, lessened eosinophilia, and clearing of pulmonary infiltrates.[6]

Although a number of different regimens are reported, they have several features in common, including aggressive treatment for the first couple of weeks of therapy, slow tapering of the steroid dose over the next several weeks to months, and a universal improvement in the patient's clinical course.[6,14] Immunoglobulin E levels, in general, quickly decrease by 35% to 50% over the first few weeks of therapy.[10,11,19] Infiltrates on chest radiographs resolve, or at least improve, over the first 1 to 2 months of therapy. Pulmonary function (particularly FEV_1) improves during this time.

The 2003 consensus statement recommends the following steroid dosing schedule: prednisone at 0.5 to 2.0 mg/kg/d (with a maximum dose of 60 mg/d) for 1 to 2 weeks, followed by tapering to every-other-day dosing for 1 to 2 weeks, and then tapering the dose over the next 2 to 3 months as clinically able.[6] Dose elevation might be needed if symptoms start to worsen. Often, increasing the steroid dose back to the previously effective dosage will bring symptoms under control. Serial IgE levels and follow-up chest radiographs are useful for monitoring the progress of the treatment plan.

Steroids treat the patient's inflammatory burden but do nothing to decrease the antigen load to which the patient's immune system is being exposed. Various antifungal regimens have been used to eradicate, or at least decrease, the disease burden of *A fumigatus.* Unfortunately, these regimens have met with limited success. Only a few studies have been attempted, and most were small in number.[21,22] The most successful agent used has been itraconazole. This drug has been found to be effective as a steroid-sparing agent.[23] It acts by inhibiting ergosterol synthesis in the fungal cell membrane, which decreases the organism's growth. In combination, itraconazole and oral steroids are useful at treating exacerbations or relapses of ABPA.[6,21,22]

As with oral steroids, several dosing regimens have been published for antifungal agents, though they have similar limitations to those discussed in the steroid studies. The 2003 consensus statement[6] recommends itraconazole at 5 mg/kg (up to 200 mg/dose) once per day. If more than 200 mg/d is indicated, the dose should be split into a twice-per-day schedule (with a maximum dose of 400 mg/d). Treatment with itraconazole is typically continued for 3 to 6 months or longer if symptoms persist or IgE levels remain elevated. A search for and elimination of continued exposure to *Aspergillus* may be helpful in patients with persistently high IgE levels.

Itraconazole has many adverse effects as well as several drug-drug interactions. Hepatic toxicity is problematic, so close monitoring of liver function is warranted. Liver function tests should be obtained before starting therapy and then repeated after 1 month of treatment. Liver function also should be monitored every 3 to 6 months while the patient is receiving therapy or if any liver-related toxicity appears. Levels should also be checked if there is no clinical response to therapy, if there are possible drug-drug interactions, or if there are concerns regarding poor drug absorption or poor adherence to the medication regimen.[6]

Common side effects of itraconazole include gastrointestinal upset, fever, rash, headaches, dizziness, and fatigue. Concomitant use of drugs that lower stomach acid (such as histamine-2 blockers or proton pump inhibitors) can decrease absorption. Taking the medication with an acidic drink such as orange juice may aid absorption. Grapefruit juice, however, should be avoided because it interferes with the liver's CYP3A4 enzyme, which can have an effect on itraconazole metabolism.[6] The treatment protocols presented in the consensus statement are summarized in **Table 9-2**.[6]

Table 9-2. Treatment Protocol for Allergic Bronchopulmonary Aspergillosis (ABPA)

Treatment, Factor	Explanation
Corticosteroids	
Indications	All patients except those with steroid toxicity
Initial	0.5–2.0 mg/kg/day po prednisone equivalent, maximum 60 mg/day, for 1–2 weeks
Begin taper	0.5–2 mg/kg/day every other day for 1–2 weeks
Taper off	Attempt to taper off within 2–3 months
Relapse	Increase corticosteroids, add itraconazole, taper corticosteroids when clinical parameters improve
Itraconazole	
Indications	Slow or poor response to corticosteroids, relapse, corticosteroid-dependent, or corticosteroid toxicity
Dosing	5 mg/kg/day, maximum dose 400 mg/day po unless itraconazole levels determined; bid dosing required
Duration	3–6 months
Monitor	Liver function tests for all cases; itraconazole serum concentrations if concern of adequate absorption, lack of response, possible drug- drug interaction; serum concentrations of concomitant drugs with potential for drug-drug interaction
Adjunctive therapy	
Inhaled corticosteroids, bronchodilators, other anti-asthma drugs	No evidence for use in ABPA; may be used for the asthma component of ABPA
Environmental manipulation	Attempt to search for and modify mold spore exposure in refractory cases

Abbreviations: bid, twice a day; po, orally.

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Other medications have been used, with anecdotal evidence of improvement. Several case reports using omalizumab (a humanized anti-IgE monoclonal antibody) have been published demonstrating clinical improvement, fewer respiratory exacerbations, reduced need for oral steroids, and lower IgE levels. These studies, however, were observational in design with low numbers of enrolled patients. No large, well-controlled study has been completed to date. Case reports assessing the efficacy of other medications (such as inhaled amphotericin as well as voriconazole and posaconazole) have been published, with preliminarily promising results; however, larger studies confirming their efficacy remain to be undertaken. For now, oral steroids, with the potential addition of itraconazole, remain the standard of care.[24]

In addition to the use of oral steroids and itraconazole, supportive care for the underlying disease processes (asthma and CF) is needed. Long-term anti-inflammatory therapy for asthma is required. Although use of inhaled steroids (such as budesonide or fluticasone) has been attempted to treat the ABPA, with questionable success, their use in treating the underlying asthma is not questioned. Supportive care for CF is required and includes nutritional support (pancreatic enzymes and vitamins), aggressive airway clearance (mucolytic agents and chest physiotherapy), and treatment with suppressive antibiotics (inhaled tobramycin or aztreonam). Oral or intravenous antibiotics are warranted if a pulmonary exacerbation is occurring. Distinguishing between a classic CF exacerbation and an ABPA flare can be difficult. If there is no overwhelming evidence that the symptoms are due to an ABPA flare, then aggressive use of antibiotics is indicated. If the patient's condition does not improve, then an ABPA flare needs to be addressed and appropriately treated.

Prognosis

Allergic bronchopulmonary aspergillosis is a chronic and recurrent disease that can often mimic the asthma and/or CF with which it is frequently associated. While therapy is available to successfully treat ABPA, it is not curative and may lead to significant adverse effects because of the long-term therapy often required. When ABPA is aggressively treated early in its course, the chance is minimized that the disease will progress to end-stage fibrosis.[5,14] Lifelong monitoring is required to prevent complications and achieve the most beneficial outcome.

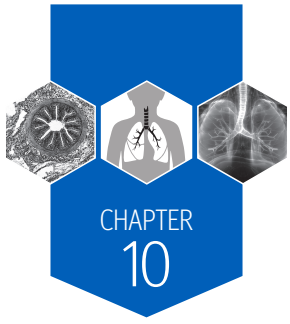
key points

- The physician should consider the possibility of ABPA in patients with poorly controlled asthma or CF.
- Suspect ABPA *in children with asthma* when asthma is under poor control despite the patient's being on an appropriate treatment plan.
  - Infiltrates are seen on chest radiography.
  - Atopic dermatitis is present.
  - Elevated IgE levels are present.
- Suspect ABPA *in patients with CF* who have
  - increasing numbers of pulmonary exacerbations.
  - unexplained deterioration in pulmonary function.
  - new onset of wheezing.
  - increasing IgE levels measured at annual studies.
- No single diagnostic test is sufficient to establish the diagnosis. Many patients might have positive ABPA-related test results but do not have the illness, while a smaller number of patients might have negative study findings and have the illness. History, physical examination findings, laboratory study findings, and clinical judgment are needed to establish the diagnosis.
- Because of the challenges inherent in diagnosing ABPA and its overall low prevalence, all suspected cases are best evaluated and managed by a pediatric pulmonologist.
- Annual screening for ABPA with yearly measurement of IgE levels is advisable. IgE levels should also be routinely measured during exacerbations of CF that require intravenous antibiotics to make sure an ABPA exacerbation is not being overlooked.
- Therapy consists of
  - Oral steroids (prednisone)
  - Antifungal therapy (itraconazole)
  - Supportive care
    - In children with asthma: chronic anti-inflammatory therapy
    - In children with CF: nutritional support, airway clearance, appropriate use of antibiotics

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Hypersensitivity Pneumonitis

Katharine Kevill, MD, MHCDS, FAAP

CASE REPORT 10-1

A 12-year-old boy presented to the primary care clinic with a 3-month history of cough and shortness of breath when he played soccer. In addition, he had lost 3.18 kg (7 lb) during this time and had had intermittent fevers. The physical examination revealed tachypnea with bibasilar crackles and oxygen saturation of 89%. He was admitted to the hospital and treated with antibiotics. His symptoms improved, and he returned home. Within a short time, his cough and dyspnea recurred, and he was referred to a pulmonologist. Pulmonary function testing revealed a restrictive pattern, and chest radiographs showed increased interstitial markings. An in-depth history revealed that his symptoms started shortly after the family had moved into a house with pigeons nesting in the garden.

Introduction

Hypersensitivity pneumonitis (HP) is a complex disorder with variable clinical presentation, intensity of symptoms, and natural history. It results from immunologically mediated inflammation of the lung parenchyma in response to an array of inhaled antigens.[1] Hypersensitivity pneumonitis is also known as *extrinsic allergic alveolitis*[1] and has been described as a "group of granulomatous, interstitial, bronchiolar, and alveolar-filling pulmonary diseases."[2] Initially, HP was thought to be an adult disease resulting from occupational exposure to environments such as moldy hay (*farmer's lung*), moldy maple bark (*maple bark stripper's lung*), and pigeon breeding. Hypersensitivity pneumonitis was first reported in children in 1967 as *pigeon breeder's lung*. The children who were affected had severe interstitial pneumonitis and presented with chronic symptoms of cough, progressive dyspnea, and weight loss, as well as acute symptoms of fever and chest pain. The children had had prolonged exposure to pigeons.[3] In the decades since, no universally accepted definition of HP has emerged, and its mechanism remains incompletely described. Hypersensitivity pneumonitis has continued to be a rare diagnosis in pediatrics. However, the incidence of HP diagnosis

in children could increase sharply in the future. It has been described as a manifestation of e-cigarette or vaping use–associated lung injury, a problem tracked by the Centers for Disease Control and Prevention as an outbreak in the summer of 2019.[4–6]

Clinical Manifestations

The clinical and pathological manifestations of HP vary with the chronicity of symptoms, with the intensity of the exposure to the offending antigens, and with the host response to the antigen. It has been described in acute, chronic, and recurrent forms.[1,7] In the pediatric literature, HP is described via a series of case reports, many of which describe children who have had symptoms for months or years. Regardless of the duration of symptoms, most adults and children with an ultimate diagnosis of HP present with symptoms of cough, dyspnea, decreased exercise tolerance, and fever. Fatigue and weight loss are common. Crackles are heard during examination in most patients with tachypnea and hypoxemia, and in chronic cases clubbing of the fingers is seen. Wheezing may be heard. Hemoptysis and pneumothorax have also been described at presentation in children. The severity of disease can vary from asymptomatic to severe, leading to pulmonary fibrosis and even death.

Most children with HP have abnormalities seen on plain chest radiographs, often with reticulonodular shadowing or increased interstitial markings suggestive of interstitial lung disease.[1] High-resolution computed tomography of the chest is more sensitive than plain radiography for detecting parenchymal lung disease. Pediatric case reports have described ground-glass opacities, centrilobular nodules, and air trapping,[8–12] as well as honeycombing in a case diagnosed late in the disease.[13]

Investigators in most pediatric cases with pulmonary function studies describe restrictive lung disease manifested as decreased lung volumes and often decreased diffusing capacity for carbon monoxide (D_{LCO}). Investigators in 2 large case series of HP that included adults and children found a restrictive pattern in the majority of patients (53% to 77%), with a substantial minority (9% and 13%) of patients having a purely obstructive pattern[14,15]; 26% of patients had air trapping as indicated by an increased residual volume; and 85% had a decreased D_{LCO}.[15] Reversible pulmonary artery hypertension has been described in some children with HP.[11,16] See **Table 10-1** for a summary of common and uncommon symptoms.

Table 10-1. Occurrence of Signs and Symptoms in Patients With Hypersensitivity Pneumonitis

Characteristic	Occurrence			
	Usually	**Often**	**Sometimes**	**Late in Disease**
Symptoms	Cough Dyspnea Fatigue	Weight loss Fever	Hemoptysis	—
Signs	Crackles Hypoxemia	Tachypnea Clubbing	Wheezing	—
Pulmonary function	Restrictive pattern only Decreased diffusing capacity for carbon monoxide	—	Obstructive pattern only Mixed obstructive and restrictive pattern	—
Plain radiography findings	Reticulonodular pattern Increased interstitial markings	—	—	—
High-resolution computed tomography of the chest findings	Nodules in a centrilobular distribution	—	Ground-glass opacities	Honeycombing Traction bronchiectasis Lobar volume loss
Other complications	—	—	Pulmonary artery hypertension Congestive heart failure Pneumothorax	—

Epidemiology and Etiology

Few articles address the epidemiology of HP in children. It is considered a rare, but underreported, condition. Most information about pediatric HP comes from case reports in small series of patients, which included approximately 95 cases reported between 1960 and 2005.[1] Although most pediatric cases of HP have been reported in school-age children, it has also been reported in infants and in young children.[17,18] Investigators in a retrospective Danish study identified children with HP from a national cohort of children with interstitial lung disease, all of whom underwent lung biopsy; they found HP in 26% of the cohort of 73 pediatric patients with interstitial lung disease, for a point prevalence of 4/1,000,000 Danish children.[19] Investigators in a German study found the incidence of new cases of diffuse parenchymal

lung disease in children to be 1.32 new cases per 1 million children per year; HP was the final diagnosis in 11 of the 38 cases (29%) described.[20]

The epidemiology of HP reported in the general population varies greatly with age, location, and occupation. A claims-based cohort in the United States that included 150 million people had 7,498 cases of HP over a 10-year period, for an annual incidence of 1.28 to 1.94 cases per 100,000 individuals; the prevalence increased with age from 0.95 per 100,000 in the 0- to 9-year-old age group to 11.2 per 100,000 in the 65 years or older group.[21] A retrospective Danish study's results showed an incidence of interstitial lung disease of 4.1 per 100,000 inhabitants per year, with HP being 7% of those cases.[19] By contrast, investigators in a prospective study identified 1,084 new cases of interstitial lung disease from 19 Indian cities and found final diagnoses of HP in 47% of the cases.[22] In England and Finland, the prevalence of farmer's lung has been estimated to range from 10 to 200 per 100,000 inhabitants.[23]

More than 200 antigens are known to provoke HP. The antigens are often tied to occupational exposure, with the name of the disease reflecting the profession or hobby of the patient: farmer's lung, bird fancier's lung, malt worker's lung, hot tub lung, wind instrument alveolitis.[24] Antigens can be divided into 6 categories—bacteria, fungi, mycobacteria, proteins, chemicals, and metals.[24,25] However, the causal antigen is not identified in 30% to 60% of cases. Reported cases of HP related to e-cigarette use highlight the difficulty of pinpointing a specific antigen.[5,6] In pediatric reports, most cases are attributed to proteins in the serum or droppings of birds, including pigeons, doves, parakeets, budgerigars, canaries, and cockatoos. In these cases, duration of exposure ranged from weeks to years, with location of exposure often within the house itself or a nearby pigeon coop. A source of HP in children can be exposure to a variety of molds, especially *Aspergillus* species, found in locations such as hay in a barn,[26] grain dryers kept near the home on a farm,[17] a basement shower,[8] and standing water under the house.[10]

The immunologic pathogenesis of HP is complex and remains incompletely understood. In 1967, Stiehm et al[3] described features of both immune complex–mediated (type III) and T-cell–mediated (type IV) reactions in their cohort. There is no evidence of a role for either immediate-type hypersensitivity (type I) or cytotoxic-mediated (type II) allergic reactions in the pathogenesis of HP. People with atopic tendencies are not affected more frequently than those without atopic tendencies.[27,28] The incidence of HP is lower in smokers than in nonsmokers,[29] and current cigarette smokers had lower levels of serum immunoglobulin (Ig) G against pigeon antigens than did pigeon fanciers who did not smoke.[30] The inhibitory effect of nicotine on alveolar macrophages has been suggested as a potential mechanism.[29] A key unanswered question regarding the pathogenesis of HP is why relatively few individuals develop the disease given the universal presence of the instigating

antigens. Selman et al[31] depicted a 2-hit hypothesis in which "antigen exposure acts as the inducing factor, and genetic or environmental factors act as promoting risk factors" (**Figure 10-1**).

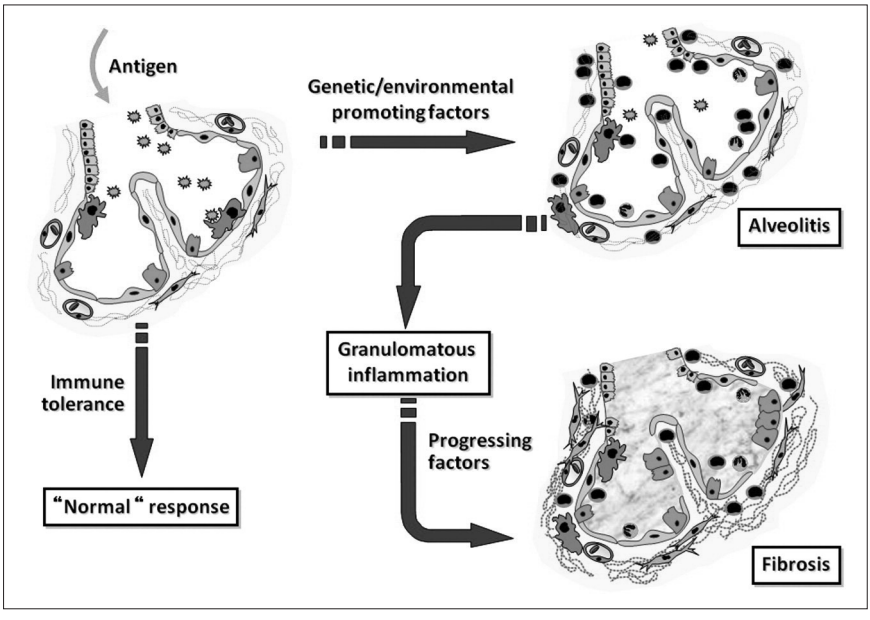


Figure 10-1. Proposed mechanisms in the pathogenesis of hypersensitivity pneumonitis. Most exposed individuals develop an immune tolerance, and the antigen inhalation may result at most in a mild increase of local lymphocytes, without clinical consequences. The coexistence of genetic or environmental promoting factors provokes the development of an exaggerated immune reaction that results in marked lung inflammation. The generation of the granulomatous inflammation requires, among others, the expression of Th1 cytokines, including tumor necrosis factor-α, IL-12, and interferon-γ, as well as a toll-like receptor 9–mediated dendritic cell response, which is believed to promote Th1 skewing and prevent Th2 skewing during the development of the adaptive immune response. Subsequently, in the presence of progressing factors (ie, further exposure) or genetic predisposition, critical immunopathological changes occur in the lung microenvironment.

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Differential Diagnosis and Evaluation

Diagnosing HP in children can be difficult because it is a relatively rare disease with variable manifestations and environmental triggers. Many of the signs and symptoms overlap with those of a range of infectious and respiratory illnesses (**Box 10-1**). Diagnosis depends on a high index of suspicion. The diagnosis of HP should be entertained in any child with fulminant respiratory symptoms with hypoxemia and restrictive physiology that resolves in the hospital and then recurs after discharge, prolonged respiratory symptoms of unknown cause, restrictive lung disease or interstitial lung disease without a clear cause, or a history of vaping.

Box 10-1

Differential Diagnosis of Hypersensitivity Pneumonitis in Children

Infectious
- Bacterial pneumonia
- Blastomycosis
- Brucellosis
- Coccidioidomycosis
- Histoplasmosis
- HIV infection
- *Legionella* infection
- *Mycoplasma* infection
- Psittacosis
- Tuberculosis

Respiratory
- Allergic bronchopulmonary aspergillosis
- Asthma
- Bronchiolitis obliterans organizing pneumonia
- Cystic fibrosis
- E-cigarette or vaping use–associated lung injury
- Interstitial lung disease of childhood of unknown cause
- Recurrent pneumonia

Other
- Immune deficiency
- Malignancy
- Sarcoidosis
- Systemic lupus erythematosus

There is no definitive test for HP. Multiple diagnostic criteria have been proposed, but currently there is no universally accepted definition.[1,7,32] The 4 major criteria Richerson et al[7] detailed are among the more commonly used: (1) history and physical examination findings and pulmonary function findings indicate interstitial lung disease, (2) radiographic findings are consistent with HP, (3) there is exposure to a recognized cause, and (4) there is antibody to the causative antigen. However, the causative agent is not always known. In a large case series, Hanak et al[14] did not identify the cause in 25% of cases of HP. A common practice is integration of the clinical, radiological, and histological findings by a multidisciplinary team that reaches a consensus. Algorithms have been proposed for subacute or chronic HP.[32,33] Uncommonly, HP has been diagnosed at explant in adult patients undergoing transplant for progressive interstitial lung disease.[34]

Given the prevalence of both respiratory infections and asthma in children, it is not surprising that many children ultimately receiving a diagnosis of HP are first treated with antibiotics or asthma medications. Recurrence of symptoms or failure to improve with time and

treatment differentiates HP from most acute respiratory illnesses and from asthma. Restrictive lung disease, clubbing, and reduced D_{LCO} are frequent findings in children with HP but rare in those with asthma. A prolonged course of illness, weight loss, and fevers may prompt an evaluation for tuberculosis, HIV, malignancy, or immune deficiency. A false-positive enzyme-linked immunosorbent assay for HIV has been reported in a boy with symptoms of cough, progressive dyspnea, and weight loss who eventually had HP diagnosed.[35] Cystic fibrosis and allergic bronchopulmonary aspergillosis (ABPA) are often considered in these patients. Sweat chloride quantitation and genetic studies permit evaluation for cystic fibrosis. Allergic bronchopulmonary aspergillosis occurs primarily in those with asthma or cystic fibrosis and is always associated with allergen-specific IgE to *Aspergillus* detectable with an allergy skin test or an in vitro blood test.[36] Although a positive test for precipitins to *Aspergillus fumigatus* can be found in both HP and ABPA, eosinophilia is present in ABPA but not in HP. Allergic bronchopulmonary aspergillosis typically has a pattern of obstructive lung disease in contrast to that of HP, which usually manifests as restrictive lung disease. The sequela of ABPA is bronchiectasis of the proximal airways, whereas long-standing or recurring HP can lead to pulmonary fibrosis.

Evaluation of any patient suspected of having HP should include a detailed history, with specific inquiries about exposure to known sources of HP, such as birds, hay, and e-cigarettes. A thorough physical examination is important, with particular evaluation for weight loss, tachypnea, hypoxemia, crackles, and clubbing. Pulmonary function studies, including spirometry, total lung volumes, and D_{LCO} should be performed if the child is able to cooperate. A chest radiograph will usually demonstrate findings consistent with interstitial lung disease. High-resolution computed tomography is more sensitive, but not specific. Depending on the clinical presentation, one may choose to evaluate the patient for pulmonary artery hypertension, which has been described in HP.[12,16]

Laboratory evaluation for HP may reveal neutrophilia or lymphopenia after acute exposure, but eosinophilia is not expected.[7] Elevated levels of IgG, IgM, or IgA subtypes; erythrocyte sedimentation rate; or C-reactive protein levels occasionally occur. These findings are not specific and are consistent with acute and chronic inflammation. An elevated IgE level does not indicate HP because an elevated IgE level accompanies a type I allergic process, whereas HP is characterized by type III inflammation and an elevated IgG level.[37] Positive precipitating antibodies specific to the suspected agent confirm adequate exposure to the agent to generate a humoral immune response and are supportive of a diagnosis but do not indicate disease.[7] People who have been exposed but do not have symptoms may have positive precipitins to a given antigen.[30,38] Although commercial tests for common serum precipitins

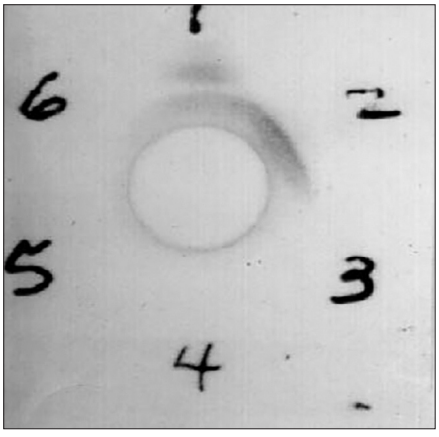


Figure 10-2. Precipitin test. The patient's serum is in the center well. The peripheral wells contain (1) pigeon droppings, (2) pigeon serum, (3) chicken serum, (4) canary serum, (5) parakeet serum, and (6) parrot serum. Wells 1 and 2 are positive.

are available (**Figure 10-2**), negative test results do not rule out the diagnosis of HP. Commercial tests have been inaccurate in some cases and may not include the source of exposure.[9,10] In 2017, Rouzet et al[39] identified 2 biomarkers of bird fancier's lung that discriminate between those who have been exposed and those with disease with good sensitivity and specificity, and they proposed using these markers for future diagnosis.

When the evaluation results provide a high probability of an HP diagnosis,[40] proceeding to bronchoscopy or lung biopsy is not needed. When bronchoscopy is performed, the bronchoalveolar lavage fluid of patients with HP demonstrates lymphocytosis.[10,15,41] The cellular profile may depend on the timing of exposure to the antigen, with CD8 cells predominating after recent exposure.[15] The lung biopsy histological findings in children[3,12,13] are consistent with the characteristic findings of bronchiolocentric interstitial inflammation, composed mostly of lymphocytes.[1] Interstitial nonnecrotizing granulomas are found in many cases.[1,42] In individuals with interstitial lung disease of unknown cause, lung biopsy results can be essential for diagnosing HP (see **Case Report 10-2**).[8,42]

Provocation tests, in which the suspected antigen is administered in an aerosolized form, have been used to aid in diagnosing HP and to confirm the environmental trigger. After the exposure, the patient is observed for recurrence of symptoms. The use of this type of test is limited by lack of standardized antigens, the possibility of contamination of the aerosol by nonspecific irritants, and the need to administer the test in a specialized center.[1] In some patients, purposeful exposure to the environment in question can be helpful diagnostically, as can a trial period during which the patient is not exposed to the suspected trigger.[7]

Treatment and Prognosis

The usual treatment for HP is removing the suspected antigen from the patient's environment. Corticosteroids are indicated for clinically significant symptoms. Outcomes in adults and children depend on cessation of exposure to the trigger. Studies document improvement after the exposure to the antigen in question was halted but continued or recurrent deterioration in respiratory

CASE REPORT 10-2

A 10-year-old boy presented with symptoms of fever, night sweats, chronic cough, and wheezing. No environmental history of exposure to birds, farm animals, or farm materials was obtained. Chest radiography and pulmonary function testing indicated restrictive lung disease. Commercial serum precipitin tests were negative. The boy had many features consistent with sarcoidosis, including restrictive lung disease, decreased diffusing capacity, increased angiotensin-converting enzyme levels, suggestive gallium scanning results, and a positive response to corticosteroids. Lung biopsy results revealed predominant lymphoid interstitial infiltrate with features that distinguished hypersensitivity pneumonitis from sarcoidosis. There was a noncaseating granuloma that was peribronchiolar rather than interstitial in location and composed of poorly organized aggregates of giant cells rather than the large, discrete granulomas characteristic of sarcoidosis. The lung biopsy results prompted further environmental evaluation and ultimately yielded discovery of the inciting antigen.

status when exposure continued.[8,43] Antigens can remain in the home even 18 months after removal of the source, and, in some cases, families have moved from their homes to halt exposure.[13,17] Prognosis ranges from complete resolution of symptoms[3] to death.[44] Risk factors for worse prognosis include pulmonary fibrosis documented at lung biopsy at the time of diagnosis,[45,46] increased levels of the chitinase-like protein YKL-40,[47] and coexisting autoimmune disease.[48] Patients who undergo lung transplant because of HP have a reduced risk of posttransplant death than do patients with idiopathic pulmonary fibrosis.[34]

Few studies address the efficacy of systemic corticosteroid treatment in HP. Available data suggest that corticosteroids hasten the recovery from acute HP but have no beneficial effect on long-term prognosis.[49,50] A case report describes clinical efficacy of inhaled corticosteroid for a patient's recurrent HP, but not for her initial presentation of HP, which was more severe than the recurrent episodes.[51]

There are no clinical trials that address the merits of treatment with corticosteroids for HP in children, in either the short or long term. Prednisone is the corticosteroid most frequently used, with treatment duration ranging from weeks to months. The usual starting dose would be 1 to 2 mg/kg for 2 weeks and subsequent doses depending on response. Monthly methylprednisolone has also been used, as well as other immunosuppressive drugs.[52] Investigators in a retrospective, single-center Danish study described the outcomes in 19 children with biopsy-confirmed HP who were not treated with a standardized protocol but who all were treated with monthly high-dose

intravenous methylprednisolone. Multiple lung function parameters, including FEV_1, FVC, total lung capacity, D_{LCO}, and the ratio of D_{LCO} to alveolar volume, improved in all children at 3 and 6 months of treatment.[19] In a cross-sectional, follow-up study of this cohort, 47% of 22 patients had a low lung clearance index, but 90% had normal spirometry results.[52]

key points

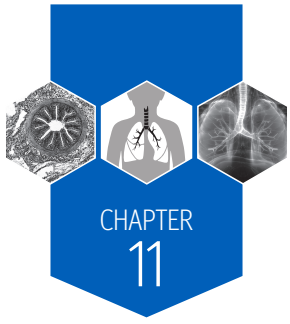
- Hypersensitivity pneumonitis is a complex disorder with variable manifestation.
- Consider a diagnosis of HP in any child with
  - Restrictive lung disease.
  - Interstitial lung disease without a clear cause.
  - Fulminant respiratory symptoms that resolve in the hospital and then recur.
  - Unexplained persistent respiratory symptoms or recurrent pneumonia.
  - Bronchiolitis obliterans organizing pneumonia without an underlying risk factor.
  - A history of vaping.
- Take an environmental history and consider an unknown or not yet described environmental trigger.
- Hypersensitivity pneumonitis is not mediated via IgE; normal IgE levels or negative results of a skin prick test to a specific antigen are not relevant for the diagnosis.
- If pediatric interstitial lung disease is without a clear cause, a lung biopsy may prove essential to ascertain the diagnosis.
- A timely HP diagnosis can have a substantial effect on outcomes.
  - Lack of diagnosis and continued exposure to the antigen can lead to end-stage lung disease from pulmonary fibrosis and even death.
  - Prompt diagnosis and removal from exposure to the antigen can result in complete recovery.
- Consider consultation with a pediatric pulmonologist in the evaluation of any child in whom HP is suspected or in any child treated for asthma whose symptoms do not improve as expected.
- Expect to see this diagnosis more often in the future.
  - The underdiagnosis of HP is likely to change as diagnostic criteria become more clear.
  - The epidemiology of HP may change with increased exposure of the pediatric population to inhaled antigens contained in e-cigarettes and other sources.

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CHAPTER 11

Eosinophilic Pneumonia

Peter H. Michelson, MD, MS

Introduction

Eosinophilia is found in a wide variety of respiratory illnesses, but *eosinophilic pneumonia* is a specific condition characterized primarily by infiltration of eosinophils into the lung parenchyma.[1,2] Eosinophilic pneumonia can be further divided into acute and chronic eosinophilic pneumonia based on the duration of symptoms and the response to therapy.[3,4] Although no specific causative agent has been determined, acute eosinophilic pneumonia (AEP) has been reported following exposures to multiple agents, including medications, industrial agents, high dust exposure, and tobacco smoke.[5] Environmental contaminants have been reported with AEP described in US military personnel in Iraq[6] as well as in rescue workers exposed following the September 11, 2001, terrorist attack on the World Trade Center.[7]

Case series of AEP suggest that more than 80% of patients present with acute onset fever, severe hypoxemia, dyspnea, and cough.[8] Diffuse pulmonary infiltrates are seen on chest radiography; high-resolution computed tomography (CT) scanning reveals ground-glass opacity in most patients.[9–11] In children, the onset of symptoms is rapid, with progression to respiratory failure requiring mechanical ventilation.[12] Since this condition so closely simulates acute respiratory distress syndrome, aggressive therapeutic interventions should be undertaken concurrently with the initial diagnostic steps.[5] Fluid stabilization, ventilatory support, and the initiation of broad-spectrum antibiotics are usually warranted. Bronchoscopy and bronchoalveolar lavage (BAL) can be used to document eosinophilia in a lower airway sample.[13,14]

Chronic eosinophilic pneumonia (CEP) is less commonly seen in pediatrics and differentiated by its female predominance (2:1 female to male ratio), older age of disease onset (mean age 45 years), and increased incidence of both asthma and atopy.[1,15–17] Symptoms of CEP are similar to AEP in presentation but progress more slowly, often extending months from the initial presentation. Bronchoalveolar lavage examination is also indicated to evaluate for CEP and has replaced open lung biopsy as the predominant diagnostic

procedure. If there is concern about associated extrapulmonary involvement, then the systemic eosinophilic syndromes need to be considered.[18]

Presentation

Patients with AEP predominantly present with acute onset fever, dyspnea, hypoxemia, and cough.[5,19] The age at presentation ranges from adolescence to young adult; the average onset of symptoms prior to diagnosis is approximately 4 days.[20] In addition to the acuity of presentation, the severity of the hypoxemia and the lack of a confirmed diagnosis of the respiratory distress are features of AEP. Pope-Harman et al proposed diagnostic criteria[14] that included (1) acute onset (< 7 days of symptoms); (2) fever; (3) bilateral infiltrates on chest radiograph; (4) severe hypoxemia (arterial P_{O_2} on room air ≤ 60 mm Hg); (5) lung eosinophilia; and (6) no other evidence of infection, hypersensitivity to drugs, or other known causes of acute eosinophilic lung disease. More recent recommendations, the modified Philit criteria, suggest "definite" AEP can be diagnosed by (1) acute respiratory illness of ≤ 1 month duration; (2) infiltrates on either chest radiograph or CT; (3) pulmonary eosinophilia, as demonstrated by either ≥ 25% eosinophils in BAL fluid or eosinophilic pneumonia on lung biopsy; and (4) absence of other specific eosinophilic lung diseases.[3,20] To assess for lung eosinophilia, bronchoscopy with BAL is needed to document a differential of ≥ 25%, which has been proposed to be one of the diagnostic criteria for AEP, as well as to confirm no other infectious etiology.[14,21,22] The approach to evaluation of AEP is shown in **Box 11-1**.

The age range at presentation for AEP has been reported with a mean of 30 years; patient series have reported pediatric patients, aged 15 to 20 years,[5] with a maximum reported age of 86 years. Presentations are typical across all age ranges with no consistent association of asthma and only an inconsistent history of atopy. Tobacco use has been commonly linked to AEP, with some studies reporting up to two-thirds of patients having a history of tobacco use, many with recent initiation of smoking. In considering the rate of tobacco usage contrasted with the rarity of AEP, a direct causative relationship is unlikely, but further investigation of this link is needed.[23] More likely, lung injury, perhaps enhanced by or associated with tobacco use, contributes to the development of AEP.[24] Case reports have linked e-cigarette use to AEP[25]; however, vaping-related acute lung injury (VpALI) and e-cigarette or vaping use-associated lung injury (EVALI) appear to be more frequently consistent with either a toxic inhalation injury or lipoid pneumonia.[26–28]

Outdoor exposures to dust and other triggers have been reported to result in AEP.[3] These exposures include tear gas, workplace renovations, fungal spores, and medications.[9] Triggers resulting in AEP have also included

firefighters exposed to debris and dust from the destruction of New York City's World Trade Center[7] and military personnel exposed to sand and other possible toxins while serving in the Middle East.[6] Similarities to hypersensitivity pneumonitis also need to be considered in the differential diagnosis, as similar exposures are noted, but the diagnostic criteria should differentiate between these 2 conditions.[25,29]

In contrast, CEP presents in a more progressive fashion over a period of months.[2] Symptoms at presentation include chest pain, dyspnea, and cough, with a history of atopy and asthma reported in as many as two-thirds of patients.[24] The mean age at presentation is in the fifth decade; there is a 2:1 female predisposition[9]; the majority of patients report little to no history of tobacco use; and relapse can occur in up to 50% of cases.[30]

Box 11-1

Algorithm for the Evaluation of Acute Eosinophilic Pneumonia

A. History

1. Previously healthy individual
2. Acute onset dyspnea
3. Recent outdoor activity with extensive dust exposure
4. Possible recent tobacco use

B. Presentation

1. Cough
2. Fever
3. Chest pain
4. Tachypnea
5. Tachycardia
6. Crackles on physical examination

C. Laboratory evaluation

1. Bilateral infiltrates on chest radiography
2. Computed tomography with ground-glass opacities
3. Room air $Pao_2 < 60$ mm Hg
4. Bronchoalveolar lavage eosinophilia ≥ 25%
5. Negative infectious workup

D. Diagnostic criteria

1. Acute onset of symptoms within 7 days of presentation
2. Fever
3. Bilateral infiltrates on chest radiography
4. Severe hypoxemia
5. Bronchoalveolar lavage or pulmonary eosinophilia
6. No other known cause of acute eosinophilia

E. Treatment

Systemic steroids

Diagnostic Testing

Across all series, chest radiography findings are consistent. Bilateral infiltrates with alveolar, interstitial, or mixed alveolar and interstitial infiltrates have all been reported.[3] Pleural effusions are not uncommon and persist during the recovery period. Although CT findings of nodular infiltrates with ground-glass opacities have been frequently reported,[13,24] these findings are not required to confirm the diagnosis. The radiologic differential diagnosis includes conditions such as viral or atypical bacterial pneumonia, pulmonary hemorrhage, and diffuse alveolar damage (DAD).

Neither elevation of the peripheral white blood cell count nor isolated eosinophilia has been consistently reported.[5] Obtaining BAL is critical to examine for lower airway eosinophilia. Cell differential examination of the BAL is needed to establish the diagnosis with eosinophil differential counts up to and in excess of 50%. Diagnostic criteria require a differential of $\geq 25\%$ eosinophilia, which can preclude the need for open lung biopsy.[14] Eosinophilia has also been shown to persist in the pleural fluid and sputum.[9]

Characterization of the oxygen requirement, either by pulse oximetry or arterial blood gas, is needed in addition to chest radiography, BAL cell count, and differential and examination findings to meet the established diagnostic requirements. Unfortunately, until bronchoscopy cultures are completed and negative for infectious pathogens, AEP can only be implicated but not confirmed.[3]

In contrast, the workup of CEP is altered by its slow onset of symptoms. In this condition, pulmonary function testing may be indicated and a more complete assessment of the extrapulmonary manifestations is advisable. Bronchoalveolar lavage and sputum examination for eosinophils as well as for markers of eosinophil degranulation will help to confirm the diagnosis.[18,31] Additional laboratory characteristics reported in CEP include elevated erythrocyte sedimentation rate and C-reactive protein, as well as a marked increase in IgE, which is seen in approximately half of patients.[24]

Lung function may be practical in only the mildest of presentations. Most commonly reported are mild restrictive changes, with a reduced diffusing capacity for carbon monoxide and obstructive features in patients with CEP, especially with a previously reported history of asthma or atopy.[1,14]

Pathophysiology

The histologic presentation of AEP is similar to that of DAD, with features of interstitial and alveolar eosinophilic infiltration.[13] Like DAD, the acute phase is notable for hyaline membranes, interstitial edema, and microthrombi. More chronic histology demonstrates organizing exudates with prominent type II pneumocyte hyperplasia.[32] Because the eosinophilic infiltration is so responsive to corticosteroids, patients who receive steroids prior to diagnostic evaluation may have reduced or incomplete eosinophilic predominance that may obscure these findings.[3,4]

The respiratory distress and respiratory failure associated with AEP seems to be most directly related to the influx of eosinophils.[33] Although peripheral eosinophilia is not universally present, eosinophilic infiltration into the lung parenchyma is what is responsible for the hypoxemia and radiographic findings characteristic of AEP.[34] The immunologic response appears to involve both lymphocyte and eosinophilic recruitment, as demonstrated by Katoh et al.[35] Activated T lymphocytes secrete IL-5 and IL-33, together with multiple other cytokines. Chemokines help to both recruit eosinophils and inhibit their apoptosis.[19,36,37] Once localized to the pulmonary interstitium, these cells degranulate further, releasing inflammatory mediators and toxic products such as major basic protein, eosinophilic cationic protein, and leukotrienes.[38] These products have been implicated in causing the histopathologic findings (**Figure 11-1**) of interstitial infiltration, airway inflammation, and exudate deposition.[39,40]

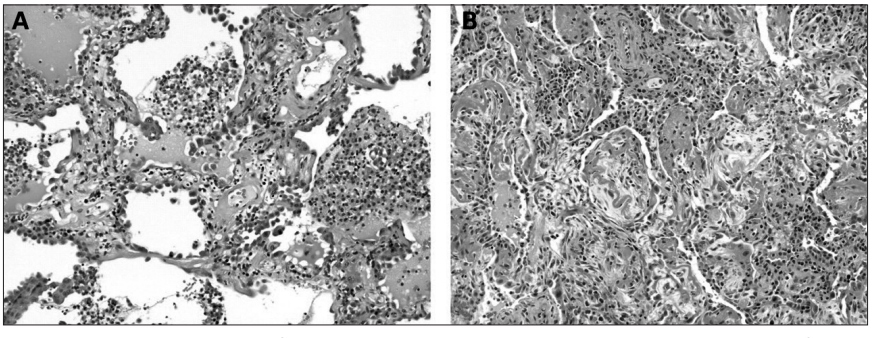


Figure 11-1. Histopathology of a patient with acute eosinophilic pneumonia. Note the diffuse airway inflammation, hyaline membrane formation with many eosinophils within the alveolar spaces. H&E stain, 100X.

From Leslie KO. My approach to interstitial lung disease using clinical, radiological and histopathological patterns. *J Clin Pathol*. 2009;62(5):387–401. © Leslie 2009.

Treatment

Effective treatment of AEP is aimed at the underlying cause. Corticosteroids have been shown to provide rapid successful resolution of the pulmonary pathology.[14] Either oral prednisolone or intravenous methylprednisolone is most commonly prescribed for a duration of 1 month after resolution of symptoms and radiographic findings.[5] More recent data support shorter courses of steroids, even less than 2 weeks, especially with patients who respond more dramatically to initiation of anti-inflammatory therapy.[11,41] Additional treatment options have included inhaled corticosteroids and bronchodilators, especially if the symptoms involve airflow obstruction.[39]

Supportive therapy, including supplemental oxygen and fluid management, is part of initial therapy for AEP.[5,39] If respiratory failure ensues as a result of advanced involvement, ventilator support, initially with bilevel positive airway pressure, progressing to intubation and ventilation, is indicated. With rapid responses to corticosteroids reported, there is rarely a need for long periods of mechanical ventilator support.[3]

Most treatment regimens begin with intravenous corticosteroids with doses up to 1 g/d. Steroid dosing is usually tapered once symptoms resolve, but the duration of treatment may extend up to 3 months.[5] Relapse has not been reported in AEP responsive to corticosteroids. Chronic eosinophilic pneumonia is similarly responsive to the initial course of treatment; however, relapses[24] require reinitiation of steroid therapy with chronic maintenance dosing. Targeting therapies with newly available biologics, such as mepolizumab, a human monoclonal antibody to IL-5, have been trialed in some patients with CEP with some success in reducing corticosteroid adverse effects.[42]

Conclusions

Idiopathic eosinophilic pneumonias are the result of localized eosinophilic recruitment and activation. Eosinophilic degranulation-damaged lung tissue may result in hypoxemic respiratory failure, which may be life-threatening. Recognition of this condition and early treatment with corticosteroids is highly effective, and in most cases the prognosis is good with minimal clinical sequelae.[8]

key points

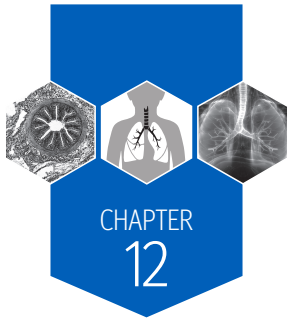
- Acute eosinophilic pneumonia is marked by its acute onset, the severity of the hypoxemia, the presence of eosinophils on BAL, and lack of other causes of the respiratory failure.
- Acute eosinophilic pneumonia is characterized by the short duration of symptoms prior to presentation and the rapid deterioration to respiratory failure, which may require mechanical ventilation.
- Treatment for AEP is high-dose steroids, which lead to good clinical response; recovery is rapid with no clinical sequelae.
- Acute eosinophilic pneumonia is distinguished from CEP by its rapid progression, the severity of the hypoxemia, and the lack of history of hypersensitivity to medications or atopy.
- Chronic eosinophilic pneumonia differs from AEP in its infrequent need for mechanical ventilation and the high frequency of relapse upon the withdrawal of corticosteroids.

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CHAPTER 12

Asthma

Miles Weinberger, MD, FAAP
Mutasim Abu-Hasan, MD
Leslie Hendeles, PharmD

Introduction

What is asthma? Can it be defined?[1] This question is of importance in evaluating respiratory disease in the child for whom euphemisms for asthma have been commonly used, including *reactive airway disease (RAD), wheezy bronchitis, obstructive bronchitis, recurrent bronchiolitis,* and others. Moreover, the symptoms associated with asthma—wheezing, cough, and dyspnea—are not unique to asthma. They can also be associated with other respiratory disorders.[2] Asthma is a heterogeneous disorder that includes various phenotypes and endotypes that share a common final pathway, reversible airway narrowing from bronchial smooth muscle spasm, and airway mucosal inflammation. Treatment decisions and counseling of families regarding the expected outcome often relate to the specific phenotype, and future treatment may target specific endotypes.

Asthma, in its various phenotypes, is the most common medical diagnosis among children hospitalized in the United States. Asthma has accounted for more than 5% of nonsurgical admissions to the hospital in children and adolescents.[3] Asthma is also a leading cause for emergency care visits; a leading cause for missed school; and a cause of considerable morbidity, disability, and occasional mortality at all ages.[4]

A National Asthma Education and Prevention Program (NAEPP) was initiated in 1989 to address asthma as a national health problem. The NAEPP provided a venue for stakeholders with an interest in improving asthma management. Guidelines for asthma management were published by the NAEPP in 1991, 1997, 2002, and 2007. A focused update was published in 2020.[5] Asthma guidelines were also published by the Global Initative for Asthma (GINA) as the *Global Strategy for Asthma Management,* first in 2002 and then with annual updates. Comparisons of the NAEPP and GINA guidelines show similarities and some differences.[6] Despite these excellent published guidelines, outcome of asthma continues to be concerning.[7]

Convincing data indicate that failure of asthma management is not generally due to lack of adequate therapeutic options but more commonly is due to ineffective delivery of appropriate medical care.[8] Asthma specialty programs, which provide patients with continuity of care, an evidence-based treatment plan, and effective patient education, result in improved asthma outcomes.[9] In this chapter, we will discuss the challenges of asthma diagnosis in children, the different asthma phenotypes, and their clinical characteristics. Finally, we will discuss the different treatments available for asthma and outline a preventive and therapeutic approach to children with asthma on the basis of their clinical phenotype.

Diagnosis of Asthma

Asthma diagnosis should be considered when children have 1 or more of the following symptoms:

- Recurrent or chronic wheezing, with or without shortness of breath
- Recurrent or chronic coughing
- Repeated diagnoses of bronchitis or bronchiolitis
- Repeated diagnoses of pneumonia not clinically consistent with pyogenic infection

In this section, we discuss how asthma should be confirmed and when alternate diagnoses should be considered when the clinician is presented with a child who has any combination of these symptoms or diagnoses.

Asthma is characterized by hyperresponsiveness of the airways to various stimuli resulting in airway obstruction that is reversible to a substantial degree either spontaneously or because of treatment. The airway obstruction is a result of varying degrees of bronchospasm and inflammation (**Figure 12-1**).

Besides causing bronchospasm, airway inflammation also results in mucosal edema and mucous hypersecretion, which further contributes to airway obstruction. The diagnosis of asthma, therefore, is most efficiently confirmed in patients with suggestive symptoms by demonstrating improvement of symptoms and/or spirometric measurements of airway obstruction after use of an inhaled β^2-agonist or after treatment of airway inflammation with a 5- to 10-day course of oral corticosteroids.[10]

In children who still have symptoms after a course of oral corticosteroids or who do not have substantial reversal of airway obstruction with these measures, a disorder other than asthma should be suspected. For example, obstruction of an airway from bronchomalacia, bronchial compression from a vascular ring, or foreign body aspiration can cause wheezing and result in an incorrect diagnosis and inappropriate treatment. Also, chronic airway

infection and inflammation due to poor airway clearance such as in cystic fibrosis and primary ciliary dyskinesia or immune deficiency can manifest with asthma-like symptoms. Because of the chronic and recurrent nature of the disease process and its symptoms, it is prudent to avoid assigning the definitive diagnosis of asthma until there have been several distinct episodes of wheezing or prolonged cough with at least 1 definite response to anti-asthma medications.

The diagnosis of asthma has no lower age limit; however, in young children, the diagnosis of asthma has been particularly associated with controversy.[11] Symptoms resulting from airway inflammation associated with asthma are frequently misdiagnosed as pneumonia, bronchitis, and recurrent bronchiolitis, which can result in ineffective and unnecessary use of antibiotics. However, persistent wheezing in infants may be caused by airway malacia, chronic aspiration, and unusual congenital abnormalities such as vascular rings, and these children often receive asthma medications with little benefit. Alternative terminology for asthma, such as reactive airway disease, adds to the confusion.[12] Both overdiagnosis and underdiagnosis of asthma in children can result in unnecessary and ineffective treatment.[13,14]

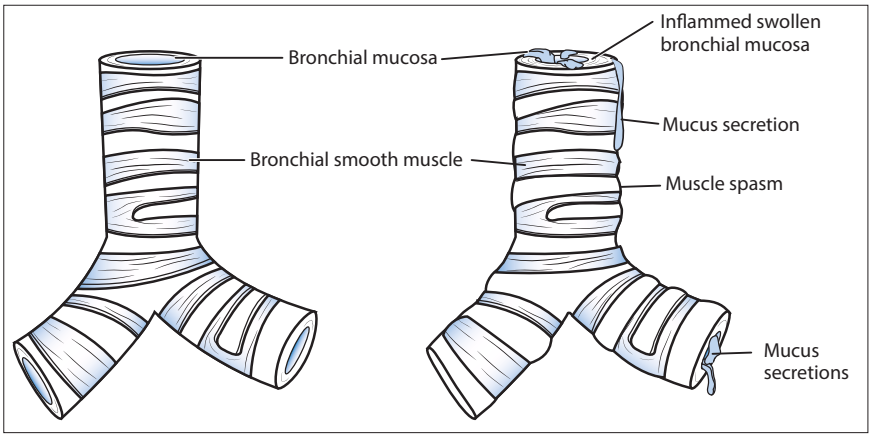


Figure 12-1. The 2 components of airway obstruction in asthma—bronchospasm and inflammation with mucosal edema and mucous secretions illustrated on the right. The normal airway is illustrated on the left.

Clinical Characterization of Phenotypic Patterns of Asthma

Because of the heterogeneous nature of asthma, simply establishing the diagnosis of asthma is not sufficient for development of the most appropriate treatment plan. Planning effective and efficient strategies for managing asthma requires identifying the clinical pattern of disease. These clinical patterns or phenotypes can generally be determined by obtaining a brief

history that addresses the age of onset and pattern of symptoms, as well as the nature of triggers. The following questions are specifically helpful:

- What was the age of onset of lower respiratory symptoms?
- Are symptoms of asthma associated only with the clinical symptoms of a viral respiratory infection?
- Are there extended periods between episodes of respiratory symptoms when there is no cough or wheeze?
- Is there a seasonal variation in symptoms, and does the season match those of inhalant allergens for which the patient has allergen-specific immunoglobulin E (IgE)?
- Are respiratory symptoms related to specific environmental exposures?
- Do lower respiratory symptoms occur daily for extended periods?

From the responses to those questions, 3 distinct clinical patterns of asthma can be identified—intermittent asthma, persistent asthma, and seasonal allergic asthma.

Intermittent Asthma

Intermittent asthma is characterized by episodic symptoms with absence of active asthma symptoms between episodes. This common asthma phenotype is triggered primarily by viral respiratory tract infections. More importantly, patients with intermittent asthma are both completely without symptoms and without airway obstruction during the periods between episodes. Typically, parents will say, "Every time my child gets a cold, it goes into the chest." This pattern of asthma generally begins in the first 1 or 2 years after birth. The typical course starts with the onset of coryza from a common cold virus followed by cough, wheezing, and respiratory distress of varying severity that progresses over the next 1 to 2 days. The duration of symptoms without effective intervention can be days or weeks. During asymptomatic periods between episodes, patients with this pattern of asthma have no evidence of airway inflammation when examined with bronchoalveolar lavage.[15]

The absence of allergen-specific IgE in an infant or toddler in association with a clinical pattern of intermittent viral respiratory tract infection–induced asthma is generally predictive of a reduced frequency of symptoms or remission over time. Although most infants and toddlers with asthma have this intermittent viral respiratory infection–induced pattern, allergy testing can identify those who are at risk for more persistent symptoms in the future.[16] Preschool-age children average 7 colds per year, with 15% of children experiencing 12 or more colds per year.[17] For some children, that can result in the appearance of almost continuous symptoms. Summer is generally associated with an abatement of symptoms in these children. Distinguishing asthma

limited to viral respiratory infections from a chronic or seasonal allergic pattern is important because, unlike with the latter, the most effective of maintenance therapies will not reliably prevent the viral respiratory infection–induced asthma that characterizes this common intermittent pattern.[18–20]

Persistent Asthma

Children with persistent asthma experience year-round chronic symptoms and, in the absence of effective maintenance therapy, do not have extended symptom-free periods. Most children with a persistent pattern of asthma have an allergic component to the asthma. Symptoms in these children may have begun with a viral respiratory infection–induced intermittent pattern of symptoms. Those who develop IgE-mediated allergy (ie, atopy) are at risk for more persistent symptoms. The early presence of allergen-specific IgE is predictive of more persistent symptoms.[21]

Contrary to the belief of some, there is no age limitation for allergy testing, and some children can have evidence of inhalant allergy contributing to asthma even in infancy (**Figure 12-2**).

Seasonal Allergic Asthma

Children with seasonal allergic asthma experience persistent symptoms only during an inhalant allergy season. For example, in the North Central United States, this is most commonly from an outdoor mold, Alternaria, which grows on decaying vegetation from early spring through late fall, with peaks particularly in the spring and fall, when it has been associated with near-fatal asthma exacerbations.[22] In the valley areas of the Pacific Northwest and Northern California, grass pollens are the major allergens causing seasonal allergic asthma, generally accompanied by symptoms of allergic rhinoconjunctivitis.[23] Because allergens and seasonal patterns vary with the geographic region, seasonal symptoms in other regions may be from molds, pollens, flying insects, or a combination of those airborne allergens. The physician caring for a child with asthma needs to have some knowledge of the local aerobiological environment to establish a correct diagnosis.

Additional Phenotypes

Besides these main 3 common phenotypes of asthma in children, there are other less common phenotypes. Late-onset allergic asthma can follow allergic rhinitis. Nonallergic persistent asthma, common in adults, also occurs occasionally in children. Catamenial asthma, characterized by exacerbations associated with menses in adult women, is seen occasionally in female adolescents. These phenotypes and sudden asphyxic asthma in adolescents and preadolescents are discussed in a previous publication.[24] Notably, there is potential overlap among all clinical patterns of asthma. For example, patients with persistent disease often have intermittent exacerbations from viral

respiratory illness and may have seasonal allergic exacerbations. Identification of the clinical pattern in each patient contributes to a rational and optimally effective therapeutic strategy for that patient.



Figure 12-2. Allergy skin testing in an 11-month-old infant. He was hospitalized aged 9 months with severe acute asthma preceded by rhinoconjunctivitis during the peak of the grass pollen season in a Northern California valley area, where grass pollen is a major inhalant allergen. The typical wheal and flare of the multiple related species of grass pollen native to that area are on the left side of the infant's back. They are much larger than the histamine control (H) with no reactivity to the diluent control (C). Skin tests on the right side of the back to other common inhalant allergens were all negative. Although immunotherapy using injections of allergenic extracts is rarely indicated at this age, this infant illustrates a striking exception for whom benefit could reasonably be expected.

From Weinberger M. Pediatric asthma and related allergic and nonallergic diseases: patient-oriented evidence-based essentials that matter. *Pediatric Health*. 2008;2(5):631–650.

Exacerbations of Asthma

An exacerbation of asthma may be nothing more than transient bronchospasm from exercise or a specific exposure. Rapid response to a bronchodilator such as an albuterol aerosol from a metered dose inhaler (MDI) may then be sufficient to end that type of exacerbation. However, a more prolonged exacerbation generally involves mucosal edema and mucous secretions. While that is sometimes self-limited, a corticosteroid may be necessary to prevent that exacerbation from progressing and to end the increase in symptoms. Viral respiratory infections are common causes of more severe exacerbations.

Common cold viruses exacerbate all asthma phenotypes, possibly because of a defect in innate immunity related to mucosal interferon.[25] While common cold viral infections affect only the upper respiratory mucosa in those without asthma, infection and inflammation of the lower airways occur in those with asthma. The frequency of common colds in preschoolers is usually higher for those who attend child care or have siblings in school. Symptoms of asthma exacerbations parallel the seasonal pattern of cold viruses that begin with the onset of the school year and its associated increase in contact with other children and continue throughout the fall, winter, and spring (**Figure 12-3**).[26]

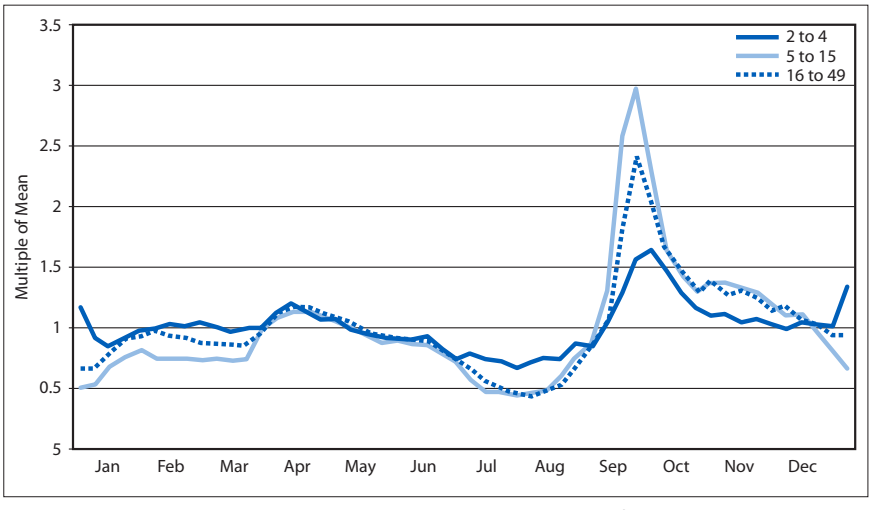


Figure 12-3. Typical autumnal increase in asthma at the beginning of the school year with the younger school-age children beginning first followed by their older and younger siblings.

Reprinted from Johnston NW, Johnston SL, Norman GR, Dai J, Sears MR. The September epidemic of asthma hospitalization: school children as disease vectors. *J Allergy Clin Immunol.* 2006;117(3):557–562. Copyright © 2006 American Academy of Allergy, Asthma and Immunology.

Assessing Asthma Severity

Asthma can vary in severity from mild symptoms of cough and wheezing to life-threatening symptoms of respiratory distress and respiratory failure. Symptoms can also vary in frequency. Questions to assess severity include the following:

- Do respiratory symptoms interfere with activity?
- Do respiratory symptoms interfere with sleep?
- What is the frequency of intermittent medication use with bronchodilator and systemic corticosteroids?
- With what frequency is urgent care required—a physician's office? Or the emergency department? What is the frequency of hospitalization?
- How often has there been a requirement for intensive care?
- Has there been a requirement for ventilatory assistance?
- Have there been acute life-threatening events?

Treatment of Asthma

Intervention Medication ("Rescue" Medications)

Intervention medications are those used for acute symptoms (**Table 12-1**). A short-acting inhaled β_2-agonist is typically the initial intervention for acute symptoms. Older children generally can successfully use these medications with a metered-dose inhaler (MDI). In younger children and infants, nebulizers were a previous method for delivering aerosol. An MDI with a valved holding chamber has generally replaced the nebulizer for delivery of aerosol medications for asthma. The simplicity, more rapid administration, lower cost, and greater portability of the MDI with an antistatic valved holding chamber has made this the method of choice for aerosol administration in younger children with asthma. Nebulized medication takes longer to deliver and is associated with more adverse effects such as tachycardia and jitteriness because of the much higher dose. An exception for use of a nebulizer for a bronchodilator is the use of continuous nebulized albuterol for treatment of severe acute asthma in the intensive care setting.

A valved holding chamber with a mask provides lung delivery from an MDI for a patient too young to be able to form a seal with their mouth on a holding chamber. This method of drug administration has proven efficacy for young children, even in the emergency care setting.[27] Parents and patients must be properly instructed for whatever device is used for aerosol delivery and should demonstrate appropriate use of these devices when prescribed (**Figure 12-4**).

Table 12–1. Intervention Medication: Dosage and Decisions for Usual Treatment of Acute Symptoms of Asthma

Medication	Dosage	When to Use
Albuterol or levalbuterol metered-dose inhaler Albuterol dry powder inhaler and dry powder digital inhaler	2–4 inhalations, up to 6 inhalations, can be used at a time	As needed for cough, wheezing, labored breathing. Scheduled use has no advantage over as-needed use and may be deleterious for some patients. Repeated need during exacerbations warrants consideration for a short course of an oral corticosteroid.
Prednisone, prednisolone, methylprednisolone, and dexamethasone as tablets Liquid formulations and oral disintegrating tablets of prednisolone for young children (Parenteral forms indicated only in the case of concern about oral retention)	Prednisone, prednisolone, methylprednisolone doses to obtain maximal effect in asthmatic airways Infants—15 mg twice a day 1–3 years of age—20 mg twice a day 3–13 years of age—30 mg twice a day > 13 years of age—40 mg twice a day Because dose-response data are insufficient to support recommendations based on weight or body size, these are empirical doses based solely on experience that lower doses less reliably provide complete cessation of symptoms with the goal of a short course (5–7 days). Lower doses almost certainly are adequate for some patients, and minor adverse effects justify limiting dosage in some patients to once daily in the morning only. There is no reason to taper short courses. Dexamethasone dose—one-fifth the milligrams of prednisone or prednisolone dose is considered equivalent in effect, but dexamethasone is longer acting.	When bronchodilator subresponsiveness is identified by means of incomplete resolution of symptoms and signs from repeated use of the bronchodilator. Re-evaluate if not improving within 5 days or asymptomatic within 10 days. Do not taper.
Ipratropium metered-dose inhaler: ipratropium combined with albuterol in soft-mist inhaler and ipratropium solution added to albuterol solution for use in nebulizer	0.5 mg with 2.5–5 mg albuterol by nebulizer	Indicated only for severe acute asthma exacerbation in the emergency department when response to β_2-agonist is inadequate for relief of respiratory distress.



Figure 12-4. Various ways to deliver an aerosol to children from a metered-dose inhaler (MDI). (**A**) A school-age boy being instructed by the doctor on proper use. (**B**) A 5-year-old girl who used the MDI but did not inhale it as evidenced when she opened her mouth and the aerosol mist was visibly expelled. (**C**) An infant receiving an aerosol from an MDI via a valved holding chamber. (**D**) How to hold the chamber mask so that the hand of the adult moves with the child maintaining the mask in contact with the face to avoid leakage of the aerosol.

Images A and C from Alamy Images. Images B and D from Weinberger M. Pediatric asthma and related allergic and nonallergic diseases: patient-oriented evidence-based essentials that matter. *Pediatric Health.* 2008;2(5):631–650.

Albuterol is the most common β_2-agonist used for acute bronchodilatation in North America; terbutaline, less potent on a microgram basis than albuterol, is commonly used in Northern Europe. Albuterol is a racemic mixture of 2 optical isomers with levalbuterol being the therapeutically active moiety. Although levalbuterol is available as the sole isomer, it is therapeutically equivalent in both efficacy and toxicity to the racemic preparation when administered in a dosage equivalent to the levalbuterol component of racemic albuterol (ie, one-half of the milligram quantity of racemic albuterol is levalbuterol).[28] Despite initial marketing claims and continued factitious beliefs, there is no evidence for any pharmacological effect of the inactive moiety of racemic albuterol, and there is therefore no therapeutic difference in efficacy or toxicity between levalbuterol alone or in racemic albuterol.

Because β_2-agonists do not alter the inflammatory component of airway obstruction, anti-inflammatory therapy is essential to relieve that component. Inflammation contributing to airway obstruction can be identified clinically by increased frequency of using albuterol with decreasing clinical response. Early aggressive use of systemic steroids provides impressive clinical benefit for children having an acute exacerbation of asthma.[29] Administration of oral corticosteroids during the early symptoms of a viral respiratory infection appears to prevent progression to severe acute asthma in children who have previously required hospitalization. Earlier discharge after hospitalization for acute asthma results from early administration of systemic corticosteroids,[30] and prompt administration of systemic steroids in the emergency department decreases the likelihood of subsequent admission of patients seen for emergency care for asthma.[31,32] Administration of a short course of a systemic corticosteroid also prevents progression of asthma exacerbations in patients who are ambulatory and have a history indicating a risk for requiring urgent care (dosage is indicated in **Table 12-1**).[33,34] Tapering is not indicated for a short duration of systemic corticosteroid.[35] Although care should be taken to avoid excessive systemic corticosteroid exposure, no evidence of adverse effects on bone metabolism, bone mineralization, or adrenal suppression was seen in a study in 48 children who received a median of 4 courses of oral glucocorticoids (range, 3–11 courses) compared with 35 similar children who had not received corticosteroids in the preceding year.[36]

The most appropriate place to treat acute symptoms of asthma is where they occur—at home, at school, or at play. The issue for many children is not whether they will have another exacerbation, but when they will have one; and that "when" is not predictable. Treatment in the doctor's office, emergency department, or hospital is stressful and disruptive for patients and parents and should generally be considered damage control for a treatment failure. The measures for treating acute asthma are inhaled β_2-adrenergic bronchodilators and systemic corticosteroids, usually administered orally. These measures are most effective when used before the need for urgent medical care, rather than waiting until presentation to the emergency department, clinic, or physician's office.[29] Thus, for patients closely followed up by the physician managing the child's asthma, having the oral corticosteroid available at home to be used at the early signs and symptoms of asthma exacerbation is most appropriate.[37] When questioned, parents frequently can identify the early signs of previous exacerbations. That information can be used to identify when a future oral corticosteroid should be started before the need for urgent medical care.[38]

Box 12-1

Measures to Maximize Benefit and Minimize Risk for Home Use of Oral Corticosteroids to Treat an Asthma Exacerbation

- **Prescribe a dose sufficient for 1 week with no refills.**
- **Instruct the patient and family on how to recognize an impending exacerbation; questioning them regarding previous experience can provide useful guidance.**
- **Provide an adequate dose; the absence of reliable dose–response data for children suggests that erring high may be more likely to prevent urgent care.**
- **The oral corticosteroid should be continued until the increase in symptoms stops, whether 3, 5, or 7 days, so long as progressive improvement is occurring. Tapering is not indicated.**
- **The patient or family should contact the prescribing physician if symptoms do not begin to improve within the first 2–3 days or are not gone by 7 days.**
- **Adjust the dose if there are minor adverse effects from the corticosteroid dose used.**
- **Provide verbal and written instructions regarding the appropriate use of the oral corticosteroid; repeat verbal instructions at scheduled follow-up.**
- **Review the appropriateness and effect of corticosteroids after each use through communication before refill—no refills without contact.**
- **The prescribing physician is responsible for adequate follow-up to review patient and family understanding and management of exacerbations. We all learn from repetition.**

Specific measures that can maximize benefit and minimize risk in the home use of oral corticosteroids are given in **Box 12-1.**

For children with intermittent asthma, as-needed inhaled corticosteroids have been suggested as an alternative to an oral corticosteroid.[39] While earlier studies have questioned the efficacy of inhaled corticosteroids for acute asthma,[11,18–20] very early use of inhaled corticosteroids at the beginning of an exacerbation may be sufficiently effective for some patients. This is discussed in a point/counterpoint discussion published in *Chest*.[40–43]

A strategy for very early use of an inhaled corticosteroid in an exacerbation is to combine an inhaled corticosteroid with a bronchodilator so that each use of a bronchodilator for acute symptoms ensures the early use of additional doses of inhaled corticosteroid. This approach is known as single maintenance and reliever therapy (SMART). A combination of an inhaled corticosteroid with formoterol, a rapid-onset, long-acting inhaled bronchodilator,[44] or albuterol,[45] for both maintenance and intervention has been shown to decrease the frequency of exacerbations.[46] While oral corticosteroids may still be needed for some exacerbations, guidelines have now included this strategy as useful for some children.[39,47,48] Concerns have been expressed regarding the practicality

of this practice based on product labeling as mandated by the US Food and Drug Administration at the time of this writing.[49,50]

In the emergency care setting, ipratropium, an anticholinergic aerosol, potentially can add value to inhaled albuterol in treating severe acute asthma not fully responsive to albuterol alone. Results of an early study showed decreased risk of hospitalization for the children with more severe disease manifested by an FEV_1 less than 60%.[51] A later Cochrane review of 20 studies consisting of 2,697 children aged 1 to 18 years who were randomly assigned came to a similar conclusion that benefit was most evident among the patients with more severe disease.[52] Ipratropium has no documented clinical role in patients who are ambulatory. Repeated use of ipratropium also has no apparent value in the outcome of patients hospitalized with acute asthma.[53] Intravenous magnesium has been used for severe acute asthma, but data generally show minimal added clinical effect.[54]

Early during acute asthma, hypoxemia is common because obstruction of small airways decreases oxygen uptake while perfusion is maintained. The hypoxemia from this ventilation/perfusion ($\dot{V}/\dot{Q}$) mismatching can be corrected with oxygen. However, hypoxemia also can occur from respiratory failure, which is associated with an increase in P_{CO_2} as airway obstruction progresses in severity. Measuring blood gas to measure pH and P_{CO_2} (capillary or venous is sufficient) is essential when hypoxemia is present to distinguish hypoxemia caused by $\dot{V}/\dot{Q}$ mismatching from hypoxemia caused by ventilatory insufficiency. Supplementary oxygen is appropriate treatment for hypoxemia from $\dot{V}/\dot{Q}$ mismatching, but an increasing P_{CO_2} indicates inadequate ventilation. This hypercarbia (ie, elevated P_{CO_2}) indicates the potential for impending ventilatory failure and the possible need for assisted ventilation. An initially normal P_{CO_2} should be carefully interpreted in the context of the clinical picture because the P_{CO_2} may have been previously low, and increased work of breathing from worsening airway obstruction can result in decreased ventilation and an increasing P_{CO_2}.

Maintenance Medication

Maintenance medications are indicated for patients with persistent asthma and for those with prolonged seasonal allergic asthma to treat frequent symptoms and, ideally, prevent exacerbations (**Table 12-2**). The goal of maintenance treatment for asthma is to use acceptably safe daily medication that effectively suppresses asthmatic symptoms, prevents exacerbations, and maintains normal lung function. Inhaled corticosteroids are the most effective medications for children with prolonged periods of symptomatic asthma. These agents can be effectively delivered with an MDI. A valved holding chamber decreases oral deposition and consequent systemic absorption. Use of a tight-fitting mask with a valved holding chamber provides effective delivery of aerosol medication to

Table 12-2. Maintenance Medications for Asthma

Medication Type	Formulation (*Brand Name in Italics*)	When to Use
ICS	**MDIs** • Fluticasone propionate (*Flovent HFA 44, 110, or 220 mcg*) • Mometasone furoate (*Asmanex HFA 50, 100, or 200 mcg*) • Ciclesonide (*Alvesco 80 or 160 mcg*) **Breath-actuated MDI** • Beclomethasone dipropionate HFA (*QVAR RediHaler 40 or 80 mcg*) **DPIs** • Budesonide (*Pulmicort Flexhaler 90 or 180 mcg*) • Fluticasone furoate (*Arnuity Ellipta 50, 100, or 200 mcg*) • Fluticasone propionate (*Flovent Diskus 50, 100, or 250 mcg; ArmonAir Respiclick and Digihaler 55, 113, or 232 mcg*) • Mometasone furoate (*Asmanex Twisthaler 110 or 220 mcg*)	First-line medication for persistent symptoms; for infants and toddlers use the MDI devices with a VHC and mask—many can use a VHC without a mask by age 4 years; most can use the breath-actuated MDI and DPI formulations effectively by age 6 years.
Leukotriene receptor antagonist	Montelukast (*Singulair 4-mg sprinkle, 4- or 5-mg chewable tablets, or 10-mg tablets*)	An alternative to an ICS for mild persistent symptoms; modest additional benefit as add-on to inhaled cortico-steroids. Black box warning regarding mood disorders.
Combination ICS/LABA	**MDIs** • Budesonide/formoterol fumarate dihydrate (*Symbicort 80/4.5 or 160/4.5 mcg*) • Fluticasone propionate/salmeterol (*Advair HFA 45/21, 115/21, or 230/21 mcg*) • Mometasone furoate/formoterol fumarate (*Dulera 50/5, 100/5, or 200/5 mcg*) **DPIs** • Fluticasone furoate/vilanterol (*Breo Ellipta 100/25 or 200/25 mcg*) • Fluticasone propionate/salmeterol (*Advair Diskus 100/50, 250/50, or 500/50 mcg; AirDuo Respiclick and Digihaler 55/14, 113/14, or 232/14 mcg; Wixela Inhub 100/50, 250/50, or 500/50 mcg*) • Fluticasone furoate/umeclidinium/vilanterol inhaled (*Trelegy Ellipta 100 mcg/62.5 mcg/25 mcg per puff, 200 mcg/62.5 mcg/25 mcg per puff*)	Use when an ICS does not maintain control and a LABA is added; occasionally a patient's condition may be made worse from the addition of a LABA. Improved lung function, but did not reduce exacerbation rates in patients with moderate to severe asthma compared to ICS/LABA treatment

Table 12-2. Maintenance Medications for Asthma *(continued)*

Medication Type	Formulation (*Brand Name in Italics*)	When to Use
Long-acting muscarinic antagonist	Tiotropium bromide (*Spiriva Respimat, Spiriva HandiHaler*)	May be substituted for LABA. Add on when control not maintained with ICS/LABA that improves FEV_1 but does not decrease need for systemic corticosteroids.
Biologic	**Anti-IgE** • Omalizumab (*Xolair*) **Anti-IL-5** • Mepolizumab (*Nucala*) • Reslizumab (*Cinqair*) • Benralizumab (*Fasenra*) **Anti-IL-4/IL-13** • Dupilumab (*Dupixent*) **Anti-TSLP** • Tezepelumab (*Tezspire*)	Omalizumab is used for poorly controlled asthma from allergen-specific IgE-mediated symptoms. Anti-IL-5 products are used for poorly controlled severe asthma with an eosinophilic phenotype. Dupilumab is effective for atopic dermatitis, asthma, and nasal polyps. Tezepelumab does not require eosinophilic phenotype or demonstration of biomarkers.

Abbreviations: DPI, dry powder inhaler; HFA, hydrofluoroalkane; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL, interleukin; LABA, long-acting β_2-agonist; MDI, metered-dose inhaler; TSLP, thymic stromal lymphopoietin; VHC, valved holding chamber.

infants and toddlers (**Figure 12-4**). Because static charge reduces drug delivery substantially, an antistatic chamber should be used. Comfortable tidal breathing is essential for effective aerosol delivery; a crying child receives little delivery of the medication to the lungs.[55]

Although inhaled corticosteroid is available as a nebulizer solution, there is no evidence that this formulation offers any therapeutic advantage over the simpler and more rapid administration with a pressurized MDI with a valved holding chamber.[56] Older children can use a dry powder inhaler (**Table 12-2**) for which no assist device such as a valved holding chamber is needed. However, specific instruction is needed because patients are required to generate high inspiratory airflow when using a dry powder inhaler to aerosolize the powder. Whichever inhaled corticosteroid preparation is used, individualized and clear instructions with direct demonstration of their use to patients and parents is important.

There is evidence for dose-related systemic effects from most inhaled corticosteroids.[57] Ciclesonide, however, has been reported to have little or no dose-related systemic effect.[58] Conventional low doses of all of the currently marketed

inhaled corticosteroids have an established safety record.[59] Measurable but small transient effects on height growth velocity have been reported for most inhaled corticosteroids.[60] Ciclesonide is an exception and is preferred if growth slows while a child is receiving one of the other inhaled corticosteroids.[61] Ciclesonide is highly protein bound, allowing less free corticosteroid to circulate, and it may be metabolized more rapidly than other inhaled corticosteroids. Monitoring growth for children receiving inhaled corticosteroids, therefore, should be a standard of care.

Montelukast, a leukotriene receptor inhibitor, is an orally administered drug that has some clinical benefit for patients with mild persistent asthma, as compared with placebo, and has some potential additive effect with inhaled corticosteroids.[62] However, the clinical benefit of adding montelukast to an inhaled corticosteroid does not appear to be as great as is seen with an inhaled long-acting β_2-agonist (LABA).[62] Although montelukast is generally well tolerated, postmarketing study results have shown serious neuropsychiatric adverse drug reactions.[63] Consequently, the US Food and Drug Administration has added a boxed warning.

Adding a LABA to an inhaled corticosteroid is generally more effective than using a higher dose of the inhaled steroid in patients who continue to have symptoms with use of initial doses of inhaled steroids.[64] A small subset of patients appears to be at risk from downregulation of the β_2-adrenergic receptors with continued use of LABAs alone or even with inhaled steroids.[65] A particularly dramatic example was seen in 2 boys who had life-threatening asthma exacerbations that were documented to be from salmeterol.[66] This uncommon adverse effect of LABAs is best recognized by clinical worsening of asthma symptoms when a LABA is added or by clinical improvement when discontinued. Careful monitoring of the patient with regularly scheduled return visits is important to identify the patient who worsens rather than the more usual benefit seen from the addition of a LABA.

Tiotropium, a long-acting muscarinic receptor antagonist, has less bronchodilatation than does a β_2-agonist. In addition to the effect on airway smooth muscle relaxation, inhibition of mucous gland secretion may also contribute to a therapeutic role in asthma. Clinical trials in children and adolescents have shown increased FEV_1 but no improvement in frequency of exacerbations when treatment with tiotropium is added in patients with asthma not adequately controlled with inhaled corticosteroids and LABA.[67]

Immunotherapy (allergy shots) can reduce asthma symptoms in highly selected cases in which the symptoms can be convincingly related to a limited number of well-defined inhalant allergens to which immunotherapy has been of benefit.[68] In recent years, a number of new medications called biologics have been developed for use in patients with asthma not adequately controlled with

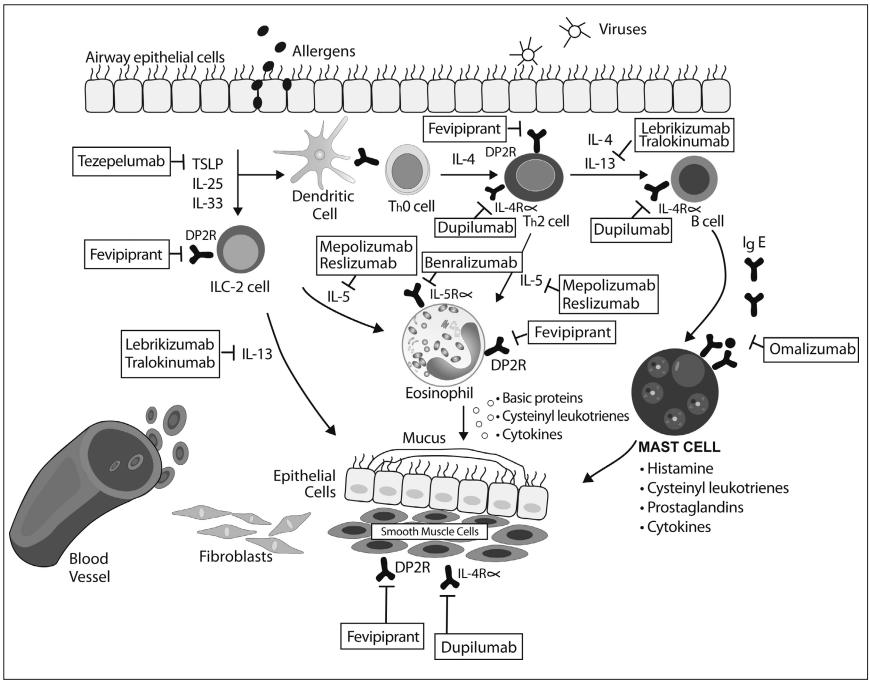


Figure 12-5. Schematic of biologics that interfere with the inflammatory pathways of asthma. Abbreviations: DP2R, prostaglandin D2 receptor; IgE, immunoglobulin E; IL, interleukin; ILC-2, type 2 innate lymphoid cell; Th, T helper; TSLP, thymic stromal lymphopoietin.

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inhaled corticosteroid, LABA, and long-acting muscarinic receptor antagonist medications (**Table 12-2**). The first of these, omalizumab, a monoclonal anti-IgE agent, prevents allergen-specific free IgE from binding to mast cells and releasing mediators from those mast cells.[69,70] Other current and possibly future biologics have been developed for severe asthma (**Figure 12-5**).[71–75]

Environmental Considerations

Identification and avoidance of asthma triggers are important components of asthma management. The physician providing asthma care should assess the child's environment and its role in contributing to asthma symptoms. Both the macro- and microenvironmental aspects need to be considered. Cigarette smoke exposure, whether primary, secondary, or tertiary, is a strong irritant for the sensitive airways of a child with asthma.[76] Indoor fireplaces and outdoor bonfires or leaf burning[77] are also important nonallergenic major irritants that contribute to asthmatic symptoms.

Children with allergen-specific IgE to common mold aeroallergens can have intense exposure to outdoor molds during procedures that stir up decaying vegetation, such as raking leaves or harvesting. Very old homes may be plagued by indoor mold, especially if there is a basement with dampness or water leakage. Forced air heating can distribute aeroallergens throughout the home but also provides an opportunity to use a high-efficiency air filter to minimize aeroallergens in the indoor environment. Pets can be a contributing factor to asthma, but those family members should not be blamed for causing symptoms without the patient demonstrating allergen-specific IgE to the species and the physician obtaining a convincing history that exposure contributes to morbidity. However, pet exposure in early infancy may prevent subsequent allergy.[78,79] Clinically important aeroallergens vary with the region and the living area. They include pollens, outdoor and indoor molds, animal dander, cockroaches, rodents, flying insects, and dust mites. Knowledge of allergen-specific IgE in the patient and the aerobiological characteristics of the patient's environment are essential to assess the importance of environmental factors.

Exercise-Induced Asthma

Bronchospasm induced by exercise is a common component of active asthma. However, exercise-induced asthma tends to be overdiagnosed as a cause of exercise-induced dyspnea. If baseline pulmonary function is normal or near normal, either naturally or with maintenance medication, exercise-induced bronchospasm can be readily prevented for most patients by pretreating with an inhaled bronchodilator, such as albuterol. If that does not block exercise-induced dyspnea, then alternative diagnoses should be pursued.[80,81] An uncommon but serious reason for losing the bronchoprotective effect from adrenergic bronchodilators is the regular use of LABA bronchodilators.[66]

Treating Difficult Asthma

Asthma may be difficult to control because of several factors. Before assuming that it is the asthma that is intractable and adding yet more medications, the physician should consider the following: (1) poor adherence to the prescribed medications, (2) improper inhaler technique resulting in suboptimal delivery of the medication to the airways, (3) poor choice of medications, (4) exposure to irritants such as cigarette smoke, (5) presence of other comorbidities such as obesity, or (6) incorrect diagnosis (ie, the child does not have asthma).[2]

The most common cause of poorly controlled asthma is that the medications are not being taken or are not being taken properly. Besides asking patients about the frequency of taking medications, the number of puffs used can be determined on the dose counters of various inhaler devices. Calling the patient's pharmacy for the number of refills can help determine whether a prescription is being filled with appropriate frequency.[82] If poor adherence is

established, address the possible obstacles that prevent patients from taking medications. Simplification of treatment regimen or switching the medication to one with a lower co-pay may improve adherence. Also, there is evidence that in patients with asthma that is severe and poorly controlled due to lack of treatment adherence, administration of asthma medications by a school nurse can improve outcome.[83]

Emergency Department and Hospitalization

The decision to hospitalize is usually made when dyspnea or hypoxemia is not responsive to home or emergency care. However, this decision may be influenced by social factors in addition to the severity of the physiological abnormality. Asthma is the leading medical cause of hospitalization for children, and these hospitalizations are mostly preventable. The treatment administered during hospitalization is essentially the same as treatment that would have prevented most hospitalizations had the treatment been performed earlier (ie, aerosol bronchodilators and systemic corticosteroids). Chest radiographs are of limited value for the child with asthma in the emergency department or hospital and infrequently influence management.[84]

Hospitalization is primarily to ensure that oxygen can be administered if needed and that respiratory failure, if it occurs, can be managed with assisted ventilation. Hospitalization is also an opportunity to provide intensive patient education and plan for appropriate ambulatory care. Adequate doses of systemic corticosteroids should be administered in any child with asthma that requires an emergency department visit or hospitalization for asthma. Inhaled albuterol can be administered for an increase in the work of breathing. Continuous nebulization of albuterol can decrease the need for assisted ventilation.[85] Discharge from the hospital should occur once the level of care is such that it can be continued at home. There is no need to continue hospitalization until all symptoms are completely gone unless there are social concerns regarding continuing medication at home. Once improvement is well established, deterioration is highly unlikely with continued medication, and appropriate ambulatory care can begin.

Treating Comorbidities

Treating comorbidities may benefit the control of chronic asthma. Although rhinitis, often called sinusitis, and gastroesophageal reflux are often associated with asthma, the evidence that asthma control benefits from their treatment is anecdotal only and inconsistent with published evidence.[86,87] Symptoms attributed to sinusitis are predominantly those of rhinitis, and there is little correlation between radiological evidence of sinusitis and clinical symptoms.[88] Although chronic allergic rhinitis should be treated with topical nasal steroids, and gastroesophageal reflux should be treated in those experiencing the

associated symptoms of heartburn, regurgitation, and substernal discomfort, there is little reason to expect clinically important benefit for the asthma itself.[89]

Obesity is a potential comorbidity associated with poor asthma control.[90] Obesity and asthma are treated more extensively in Chapter 43, Asthma and Other Respiratory Disorders Associated With Obesity. Nighttime asthma symptoms can easily overlap with symptoms of obstructive sleep apnea, and a strong correlation between the 2 illnesses has been suggested. In one study in which investigators examined the relationship between asthma and obstructive sleep apnea, the authors concluded that sleep-disordered breathing was a risk factor for poor control of asthma in children.[91]

Monitoring the Clinical Course

Successful management of asthma does not stop with providing patients with prescriptions. Physicians need to ensure that patients and parents have developed self-sufficiency in managing the disease and its exacerbations. Ideally, there should rarely be a need to see the patient during acute symptoms because the patient or family should have been taught with oral and written instructions regarding the key components of successful management at home. These include the use of maintenance medications as a preventive measure for persistent and seasonal allergic asthma, the use of an inhaled bronchodilator for acute symptom relief, and early intervention with a short course of systemic corticosteroid for acute exacerbations. Regular scheduled return visits are essential to review adherence to the treatment plan, to check inhaler technique, to assess if the patient meets criteria for asthma control (**Box 12-2**), and to adjust treatment when appropriate to meet those criteria with the least amount of medication.

Box 12-2

Criteria for Asthma Control

- **Absence of hospitalization**
- **Absence of urgent care requirements**
- **Absence of interference with sleep**
- **Absence of interference with activity**
- **Infrequent use of inhaled β_2-agonists for acute symptoms**
- **Infrequent use of oral corticosteroids**
- **Normal or near normal pulmonary function as measured with spirometry**
- **Infrequent school absences because of asthma**

Reprinted from Weinberger M. Pediatric asthma and related allergic and nonallergic diseases: patient-oriented evidence-based essentials that matter. *Pediatric Health*. 2(5):631–650. https://www.futuremedicine.com/doi/full/10.2217/17455111.2.5.631

Measuring pulmonary function with office spirometry should be a routine standard of care in order to identify airway obstruction not detected with routine stethoscopic auscultation.[92] Total airway resistance and its components, proximal large airway resistance, and peripheral small airway resistance are obtained.

There is increasing evidence regarding the importance of

assessing small airway dysfunction in the lung periphery that is not readily identified with spirometry.[93,94] In addition to identifying peripheral small airway dysfunc-tion, impulse oscillometry does not require the effort of spirometry. Only tidal voluming is needed. Consequently, even 3- and 4-year-old children, or anyone unable to perform the maximal effort of spirometry, can perform impulse oscillometry.

Although use of a peak flow meter has been proposed as a tool to monitor asthma and guide its therapy, the weight of evidence indicates that symptom monitoring is as good as or even better than the meter.[95] Measuring peak flow depends on patient effort and technique. If the value is low while symptoms are absent, the result can be unnecessarily increased patient and parent anxiety, overuse of asthma medications, and overuse of the health care system. The only situations in which a home peak flow meter or portable spirometer is useful are for those who occasionally under- or overperceive asthmatic symptoms. An objective measure of disease severity can help distinguish anxiety-induced dyspnea or nonperception of airway obstruction. Even in these clinical situations, using handheld spirometers, which are now becoming more available and increasingly less expensive, is a better alternative than using the iconic peak flow meter.

There is current interest in the use of exhaled nitric oxide (FeNO) as a marker of eosinophilic airway inflammation in asthma.[96] A review of studies in children concluded that the use of FeNO to guide asthma therapy in children may be beneficial in a subset of children, but it cannot be universally recommended for all children with asthma.[97] A conditional recommendation for use was the conclusion of an official American Thoracic Society Clinical Practice Guideline.[98]

General medical care for asthma should include routine immunizations. The varicella vaccine is particularly important because of the small but serious risk of disseminated varicella that has been reported when varicella occurs during a course of high-dose systemic corticosteroids as may be necessary for an asthma exacerbation.[99] A COVID-19 vaccine and yearly influenza vaccine are recommended for children and are especially appropriate for children with asthma.[100] Little risk from current influenza vaccines is present for those with allergy to eggs, and egg allergy is not a contraindication for influenza vaccination.[101] Also, an egg-free recombinant flu vaccine is readily available.

The best decision-making by the physician can fail unless the family or patient is adequately educated about the benefits and risks, if any, of each medication and the implementation of the treatment plan. Particularly important is having a simple written action plan that deals with periods of increased symptoms and exacerbations (**Box 12-3**). There is no advantage to complex plans with visual aids such as traffic light cartoon illustrations.[102]

Box 12-3

Intervention Action Plan Handout for an Acute Exacerbation of Asthma

Acute symptoms of asthma including cough, wheeze, or shortness of breath should be dealt with promptly. They are particularly likely to be triggered by a viral respiratory infection (common cold). Increasing cough after a day of a runny nose is often the first sign of asthma triggered by a viral respiratory infection. Medication taken daily as maintenance often does not prevent the acute flare of asthma from a viral respiratory infection. Prompt intervention can shorten the course and generally prevent the need for urgent medical care or hospitalization.

First: Use your inhaled bronchodilator.

If symptoms are not completely relieved: Repeat use of your inhaled bronchodilator.

If symptoms stop completely: Repeat use of your inhaled bronchodilator when necessary; consider a short course of oral corticosteroid after the third dose for acute symptoms within 8 hours or if you have more than 4 in 24 hours (other than for preventive use before exercise).

If symptoms are still not completely relieved: A short course of oral corticosteroids may be needed. If uncertain what to do, call your physician for advice. Otherwise, take a first dose of oral corticosteroid and notify your physician. (Dosage and instructions should already be on hand.) The response to oral corticosteroids is slow. For patients who have required emergency care or hospitalization, the oral corticosteroid should be started well before symptoms become severe.

Once corticosteroids are started, use of your inhaled bronchodilator can be repeated when needed. Maintenance medications should be continued.

Continued increase in the frequency of inhaled bronchodilator use or continued difficulty breathing may require hospitalization. Call your doctor or go to the emergency department of a hospital if you have continued difficulty breathing. Frequent intervention treatment for episodes of asthma requires reassessment of the management plan.

Natural History of Asthma

Parents frequently ask if their child will ever outgrow asthma. In the preschool- age child with episodic symptoms of asthma, the presence of atopy identified by the presence of allergen-specific IgE is predictive of continued symptoms throughout childhood, whereas those with no presence of a potential allergic component are likely to have marked reduction

or cessation of asthmatic symptoms by school age (**Figure 12-6**).[103] The long-term clinical course of asthma in young children was examined in a prospective study with repeated evaluations for more than 35 years (**Figure 12-7**).[104] On the basis of that survey, overall community prevalence for asthma symptoms in childhood was estimated to be about 20% in Australia, a rate similar to that described in the United States.[105] Continued asthma as an adult was related to the pattern of asthma in early childhood. Although inhaled corticosteroids are highly effective for decreasing symptoms of persistent asthma, the long-term disease course is not influenced. Attempts to modify the course of subsequent asthma by early use of inhaled corticosteroids have been unsuccessful.[106]

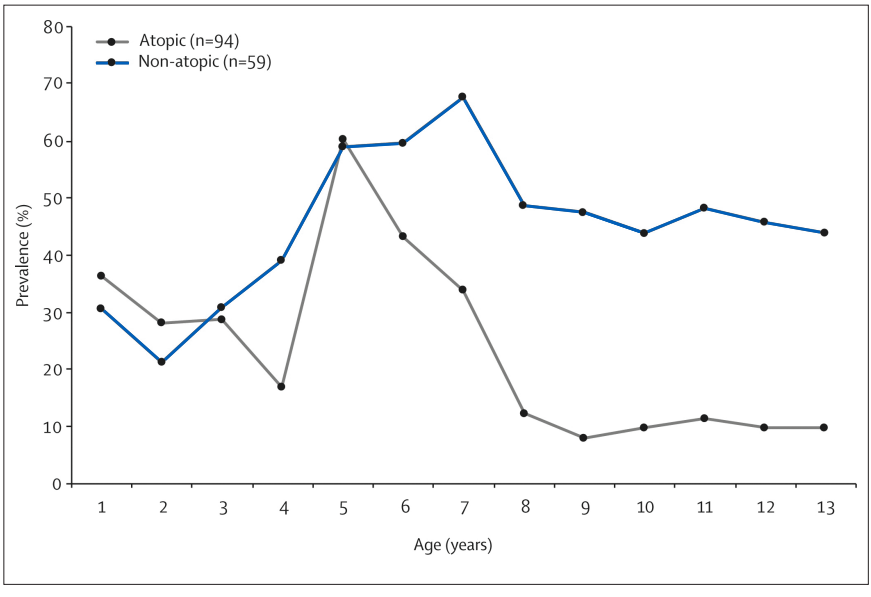


Figure 12-6. Influence of atopy on likelihood of experiencing continued symptoms of asthma from birth to age 13 years in children.

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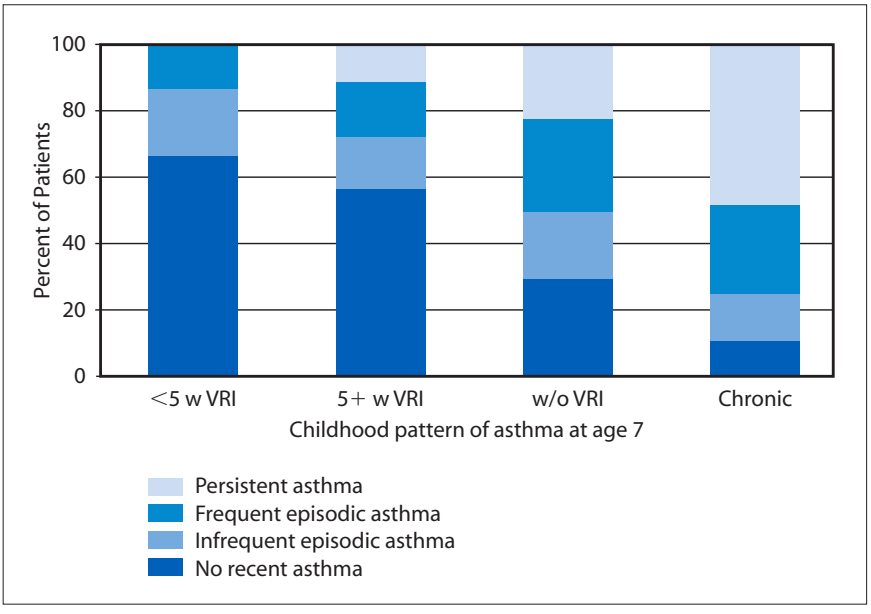


Figure 12-7. Clinical expression of childhood asthma at age 42 years among patients initially evaluated at age 7 years, with varying patterns and severity of asthma: < 5 w VRI were those who had a previous history of less than 5 viral respiratory infection–induced asthma symptoms before age 6 years. 5+ w VRI were those who had a history of having 5 or more viral respiratory infection–induced asthma symptoms before age 6 years. w/o VRI were those who had symptoms of asthma before age 6 years not limited to viral respiratory infection. Chronic were those identified at age 10 years with persistent asthma since before age 3 years. Each of these groups had about 100 children.

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Asthma Disparities

There are disparities in asthma treatment and outcomes for some populations of color and those living in underresourced communities. These disparities have been present for decades and continue to occur throughout the United

States.[107] Higher morbidity and mortality due to asthma are reported in Black, Indigenous American, and Hispanic children of Caribbean origin, compared with those in children of European descent. Black children have rates of hospitalization and emergency department visits 2 to 3 times higher than those of non-Hispanic white children and face a fivefold to tenfold higher asthma mortality rate.[108] These asthma disparities are primarily explained and driven by social factors.[109] A review of the literature on the effect of social determinants of health and discrimination is beyond the scope of this discussion, but numerous individual- and system-level factors combine to contribute to asthma disparities. Children in resource-limited communities have greater exposure to asthma triggers (eg, indoor and outdoor irritants, indoor allergens, stress).[110] They are also less likely to receive asthma treatments appropriate to their level of disease severity.[111] Interacting barriers include transportation, time, health literacy, food and housing insecurity, finances, and cultural alienation from pediatricians and other physicians. The result is difficulty in accessing optimal care and suboptimal use of the care received.[112,113]

The sensitivity and attention of pediatricians and other physicians to the challenges of caring for patients with asthma in these populations can improve outcomes.[114,115] Interventions are most likely to be successful when they involve a comprehensive multifocal approach that may go beyond the resources of individual physicians.[116] Comprehensive specialty clinic–based care should include evidence-based decisions and education to promote understanding of the disease and its treatment by the patient and family. The most successful programs are those using specialty care and employing case managers and social service workers to assist with transportation, housing quality, and food insecurity. Adverse childhood experiences as well as mental health disorders in both patients and their caregivers should be identified. Community health workers can help educate and mentor families. Alliances with medical and legal resources can ensure landlord compliance with housing codes and assist with other legal challenges. School nurses with whom children spend most of their days can review medication use and treatment of acute symptoms.[117–121]

key points

General

- Asthma is one of the most common chronic diseases of children.
- Asthma causes more hospitalizations than any other medical problem in children.
- Asthma is associated with rhinitis and atopic dermatitis as important comorbidities.

Clinical Characteristics of Asthma

- Asthma is both underdiagnosed and overdiagnosed.
- Intermittent asthma is most commonly a viral respiratory infection–induced phenotype in preschool-age children but is seen at all ages.
- The persistent asthma phenotype is characterized by the absence of extended symptom-free periods.
- The seasonal allergic phenotype is characterized by being limited to seasons that correspond to allergen-specific IgE to seasonal inhalant allergens.

Severity of Asthma

- Severity of asthma can be assessed on the basis of
  - Interference with activity from exercise limitation.
  - Interference with sleep from repeated nocturnal awakening.
  - Frequency of requirements for intervention measures, inhaled bronchodilators, and oral corticosteroids.
  - Urgent care visits or hospitalizations.

Management of Asthma

- Intervention measures for relief of acute symptoms are albuterol and oral corticosteroids.
- Maintenance medications for those with chronic or extended seasonal symptoms include inhaled corticosteroids, inhaled corticosteroids with long-acting bronchodilators, leukotriene modifiers, immunotherapy, and biologics.

Monitoring the Clinical Course of Asthma

- The patient's awareness of symptoms is essential to early intervention to prevent progression of exacerbations.
- Scheduled follow-up appointments for assessment and education are required to evaluate treatment adequacy and assess adherence to the treatment plan.

Evaluating and Managing Difficult Asthma

- Distinguishing between poor adherence and incorrect diagnosis may require calling the patient's pharmacy for a refill history of maintenance medication and observation of the patient's inhaler technique, as well as family education.

Natural History of Asthma

- Although some children will experience remission, many will continue to have symptoms of asthma well into adulthood.
- Children who have symptoms of asthma not limited to a viral respiratory infection have a greater likelihood of asthma symptoms persisting into adulthood.

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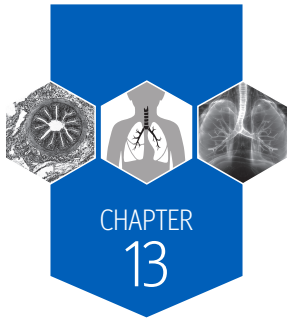
PART 3

Anatomical Disorders

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Congenital Abnormalities of the Upper Airway

James W. Schroeder Jr, MD, MBA, FACS, FAAP
Susanna A. McColley, MD, FAAP
Mary Bono Cataletto, MD, FAAP

Introduction

Obstructive lesions of the upper airway create turbulent airflow, which follows the laws of fluid dynamics. Rapidly flowing air moving across a narrowed segment of the respiratory tract creates vibrations that produce distinctive sounds, which are diagnostically useful to the clinician. The location of the obstruction in the airway will affect the phase, tone, and timing of the sound. The clinician can use this information to create a differential diagnosis. *Stertor* describes the low-pitched inspiratory snoring sound typically produced by nasal or nasopharyngeal obstruction. *Stridor* typically originates from the larynx, upper trachea, or hypopharynx. *Wheezing* is the expiratory sound produced by the turbulent flow of air through constricted lower airways (trachea and bronchi). This sound is similar to, and frequently mistaken for, other intrathoracic conditions such as bronchomalacia, tracheomalacia, or foreign bodies in the tracheobronchial tree.[1]

The timing of the noisy breathing can be particularly useful in determining the location of a congenital abnormality of the upper airway. As outlined in Holinger's laws of airway obstruction,[2] the severity of the noisy breathing in relation to the sleep-wake cycle is important. In general, when the noise is worse during sleep, the obstruction is nasal or pharyngeal, especially with tonsil and adenoid obstruction. If the symptoms are worse when the child is awake or if they are exacerbated by exertion, the obstruction is typically laryngeal, tracheal, or bronchial. These clues are helpful during the initial assessment. However, they are generalizations, and like most rules they have exceptions. For example, the initial presentation of a child with recurrent respiratory papillomatosis of the larynx is progressive upper airway obstruction during sleep rather than during exertion. In addition, infants with laryngomalacia may have inspiratory stridor with sleep.

The phase of breathing during which the sound occurs can also be diagnostic. Stertor is typically an inspiratory sound that occurs because of turbulent

airflow over a fixed or positional obstruction in the nasal cavity or pharynx. In infants, who are obligate nasal breathers, this turbulence will be greatest during inhalation. During exhalation, the infant will be able to use the oral cavity or will be able to displace nonfixed lesions and decrease or bypass the obstruction. Therefore, the noise will be less noticeable or nonexistent during exhalation. Stridor is most often an inspiratory sound. Based on the Bernoulli principle, a narrowing at the level of the larynx will cause the air flowing through the narrowing to increase in speed and therefore decrease the pressure in this area, which in turn causes the narrowed area to narrow even further, increasing the obstruction and the stridor. During exhalation, the opposite occurs. The non-fixed laryngeal lesion is forced laterally, opening the obstruction and decreasing the noise. However, if the laryngeal lesion is fixed, such as in the subglottis where the cricoid cartilage forms a complete ring, the lesion will not move during exhalation, and there will be a biphasic (inspiratory and expiratory) stridor. Intrathoracic lesions (tracheomalacia and bronchomalacia) create an expiratory sound (wheezing) owing to the exaggerated collapse of the airways during exhalation when the pleural pressure increases and compresses the bronchioles. During inhalation, when the pleural pressure decreases, the bronchioles enlarge, and no sound is produced.

Assessment

When assessing a child suspected of having a congenital anomaly of the upper airway, it is important to determine the severity and location of the obstruction. The severity of mild to moderate chronic persistent obstruction must be assessed in the presence of acute symptoms of respiratory distress (increased work of breathing, retractions, nasal flaring, and cyanosis). The mnemonic SPECS-R^3 (**Box 13-1**) is a useful tool to organize history taking and to determine the need for endoscopy in the operating room. This technique incorporates the parents' subjective interpretation of the child's obstruction along with a more objective measurement of the child's eating and sleeping behavior. Radiography is also a helpful tool in assessing obstruction in these children.

Box 13-1

Subjective Interpretation of Airway Obstruction

S: Severity—parents' subjective impression
P: Progression of the obstruction over time
E: Eating or feeding difficulties, aspiration, failure to thrive
C: Cyanotic episodes, apparent life-threatening events
S: Sleep obstruction so severe that retractions occur during sleep
R: Radiology-specific abnormalities detected on radiographs

Derived from Holinger LD. Diagnostic endoscopy of the pediatric airway. *Laryngoscope.* 1989;99(3):346–348.

Congenital Nasal Anomalies

Newborns are obligate nasal breathers. Therefore, an obstructive lesion of the nasal cavity can cause clinically significant respiratory distress in a neonate. The symptoms do not vary based on the location of the lesion in the nasal cavity. In general, the respiratory distress caused by nasal obstruction is worse at rest and can be relieved with crying because the oral cavity is open. Some common congenital nasal anomalies are listed in **Box 13-2**.

Box 13-2

Congenital Anomalies of the Upper Airway

Congenital Nasal Anomalies
- Pyriform aperture stenosis
- Choanal atresia
- Nasolacrimal duct cyst
- Nasal dermoid, glioma, encephalocele
- Cleft lip nasal deformity

Craniofacial Abnormalities
- Crouzon syndrome
- Apert syndrome
- Pierre Robin sequence
- Down syndrome

Congenital Lesions of the Tongue
- Macroglossia
- Vascular malformations
- Tumors (rhabdomyosarcoma)
- Tongue base
- Ectopic thyroid
- Lingual thyroid
- Thyroglossal duct cyst

Congenital Laryngeal Anomalies
- Laryngomalacia
- Laryngocele
- Saccular cysts
- Subglottic stenosis
- Vocal cord paralysis

Pyriform Aperture Stenosis

Pyriform aperture stenosis, also called *anterior nasal stenosis*, is caused by prenatal overgrowth of the medial maxilla, which narrows the pyriform aperture at the front of the nasal cavity. This condition is often not readily noticed at physical examination and can be diagnosed by means of a craniofacial computed tomography (CT) scan demonstrating a narrowed pyriform aperture in relation to the posterior choanae.[4,5] This stenosis can also be seen in conjunction with a mega-incisor, which may be associated with holoprosencephaly.[6] These children should be evaluated with neuroimaging and for other endocrine abnormalities associated with an abnormal hypothalamic-pituitary-adrenal axis. Conservative therapy with topical decongestants and steroids is helpful in infants with mild symptoms. The use of noninvasive airway support (such as positive airway pressure) may also be considered for infants with clinically significant obstructive symptoms. Pyriform aperture stenosis causing clinically significant respiratory distress can be corrected surgically through a sublabial incision.

Choanal Atresia

Choanal atresia is an uncommon disorder that is the most common cause of complete nasal obstruction in the neonate. It occurs when the posterior choanae fail to develop properly. The published incidence varies from 1 in 5,000 to 1 in 8,000 live births.[7] Both sexes are affected, but reports suggest a female predominance of 2 to 1; unilateral cases are more common than bilateral cases and may not be diagnosed until later in life.[8,9] Bony atresia (90%) is more common than membranous atresia (10%); however, some investigators suggest that mixed bony-membranous anomalies may have the highest incidence.[10] One way to screen for this condition is to attempt to pass a flexible catheter through each of a newborn's nasal cavities. Failure to pass a 6F catheter successfully more than 32 mm (1.3 inch) past the anterior nares requires further workup. Axial CT scanning of the nasal cavity and/or nasal endoscopy can help confirm the diagnosis. Orotracheal intubation or an oral airway device must be used to relieve the obstruction until the patient is a candidate for surgery. Unilateral atresia may not be noticed until later in life and most often manifests with persistent unilateral rhinorrhea. Choanal atresia is associated with other congenital anomalies 43% to 72% of the time.[11] It is most commonly seen as part of the CHARGE association—coloboma of the eye, heart defects, atresia (choanal), restricted growth and development, genitourinary hypoplasia, and ear anomalies. Nonsyndromic choanal atresia is usually sporadic and most likely multifactorial. Surgical correction can be performed via a transoral transpalatal approach or, more commonly, through a transnasal endoscopic approach that often requires postoperative stent placement followed by repeat dilations.

Nasolacrimal Duct Cyst

If the nasolacrimal duct is not patent at birth, it will typically become patent during the first month after birth.[12] If the nasolacrimal apparatus fails to canalize, a nasolacrimal duct cyst can develop and expand into the nose from under the inferior turbinate and enter the inferior meatus, causing nasal airway obstruction. The cyst can occasionally be seen via anterior rhinoscopy, but the diagnosis is confirmed by means of nasal endoscopy after nasal decongestion and/or CT scanning or magnetic resonance imaging (MRI) of the sinuses.[5] The cyst can become infected and cause swelling and erythema of the medial canthus and purulent orbital discharge. Treatment consists of endoscopic marsupialization and nasolacrimal duct probing.

Nasal Dermoid, Glioma, and Encephalocele

Nasal dermoids, gliomas, and encephaloceles are congenital midline nasal lesions that are believed to result from abnormal closure of the anterior neuropore. All encephaloceles and many dermoids and gliomas communicate with the central nervous system. Therefore, no congenital nasal mass or polyp in

a child should be manipulated until intracranial communication is ruled out. Computed tomography and MRI are required for diagnosis and surgical planning.[8] Dermoid sinuses and cysts generally occur in the nasal midline and can manifest as a fistulous tract or a mass anywhere from the nasal tip to the glabella.[13] Hair or sebaceous material may protrude from the pit, and patients may present with drainage. Gliomas and encephaloceles are similar in clinical appearance and histological characteristics. Gliomas are unencapsulated collections of glial cells that may retain attachments to the dura. Encephaloceles are herniations of the meninges with or without brain tissue through the skull base and communicate with the subarachnoid space.[14] They usually manifest early in life but can be unrecognized until adulthood. Unlike dermoids, they do not routinely occur in the midline, nor do they connect via a sinus tract to the skin. These lesions are surgically removed jointly by an otolaryngologist and neurosurgeon using a combination of external and endoscopic approaches.

Cleft Lip Nasal Deformity

The incidence of clefts of the lip and/or palate is approximately 1 in 800 live births.[15] The nasal deformity resulting from flattening of the nasal bridge and ala can be associated with clinically significant nasal obstruction. The nasal deformity is corrected surgically after the cleft lip is repaired.[8]

Craniofacial Abnormalities

Craniofacial abnormalities can be associated with airway compromise by obstructing the nose, nasopharynx, oropharynx, or hypopharynx (**Box 13-2**). Crouzon syndrome (craniofacial dysostosis) is defined by craniosynostosis and maxillary hypoplasia. The resulting midface hypoplasia and high-arched palate can lead to nasal obstruction. Severe cases can warrant intubation or tracheostomy. Apert syndrome (acrocephalosyndactyly) is also marked by severe maxillary hypoplasia resulting in proptosis and relative prognathism. The underdeveloped nose and high-arched palate result in clinically significant nasal obstruction. Apert syndrome is also associated with syndactyly of the hands, which differentiates it from Crouzon syndrome. Pierre Robin sequence (cleft palate, micrognathia, and glossoptosis) can cause severe pharyngeal airway obstruction at birth. In mild cases, prone positioning can help. In more severe cases, placement of an oral airway device or an intubation may be needed to bypass the obstruction caused by the base of the tongue. Mandibular distraction can eliminate the obstruction by pulling the tongue base forward and relieving the glossoptosis. A tracheostomy is occasionally needed until the distraction is completed or the mandible has grown sufficiently. This sequence can be associated with Stickler syndrome, and genetic workup is required.

Down syndrome (trisomy 21) occurs in approximately 1 in 722 live births and is the most common congenital chromosomal anomaly.[16] There are multiple head and neck morphological abnormalities in these children that predispose

them to disease. These abnormalities include midface hypoplasia, which is characterized by malformation of the eustachian tube, a shortened palate, macroglossia, and a narrowing of the oropharynx and nasopharynx.[17] In combination with systemic hypotonia, these abnormalities underlie the high incidence of recurrent otitis media and obstructive sleep apnea in children with Down syndrome. Obstructive sleep apnea is the most common cause of upper airway obstruction in children older than 1 year. Nearly 50% of parents of these children do not report a sleep disturbance despite abnormal findings during a sleep study. The true incidence of obstructive sleep apnea is unknown, and a high level of suspicion should be maintained. Laryngomalacia is seen in approximately 50% of children with Down syndrome. Tracheomalacia occurs in about one-third, most of whom have congenital heart disease.[16]

Congenital Lesions of the Tongue

Macroglossia

Beckwith-Wiedemann syndrome is the most common cause of macroglossia in children.[18] Macroglossia can also be seen with trisomy 21, congenital hypothyroidism, vascular malformations, muscular enlargement, and tumors. Lymphangiomas or hemangiomas of the tongue may cause clinically significant airway obstruction present at birth. Lymphangiomas are most common and are apparent at birth in 60% of cases.[19] Symptoms include dysphagia; drooling; disarticulation; and a dried, fissured tongue. In cases of severe obstruction, intubation or tracheostomy may be required, followed by surgical reduction of part of the tongue. In children, tumors of the tongue are rare, but rhabdomyosarcoma can occur, and 20% of these tumors that occur in the head and neck occur in the tongue (**Box 13-2**).[19]

Congenital Lesions of the Base of the Tongue

Congenital lesions of the base of the tongue are rare and include ectopic thyroid tissue, most commonly a lingual thyroid, and thyroglossal duct cysts. A lingual thyroid can manifest with upper airway obstruction in a newborn or as part of the workup for congenital hypothyroidism. Seventy percent to 100% of children with ectopic thyroid tissue in the tongue have no other thyroid tissue.[20,21] The diagnosis can be confirmed with CT scanning, ultrasonography, or MRI. Radionuclide scans will help localize functioning thyroid tissue. The ectopic thyroid tissue is subject to the same pathological changes as normal thyroid tissue (including cancer), but it is usually associated with hypothyroidism. Treatment includes suppression therapy to prevent enlargement, hypothyroidism, and malignancy.[20–22] Radioactive iodine-131 ablation has also been described.[20] However, when the obstruction is not corrected with suppression therapy or if malignancy is suspected, surgical excision is the treatment of choice and can be accomplished through transoral and transcervical approaches.

Thyroglossal Duct Cysts

Thyroglossal duct cysts are the most common malformations found in the neck and account for 70% of congenital cervical abnormalities. Although they can manifest at any age, most are detected in the first 2 decades, making them primarily a pediatric disease.[23] Thyroglossal duct cysts usually manifest as a midline cervical mass that lies either directly above the hyoid bone or just below it. The mass typically moves with protrusion of the tongue. Besides the cosmetic deformity associated with these lesions, they can become recurrently infected; therefore, surgical excision is the treatment of choice. The cyst is removed through a midline cervical incision, along with the central portion of the hyoid bone, as well as the associated tract in the base of tongue. This is called the *Sistrunk procedure*.

Congenital Laryngeal Anomalies

Laryngomalacia

Laryngomalacia is the most common cause of inspiratory stridor in infants.[24] Symptoms typically begin 1 to 3 weeks after birth and usually progress over several months. It is caused, in part, by decreased laryngeal tone leading to supraglottic collapse during inspiration.[24–26] Gastroesophageal reflux disease and neurological disease influence the severity of the disease and, thereby, the clinical course.[24–26] Greater disease severity is associated with low Apgar scores at birth. The diagnosis is established primarily based on symptoms that include stridor, dysphagia, apnea, cyanosis, and failure to thrive. The stridor associated with laryngomalacia is inspiratory and can be worsened by the patient's agitation and while feeding. It can also be worsened when the infant is supine and in a relaxed state and therefore can be heard during sleep. Flexible fiberoptic laryngoscopy with the patient awake is used to confirm the diagnosis and to differentiate the cause of the stridor from other glottic disease. In otherwise healthy children, laryngomalacia typically resolves by 1 year of age without surgical intervention. However, in 15% to 20% of patients, symptoms are severe enough to cause progressive respiratory distress, cyanosis, or failure to thrive.[27,28] In these patients, supraglottoplasty is considered. This procedure may be performed using cold knife instrumentation, carbon dioxide laser, or microdebrider techniques. All techniques focus on directed removal of the redundant cuneiform cartilages, the lysis of tight aryepiglottic folds, and the occasional removal of obstructing portions of the epiglottis. Potential complications include persistent airway obstruction requiring further surgery, supraglottic stenosis, dysphasia, aspiration, and death.[29] Supraglottoplasty is more than 90% successful in relieving upper airway obstruction caused by severe laryngomalacia.[29]

Laryngocele and Saccular Cysts

A laryngocele is an abnormal dilatation or herniation of the laryngeal saccule, which rises vertically between the false vocal cords, the base of the epiglottis, and the inner surface of the thyroid cartilage. It communicates with the lumen of the larynx and is filled with air. An internal laryngocele is confined to the interior of the larynx and extends posterosuperiorly into the area of the false vocal cords and aryepiglottic folds, causing a mass that can be seen by means of direct or indirect laryngoscopy. An external laryngocele extends cephalad to protrude laterally into the neck through the thyrohyoid membrane, manifesting as a neck mass.[30] A laryngocele may be solely congenital; it may be a congenital defect made apparent or exacerbated by habitual, increased intralaryngeal pressure; or it may be acquired solely on the basis of prolonged increased intralaryngeal pressure. A saccular cyst is distinguished from a laryngocele in that the lumen is isolated from the interior of the larynx and it does not contain air. These cysts result from a developmental failure of the saccular orifice to maintain patency.[30] Inflammation, trauma, and tumors may occlude the orifice as well. Therefore, saccular cysts can be congenital or acquired.

In infants and children, laryngoceles cause hoarseness and dyspnea that may increase with crying. Saccular cysts cause respiratory distress and stridor. Laryngocele is diagnosed by means of a soft-tissue posteroanterior radiograph of the neck. If the laryngocele is not distended at the time the image is obtained, the image of the larynx will be normal. Saccular cysts are diagnosed by means of direct laryngoscopy. Cysts can be treated endoscopically with repeat needle aspiration or with excision through marsupialization and unroofing. External excision through a lateral horizontal cervical incision can be used in recurrent cases.[30]

Congenital Subglottic Stenosis

Congenital subglottic stenosis is the second most common cause of stridor in neonates.[1] The subglottis is the narrowest part of the upper airway in a child. Subglottic stenosis is a narrowing of the subglottic larynx, which is the space extending from the undersurface of the true vocal cords to the inferior margin of the cricoid cartilage. It typically causes respiratory distress and biphasic stridor. In mild cases, the child may present with recurrent croup before the age of 1 year. The edema and thickened secretions of the common cold further narrow an already marginal airway, leading to crouplike symptoms. The stenosis can be caused by abnormally shaped cricoid cartilage; by a tracheal ring that becomes trapped underneath the cricoid cartilage; or by soft-tissue thickening caused by ductal cysts, submucosal gland hyperplasia, or fibrosis.[31] The diagnosis can be established by means of posteroanterior and lateral airway radiographs and confirmed by means of endoscopic examination. During diagnostic laryngoscopy and bronchoscopy, the subglottic larynx is visualized directly and sized objectively by using an endotracheal tube. The percentage of stenosis is determined by comparing the size of the patient's larynx to a standard of laryngeal dimensions

based on age.[32] The degree of stenosis will help dictate treatment. Children with stenosis greater than 50% tend to have more symptoms and more often require treatment. Surgical options include bronchoscopy with balloon dilation, laryngotracheal reconstruction, and cricotracheal resection. Laryngotracheal reconstruction involves augmenting the subglottis with an anterior or posterior cartilage graft placed in the cricoid cartilage. This reconstruction can be performed via an open technique through a cervical neck incision or endoscopically through the oral cavity, depending on the type and degree of stenosis. A cricotracheal resection involves removing most of the stenosed cricoid cartilage and re-anastomosing the trachea to the larynx. The postoperative care is critical and often requires multiple bronchoscopies to ensure patency and prevent repeat stenosis.

Vocal Cord Paralysis

Vocal cord paralysis in infants is the third most common cause of stridor in infants, after laryngomalacia and subglottic stenosis.[1] In approximately 40% of cases, bilateral vocal cord paralysis in infants is the result of central congenital anomalies.[33] It is found most commonly in association with myelomeningocele, Arnold-Chiari malformation, and hydrocephalus. Unilateral vocal cord paralysis is most often iatrogenic as a result of surgical treatment for gastrointestinal (tracheoesophageal fistula) and cardiovascular (patent ductus arteriosus repair) anomalies. Unilateral vocal cord paralysis is seen most often on the left because of the longer course of the recurrent laryngeal nerve on this side. Internal trauma, such as with an endotracheal tube or nasogastric tube, and external trauma, including birth trauma, strangulation injury, or motor vehicle accidents, may lead to vocal cord paralysis.

Bilateral vocal cord paralysis manifests with a high-pitched, inspiratory stridor and respiratory distress similar to the manifestation of laryngomalacia. However, in this case, it is the vocal cords that are drawn together during inspiration causing stridor rather than the supraglottic structures. The vocal cords are pushed apart during exhalation, relieving the obstruction. Children with unilateral vocal cord paralysis can experience aspiration leading to cough and a weak, breathy cry. Airway obstruction and stridor are less common in these patients because the paralyzed vocal cords tend to stay fixed in a lateral position. The diagnosis is confirmed using flexible fiberoptic laryngoscopy without anesthesia. Once the diagnosis is established, determining the cause should include pediatric otolaryngology, neurology, and cardiology consultations and may include chest and neurological imaging, depending on the patient's history.

Vocal cord paralysis resolves spontaneously within 6 to 12 months in 48% to 62% of infants.[34] If it does not resolve within 2 to 3 years, it is unlikely to do so.[33] Treatment is based on the severity of the patient's symptoms. In patients with bilateral vocal cord paralysis and respiratory distress, a trial of intubation may be warranted to allow a chance for spontaneous recovery. If this does not occur, surgical intervention may be considered. Procedures that widen the posterior

glottis to relieve the obstruction include laryngotracheal reconstruction by using an endoscopically placed posterior glottic cartilage graft, arytenoidectomy, or arytenoid lateralization. These procedures are successful in reducing the obstruction. However, they may worsen the patient's voice quality, and they may result in aspiration that can become severe. Tracheostomy is sometimes necessary. In cases of unilateral vocal cord paralysis in which aspiration and a hoarse cry are the main symptoms, vocal cord medialization is often used, most commonly performed endoscopically through an injection technique. A temporary injectable material, such as absorbable gelatin sponge or endogenous fat, may be injected into the larynx to medialize the vocal cord and decrease aspiration. The material will absorb in 3 to 6 months and, if it was successful, another injection with a more permanent substance can be used. The main complication is overinjection, leading to postoperative respiratory distress, which is most often temporary.

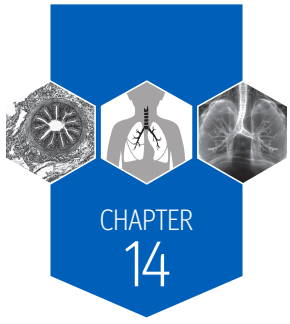
key points

- Stertor is the low-pitched inspiratory, snoring sound typically produced by nasal or nasopharyngeal obstruction.
- Stridor is an inspiratory sound (occasionally biphasic) that typically originates from the larynx, upper trachea, or hypopharynx.
- Wheezing is the expiratory sound produced by the turbulent flow of air through constricted bronchioles.
- Pyriform aperture stenosis seen in conjunction with a mega-incisor may be associated with holoprosencephaly.
- Choanal atresia should be suspected by the failure to pass a 6F catheter more than 32 mm (1.3 inch) past the anterior nares.
- The Crouzon and Apert syndromes are defined by craniosynostosis and maxillary hypoplasia, which can result in severe upper airway obstruction.
- The Pierre Robin sequence (cleft palate, micrognathia, and glossoptosis) can cause severe pharyngeal airway obstruction that is present at birth.
- Lymphangiomas are the most common cause of macroglossia in children and are apparent at birth in 60% of cases.
- Thyroglossal duct cysts are the most common malformations found in the neck and account for 70% of congenital cervical abnormalities.
- Laryngomalacia is the most common cause of inspiratory stridor in infants and typically begins 1 to 3 weeks after birth and resolves by about 1 year of age.
- Subglottic stenosis is the second most common cause of stridor in neonates.
  - It typically manifests with respiratory distress and biphasic stridor.
  - In mild cases, the child may present with recurrent croup before the age of 1 year.
- Paralysis of the vocal cords is the third most common cause of stridor in infants. Bilateral paralysis in infants is the result of central congenital anomalies in approximately 40% of cases.

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CHAPTER
14

Congenital Lung Anomalies

Brian P. O'Sullivan, MD
T. Bernard Kinane, MD

Congenital lung malformations are a spectrum of disorders arising from errors in formation of the airways or vascular supply of the lung. Although major congenital lung malformations are often presented as separate entities, there is great overlap between these abnormalities, and a single congenital abnormality may not fit neatly into one category.

The wheel theory of airway and vessel malinosculations (**Figure 14-1**) helps to understand the malformations.[1] In this approach, the developmental interactions of bronchial, acinar, and vascular components are interpreted along a continuum. A congenital abnormality may be isolated to large airways (eg, tracheomalacia), involve abnormalities in both bronchial and vascular development (eg, pulmonary sequestration), or involve the vasculature only with secondary airway involvement (eg, vascular rings). Recently, the unifying term *congenital pulmonary airway malformation* (CPAM) has been adopted to describe these malformations. However, in practice, many clinicians still refer to the malformations by specific names, and this chapter uses that approach to describe variations in clinical presentation and treatment. To appreciate these differences, a basic review of lung development is useful.

Lung Growth and Development

Prenatal lung development occurs in 5 stages: embryonic (0–5 weeks after conception), pseudoglandular (6–16 weeks), canalicular (17–24 weeks), saccular (24–38 weeks), and alveolar (38 weeks to years) (**Figure 14-2**).[2,3] There is tremendous interaction between the developing endoderm and mesoderm as airways and acini develop, and errors in regulation of differentiation depend on the 3 Cs: communication, complexity, and critical timing. For example, differentiation of the bronchial tree is complete by the end of the pseudoglandular period (16 weeks of gestation). Thus, events that disrupt the complex communication between genetic promotors and regulators at critical points in development (ie, before 16 weeks of gestation) will affect airway development, whereas events occurring after 16 weeks will affect development of terminal respiratory bronchioles and alveoli (the acinus). See also Chapter 1, Anatomy of the Lung.

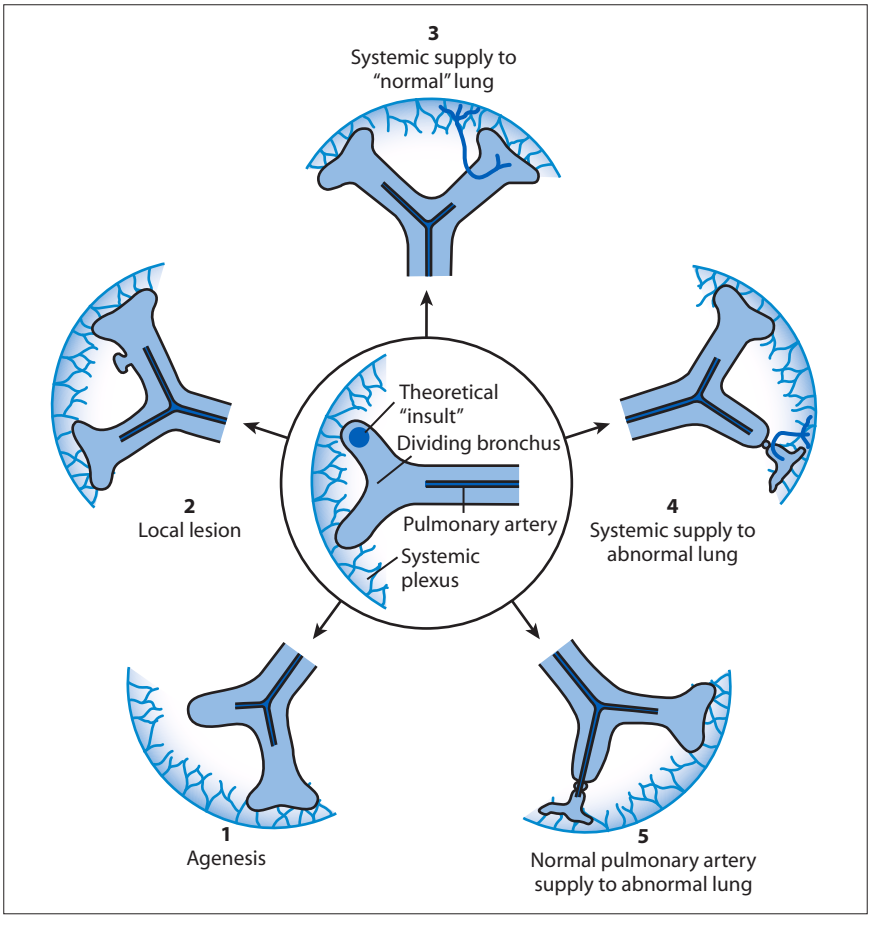


Figure 14-1. Wheel theory of abnormal lung development: (1) agenesis of lung segment, (2) budding lesion of airway (eg, bronchogenic cyst), (3) systemic blood supply to normal lung segment, (4) systemic blood supply to abnormal lung segment (eg, sequestration), and (5) normal blood supply to abnormal lung segment.

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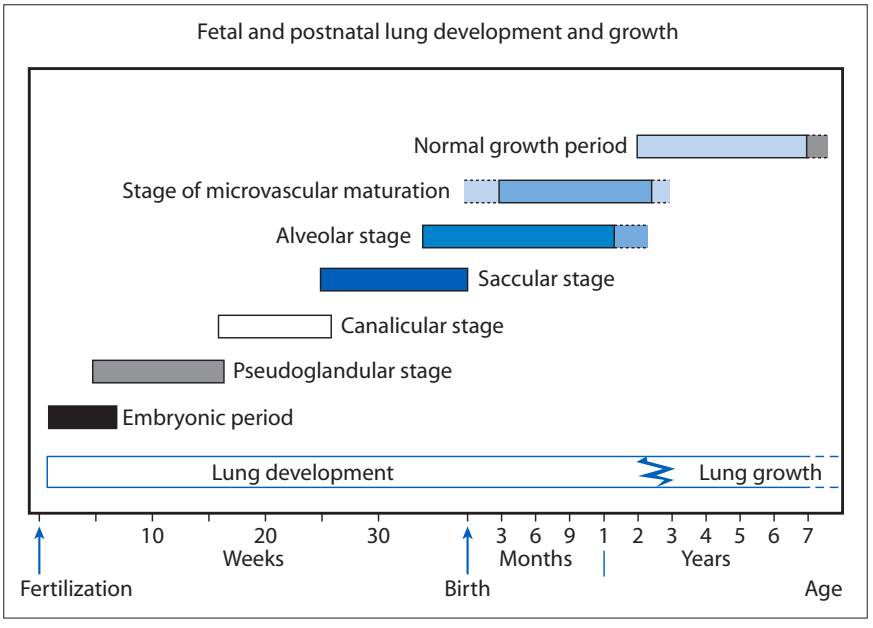


Figure 14-2. Intrauterine stages of lung development. Airway branching is complete by the end of the pseudoglandular phase (16 weeks after conception).

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Laryngomalacia

See Chapter 13, Congenital Abnormalities of the Upper Airway, for a discussion of laryngomalacia.

Tracheobronchial Abnormalities

Disorders of the large airways include tracheobronchomalacia, tracheomegaly, and tracheal bronchus. Of these, tracheal bronchus, an aberrant lobar bronchus arising above the carina, which supplies 1 or all 3 of the right upper lobe segments, is most common, occurring in up to about 2% of people (**Figure 14-3**).[4] In most instances, tracheal bronchus is a benign variant of no clinical significance. However, if the orifice of the tracheal bronchus is small and easily plugged, it can lead to recurrent right upper lobe atelectasis or infection. Similarly, obstruction of the tracheal bronchus by an endotracheal tube can lead to problems in patients requiring mechanical ventilation.



Figure 14-3. Coronal oblique computed tomography minimal intensity projection reformat image demonstrating tracheal takeoff of the right upper lobe bronchus (tracheal bronchus).

Tracheomalacia refers to an excess in compliance of the airway that predisposes the trachea to dynamic collapse. Tracheomalacia and bronchomalacia may be primary or secondary to other congenital anomalies. Mass lesions, such as vascular rings and bronchogenic cysts, can cause indentation and malacia of the developing tracheobronchial tree with resultant airway collapse and shifts in intraluminal pressure during the respiratory cycle. Primary tracheobronchomalacia occurs in about 1 in 2,000 infants and may be misdiagnosed initially as asthma.[5,6] Because of the increased compliance, the malacic airway is prone to narrowing during expiration when intrathoracic pressure is increased. A wheeze caused by narrowing of a single large intrathoracic airway during expiration differs from the wheezing of someone with asthma. The child with asthma has many small airways involved, all to a differing degree, such that the wheeze will be orchestral (polyphonic) and vary in pitch and intensity during auscultation of different chest regions. The child with tracheobronchomalacia has narrowing of a single large airway during expiration (when pleural pressure exceeds intraluminal pressure), leading to a monophonic wheeze that has the same characteristics throughout the chest. In contrast to tracheomalacia, a fixed lesion causing constant large airway narrowing that does not vary with changes in pleural pressure will cause noisy breathing during inspiration and expiration. The diagnosis can often be established by means of history and physical examination, but bronchoscopy is the gold standard for diagnosis. More recently, multidetector 2-dimensional and 3-dimensional computed tomography (CT) scans have been used to demonstrate dynamic airway collapse and offer a noninvasive diagnostic modality at the cost of increased exposure to ionizing radiation.

Common symptoms for tracheomalacia and bronchomalacia include a brassy or barking cough, monophonic wheeze, noisy breathing, recurrent pulmonary infections due to ineffective airway clearance, apnea, and episodes of pallor and apnea (ie, "dying spells").[7] Treatment consists of supportive care, including optimizing airway clearance, because dynamic collapse with cough may

lead to obstruction and infection. Use of bronchodilators such as albuterol can cause further collapse owing to relaxation of supporting musculature. Ipratropium bromide may help by decreasing airway secretions and increasing airway tone. Tracheomalacia is often associated with congenital abnormalities such as a tracheoesophageal fistula (TEF) or vascular ring and will not resolve spontaneously; however, growth of the trachea leads to an increased lumen, and a moderate degree of collapse will become less important over time. Surgery is required in cases associated with other anomalies such as TEF. In the case of primary tracheomalacia, surgery is reserved for the most severe cases and generally consists of procedures that lift major vessels away from the trachea or tether the trachea posteriorly.[8]

A much less common tracheal abnormality is tracheobronchomegaly, known more familiarly as *Mounier-Kuhn syndrome*, which results from absence or atrophy of elastic fibers and smooth muscle in the wall of the airways. The loss of tracheal wall support leads to dilatation and development of diverticula. Mounier-Kuhn syndrome has been seen in association with other disorders of connective tissue, including Ehlers-Danlos syndrome and cutis laxa.[9] Mounier-Kuhn syndrome usually manifests in the third or fourth decade of life, which has led to some debate as to whether it is a congenital or an acquired anomaly. The weakened and dilated walls of the large airways collapse during forced exhalation (cough), decreasing mucociliary clearance and increasing the probability of repeated infections.[9] Involvement of smaller, more peripheral airways will lead to bronchiectasis. Acquired forms of tracheomegaly result from intubation and high-pressure ventilation in neonates. Plain chest radiographs may lead to suspicion of the diagnosis, but CT scanning with comparison to normal tracheal diameter for age is necessary to establish the diagnosis. A CT scan is diagnostic if the trachea is more than 3 SDs above mean reference values.[10]

Tracheoesophageal Fistula

Tracheoesophageal fistula is an early embryological defect in foregut differentiation. The incidence of these malformations is approximately 1 in 3,000 births.[11] The rate is increased in multiple birth pregnancies and white babies. A genetic basis is plausible, and the reoccurrence rate is about 2% in children of an affected parent. Most cases of TEF, however, are sporadic. Tracheoesophageal fistula can occur in association with chromosomal abnormalities such as trisomies (18 and 21) and deletions of 22q11, and an increased incidence occurs in DiGeorge syndrome, Pierre Robin syndrome, Holt-Oram syndrome, and Feingold syndrome.

There are several types of TEF (**Figure 14-4**). Esophageal atresia with distal TEF accounts for 86% of cases. In this form, the proximal esophagus is dilated and usually ends high in the mediastinum. The distal esophagus is usually much smaller in diameter and usually communicates with the distal trachea via a fistula to a point about 2 cm proximal to the carina (**Figure 14-4A**). The distance between the proximal pouch and distal esophagus can vary. Isolated esophageal atresia without fistula accounts for 10% of cases. In this formation, the proximal esophagus ends high in the posterior mediastinum. The distal esophagus usually ends low in the mediastinum just above the diaphragm. The distance between the 2 ends is substantial and usually does not allow for a primary repair (**Figure 14-4E**).

H-type TEF accounts for approximately 4% of cases. In H-type TEF, both the esophagus and trachea are continuous cephalad to caudad, but there is a fistulous connection between the 2 tubular structures. The fistula is very narrow and usually is found in the lower cervical region. Usually there is a single fistula, but multiple fistulas have been described (**Figure 14-4D**).

The mechanism that underlies tracheoesophageal malformation is a subject of intensive investigation. Formation of the trachea is a multistage process. Initially, a groove forms in the posterior foregut, the sulcus laryngotrachealis, then a septum separates the groove, thus forming the primitive trachea and esophagus.[3] Both genetic and environmental factors are likely to contribute to developmental abnormalities affecting this separation and subsequent formation of a normal trachea and esophagus. Fifty percent or more of infants with tracheoesophageal malformation have at least 1 other congenital abnormality.[12] Esophageal atresia without a fistula has the highest incidence of associated abnormalities, and H-type fistula has the lowest. Tracheoesophageal fistula has been associated with a number of syndromes including the VATER association (vertebral, anorectal, tracheoesophageal, and renal or radial abnormalities), VACTERL association (C cardiac, L limb), and the CHARGE association (coloboma, heart defects, atresia [choanal], restricted growth and development, genital hypoplasia, and ear deformities).

The classic presentation of a child with esophageal atresia is coughing, choking, and aspiration during the first feeding. These infants also have excessive salivation because their saliva pools in the esophageal pouch. A plain radiograph of the chest is usually diagnostic and should show the tip of a nasogastric catheter curled up in the upper pouch at the level of thoracic vertebrae. Associated findings on the radiograph provide insight into which type of malformation is present. If air is present in the stomach, a distal TEF is probable (**Figure 14-4C**). Alternatively, the lack of gastrointestinal air suggests isolated atresia. H-type fistulas may not manifest until a child is several months old and has chronic coughing or choking with feeding and recurrent pneumonia. A

persistently distended abdomen caused by air migrating from the trachea into the intestinal tract may also occur. The diagnosis is established by performing a barium study with contrast material infused through a nasogastric tube under gentle pressure to distend the esophagus in the distal to proximal direction (**Figure 14-5**).

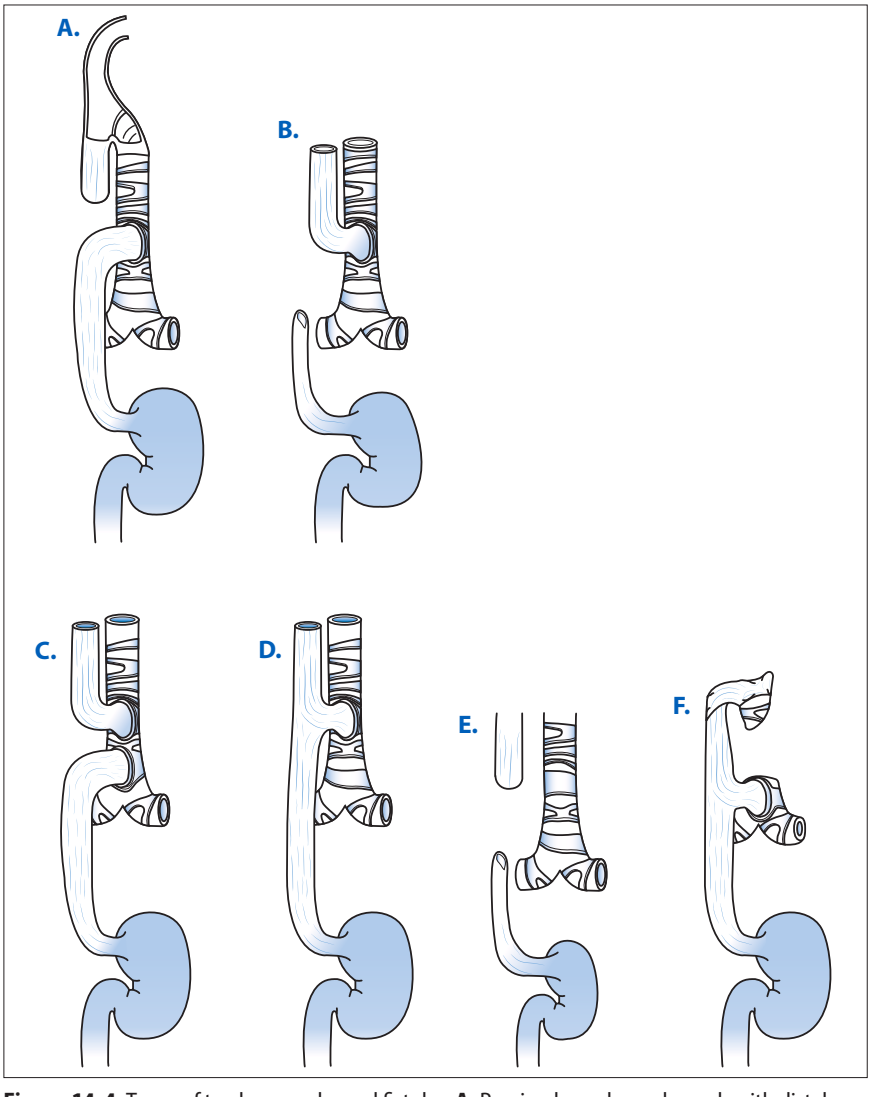


Figure 14-4. Types of tracheoesophageal fistulas. **A,** Proximal esophageal pouch with distal fistula. **B,** Proximal fistula with distal isolated esophagus. **C,** Disrupted esophagus with proximal and distal fistula. **D,** H-type fistula. **E,** Esophageal atresia without fistula. **F,** Upper and lower fistula without esophageal atresia.

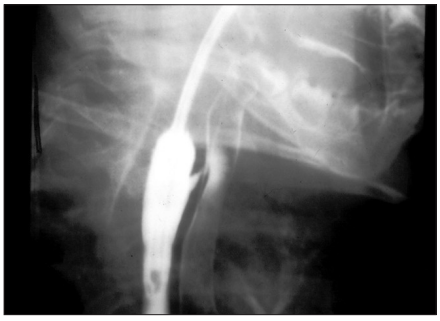


Figure 14-5. Lateral esophagram image demonstrating H-type tracheoesophageal fistula. Note the contrast in the distended esophagus with contrast material crossing across the fistula and outlining the trachea.

Surgical correction of the esophageal abnormality is mandatory. Preoperative management is critical. A suction tube (Replogle catheter) should be placed in the upper pouch to prevent aspiration. Likewise, the child should be positioned upright to prevent reflux into the trachea through the distal fistula. Surgery can normally be performed electively. The exception is when an infant with a distal fistula is in severe respiratory distress requiring ventilatory support. High-pressure gas delivered to the trachea can cross the fistula and may lead to dangerous inflation of the stomach with possible gastric rupture. In such cases, surgery should be performed emergently.

Most defects can be corrected in a single procedure. A number of strategies have been developed to facilitate a primary anastomosis and ligation of the fistula. In children with pure esophageal atresia, there may be a long gap between the 2 esophageal remnants, necessitating a modified approach. Many procedures have been developed to apply tension on the esophageal ends over a period of 6 to 10 days to approximate the pouches and allow a primary anastomosis. Rarely, patients require the placement of a large-bowel graft known as *colonic interposition*.

Postoperative complications are common, including anastomosis leakage, anastomotic stricture, and recurrent fistulas. Leaks occur in about 20% of cases, and one-third of these events leads to a major disruption and may require emergency surgery. Anastomotic strictures occur in about one-third of patients who require dilation. Recurrent TEF occurs in about 10% of cases and should be considered if the infant has respiratory symptoms during feeding or has recurring pneumonia after initial corrective surgery.

Tracheoesophageal fistula is not simply an anatomical malformation manageable with corrective surgery. Residual postsurgical issues should be expected because of the abnormal tracheal and esophageal development in utero. Among these are gastroesophageal reflux, tracheomalacia, and esophageal dysmotility. Long-term respiratory complications are common, with 40% of patients having wheezing and brassy cough at 15 years of age.[13,14] Tracheomalacia occurs in at least 15% of cases. Results from 2 long-term studies have shown that respiratory morbidity and pulmonary function abnormalities are

common in children and adolescents after TEF repair. These studies' results have shown both obstructive and restrictive issues. Birth weight, interpouch distance, and postoperative complications are important predictors of longer-term outcomes.[15,16]

Pulmonary Agenesis or Hypoplasia

The most severe form of lung malformation is agenesis of both lungs. This malformation is believed to be a result of loss of development of the trachea or the main pulmonary arteries. Complete pulmonary agenesis is incompatible with life. However, lesser degrees of agenesis, such as absence of 1 lung or 1 lobe, occur. Complete agenesis of the right lung carries a worse prognosis than agenesis of the left lung because of greater displacement of the mediastinum and heart, with increased torsion on the great vessels and remaining bronchus. Pulmonary agenesis of single lobes is uncommon but when present is predominantly a right-sided event, with the right upper lobe and right middle affected together.[17] Pulmonary agenesis is often associated with other congenital abnormalities, particularly cardiac defects, and a diagnosis of agenesis should trigger a careful assessment for other somatic malformations.

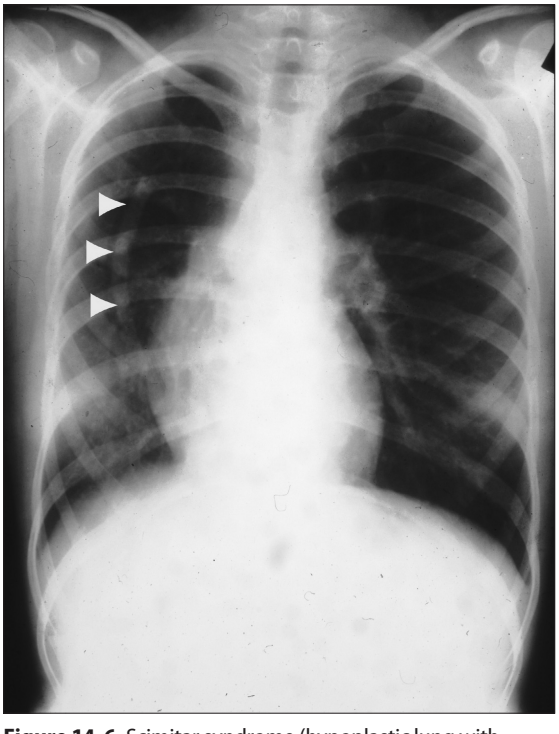


Figure 14-6. Scimitar syndrome (hypoplastic lung with partial anomalous venous return). Frontal chest radiograph showing that the right lung is smaller than the left, resulting in rightward mediastinal deviation, and a large anomalous pulmonary vein (arrowheads) draining the right lung to the subdiaphragmatic inferior vena cava.

Hypoplasia of the right lung or agenesis of a lobe therein with anomalous pulmonary venous blood flow to the inferior vena cava is known as *scimitar syndrome*, the name deriving from the curved, scimitar sword-like appearance of the vein descending through the diaphragm to the vena cava (**Figure 14-6**). This syndrome may manifest with a variety of vascular anomalies, including systemic arterial supply to the right lower lobe, agenesis of the right pulmonary artery, and congenital heart defects. Two forms, infantile and adult, have

been reported, the distinction based on age of manifestation. The infantile form is diagnosed in the first months after birth and is associated with more severe cardiac defects or congestive heart failure due to high output failure through the systemic vessels feeding the right lung, whereas the adult form with pulmonary hypoplasia and aberrant venous drainage may be asymptomatic and only discovered serendipitously.[18,19] Immediate attention to the underlying cardiac problems is essential with manifestation in the newborn period. Older children or adults in whom the scimitar syndrome is diagnosed as an incidental finding may not require any intervention at all.

Generalized pulmonary hypoplasia is more common than agenesis of a single lung or lobe. It is associated with a variety of intrauterine insults, including (1) hydrops fetalis; (2) renal anomalies; (3) hernia, including diaphragmatic hernia and omphalocele; (4) skeletal anomalies; and (5) amniotic fluid abnormalities, particularly oligohydramnios.[20] Mild pulmonary hypoplasia may cause tachypnea without serious associated lung disease, which may improve over time as the lungs achieve "catch-up" growth. More severe pulmonary hypoplasia may necessitate aggressive ventilatory support in the newborn period.

Of particular interest is the association between amniotic fluid abnormalities and pulmonary hypoplasia. Abnormalities that result in reduced or absent urine formation (renal agenesis) or oligohydramnios (eg, premature rupture of membranes) lead to physical restriction of fetal breathing movements and limited chest wall development. The earlier in gestation these problems occur, the more severe the pulmonary hypoplasia. Premature rupture of membranes late in pregnancy may have little or no effect on pulmonary function, whereas extremely early rupture of membranes will result in severe pulmonary compromise. The degree of pulmonary hypoplasia depends on the degree of oligohydramnios, its duration, and the gestational age (stage of lung development) at which it occurs. The most severe form of oligohydramnios and pulmonary hypoplasia is Potter syndrome, named for Edith Potter who in 1946 described the association of renal agenesis, unusual flattened facies, talipes, intrauterine growth restriction, and pulmonary hypoplasia.[21]

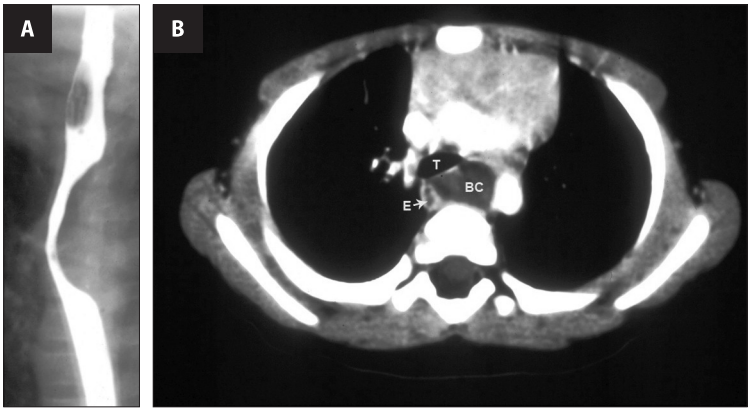
Bronchogenic Cysts

Bronchogenic cysts are the most common cysts of infancy, accounting for about 5% of mediastinal masses in infants and children. These are foregut-derived cystic malformations of the respiratory tract, usually located within the mediastinum if formed in an early stage of development or in the lung parenchyma if formed at a later stage. However, they can be in ectopic locations anywhere along the developmental pathway of the foregut.

Many bronchogenic cysts remain asymptomatic and are detected only incidentally later in life, so the true incidence of these cysts is unknown. Bronchogenic cysts are formed when a piece of bronchial tissue separates from the developing airway. In most cases there is no connection between the bronchogenic cyst and the normal airway, but such a connection can occur and may lead to chronic, recurrent infection of the cyst.[22] There is overlap between bronchogenic and esophageal cysts, given that both are anomalies in foregut differentiation. A cleft develops between the developing trachea and esophagus at approximately day 28 after conception. Anomalies in budding around this time can result in cysts with both bronchial and esophageal characteristics. Generally, bronchogenic cysts are thin walled and lined with ciliated respiratory epithelium. The cysts may contain mucoid material and frequently have cartilage in their walls (**Figure 14-7**).

Bronchogenic cysts may be asymptomatic, be minimally symptomatic, or cause extreme respiratory distress. The degree of symptoms depends on the location and size of the cyst. Infants have compressible tracheobronchial cartilage, and a space-occupying lesion in the peritracheal area will cause airway narrowing and noisy breathing. Compression of the esophagus can lead to concomitant feeding problems. More peripheral bronchogenic cysts will cause fewer symptoms but may cause recurrent infections, especially if there is communication with the bronchial tree. Rare cases of compression of vascular structures, including coronary arteries, have been reported.[23] Bronchogenic cysts do not have a known association with other congenital malformations but may be seen in conjunction with other malformations of lung development. Diagnosis is generally established by means of a barium esophagram or CT scan of the chest (**Figure 14-7A** and **B**).

Therapy for a bronchogenic cyst that is causing symptoms consists of surgical removal of the cyst. Therapy for asymptomatic cysts, often detected incidentally, is less clear. Many experts believe that surgical resection of asymptomatic cysts is indicated for pathological examination because there is a chance that the cyst may cause future symptoms, including infection and hemorrhage, and that the lesion poses an inherent oncogenic risk. There have been several case reports of different types of cancer being detected within bronchogenic cysts, including large cell carcinoma, bronchoalveolar carcinoma, and carcinoid tumor.[24–27] Other experts believe that not all mediastinal cysts need to be treated surgically, citing concerns regarding the reliability of some of the reports of malignant transformation and putting into perspective the low incidence of malignancies in simple cysts.[28] A definitive answer to the question of what to do with a bronchogenic cyst is not available because of the rarity of the lesion and the reports of only small series of patients. At present, surgical excision remains the most common way to deal with these lesions.



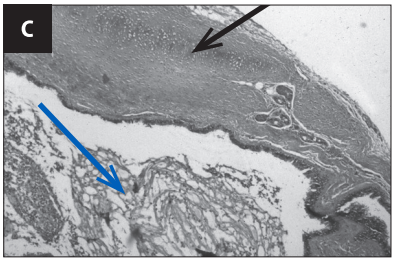


Figure 14-7. A, Frontal esophagram image demonstrating compression of the esophagus by a bronchogenic cyst. **B,** Axial computed tomography image showing the bronchogenic cyst (BC) compressing the trachea (T) and esophagus (E). **C,** Photomicrograph of a bronchogenic cyst demonstrating cartilage (black arrow) in the cyst wall with lung remnants (blue arrow) within the cyst.

Congenital Pulmonary Airway Malformation

Congenital pulmonary airway malformations consist of a group of lesions previously known as *congenital cystic adenomatoid malformations*. Congenital pulmonary airway malformations are characterized by the hamartomatous proliferation of terminal respiratory bronchioles forming a multicystic lung mass. The incidence of CPAM is not well known and has been described as being as rare as 1 in 27,000 live births and as common as 1 in 7,200 live births.[29] Congenital pulmonary airway malformation is one of the most common lung lesions diagnosed prenatally. It is usually sporadic and isolated with no familial recurrence. The genetic causes of CPAM are not known, but a number of different genes and promoters have been implicated.[30]

Congenital pulmonary airway malformations are thought to be an overgrowth of bronchi at various stages in lung development. The size of the cyst offers insight into the pathogenesis. When known as *congenital cystic adenomatoid malformations*, these malformations were classified by Stocker et al[31] into 3 histological types.

- Type I, the most common form, is composed of variable-sized cysts, with at least 1 dominant cyst greater than 2 cm in diameter.
- Type II contains multiple cysts less than 2 cm in diameter and forms a smaller fraction of cases.
- Type III is the solid, adenomatoid form and is a rarer manifestation.

The CPAM designation has been broadened to include types 0 through IV,[32] similar to the original description with the addition of a type 0 defect, which is acinar dysplasia, and type IV, which is an unlined cystic lesion. Type I is thought to arise from bronchial overgrowth, type II is bronchiolar in origin, type III is bronchiolar or alveolar in origin, and type IV is distal acinar in origin.

Congenital pulmonary airway malformations are rare. These lesions are almost always unilateral, although bilateral lesions occur in approximately 10% of cases. They affect the left and right sides equally. Associations with other congenital malformations have been described, in particular with congenital heart disease and congenital diaphragmatic hernia (CDH).

In the era of near-universal prenatal ultrasonographic examinations, CPAMs are increasingly recognized prenatally. There are reports of regression of these masses at sequential examinations and near disappearance at birth. However, residual small masses of abnormal tissue may be detectable on postnatal chest CT scans. In addition, they may manifest as an incidental finding, as an unresolving pneumonia, or as pneumothorax later in life. Congenital pulmonary airway malformations have to be differentiated from other cystic-appearing lesions, including diaphragmatic hernia, cystic hygroma, bronchogenic and enteric cysts, bronchopulmonary sequestration, and pleuropulmonary blastoma (PPB). Pleuropulmonary blastoma is a malignancy that may be indistinguishable from CPAM on radiographic studies; however, a genetic predisposition and a family history of malignancy are often present in patients with PPB and help identify the at-risk population.[33] Pleuropulmonary blastoma is less likely than CPAM to be detected with prenatal ultrasonography and is associated with the DICER1 family of neoplasms. Genetic testing for *DICER1* mutations can help differentiate PPB from CPAM preoperatively.[34] However, differentiation of CPAM from PPB may only be possible at pathological examination after resection.

Overall, the prognosis of prenatal CPAMs is based on size and growth charac teristics. Seventy percent resolve or decrease in size before birth, 10% remain unchanged, and 20% increase in size. About 10% of infants with a prenatal diagnosis of CPAM develop hydrops fetalis and have a poor outcome. There is no doubt that infants with symptoms and large lesions should undergo surgical resection. However, there is no simple answer as to the approach to asymptomatic CPAM. The lifelong risk of infection and malignant transformation is not known with certainty. Many think that removal before complications occur is the most prudent approach, but others think that performing what may be unnecessary surgery is not warranted. In the past, it has been argued that the denominator—the number of people with asymptomatic CPAM that never came to light—was unknown, but that is changing as universal prenatal ultrasonography is adopted. Risk of malignancy is greatest in type I and type IV CPAMs, and PPB should be removed, which has led to a greater tendency to remove masses of uncertain tissue type early in life to

avoid later complications or malignancy. If the child does not have symptoms, surgery can be delayed until the child is older (larger) and the surgery is easier and better tolerated.

The mortality with CPAM with hydrops if left untreated approaches 100% and is an indication for fetal intervention. The approach depends on the type of lesion. In those in which there is a dominant cyst, hydrops may respond to cyst aspiration and, if it recurs, to thoracoamniotic shunt placement. In a solid type of CPAM, open fetal surgery for resection of the CPAM may be indicated. The survival rate of such surgeries is 61%.[35] A report of prenatal sclerotherapy showed 50% survival in a cohort of 8 patients.[36]

Congenital Lobar Emphysema

Strictly speaking, the term *congenital lobar emphysema* (CLE) is a misnomer, and this condition is better referred to as an infantile large, hyperlucent lobe or congenital lobar overexpansion. (See **Figure 14-8**). The exact cause of this lesion remains obscure. The lung parenchyma is not truly emphysematous because there is no destruction of alveolar walls, nor is the condition uniformly present antenatally, although it likely has its origins in a prenatal condition. Abnormalities of the bronchi leading to partial obstruction or collapse at expiration, with a resultant ball-valve effect and air or amniotic fluid trapping in the peripheral lung, are often invoked as a causative feature, but, in fact, such bronchial defects are identified in no more than one-third of children with CLE.[37,38] Microscopic evaluation of excised lobar emphysema tissue shows 1 of 2 patterns. In classic CLE, there is a hyperexpanded lobe with a normal number of enlarged alveoli. In about 30% of cases, CLE manifests with a polyalveolar lobe, which consists of an enlarged lobe containing many more than the normal number of alveoli.[38,39] Congenital lobar emphysema most frequently affects the left upper lobe, followed by the right middle lobe and right upper lobe.[37,38] The lower lobes are rarely involved. Multiple lobes may be enlarged, but it is extremely unusual to have bilateral lesions.

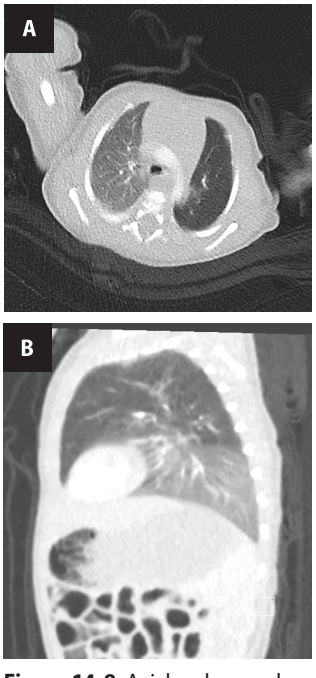


Figure 14-8. Axial and coronal computed tomography images in lung window show hyperlucency of the left upper lobe with oligemia in a child with congenital lobar emphysema.

Courtesy of Mariangeles Medina Perez, MD.

Clinically, CLE manifests in the immediate newborn period in most cases, with symptoms typical of a space-occupying mass: tachypnea, dyspnea, decreased breath sounds on the affected side, and wheezing. More than

one-half of all cases manifest in the first week after birth because of respiratory distress, and more than 80% will manifest by 6 months of age. Occasionally, a child will not have symptoms, and CLE will be diagnosed incidentally when a chest radiograph is obtained for an unrelated reason. In the newborn period, CLE may resemble neonatal pneumothorax or CPAM. The lesion may manifest as a fluid-filled mass that then becomes hyperlucent as retained fetal lung liquid is cleared. Delayed clearance of lung fluid is most common in the polyalveolar form of CLE.[38,39] In older children, the differential diagnosis should include foreign body aspiration with postobstructive hyperinflation.

Radiographic studies show hyperinflation of a lobe with compression of the ipsilateral lung and herniation of the emphysematous lung across the anterior mediastinum. The contralateral lung may be compressed and atelectatic due to the mass effect of the hyperinflated lung. The diagnosis depends on being able to recognize which lung is abnormal. The small lung may be hypoplastic or atelectatic with compensatory hyperinflation of the other normal lung. Alternately, the large lung may be emphysematous with corresponding compression of the smaller lung. Although this distinction is not always easy, CT or ventilation/perfusion scans can be helpful in distinguishing the healthy from the affected lung (**Figure 14-9**).

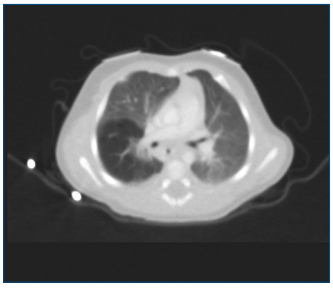


Figure 14-9. Axial computed tomography image obtained with a lung window showing hyperlucency and decreased lung markings in the right lower lobe lesion.

With the increased use of prenatal ultrasonography and fetal magnetic resonance imaging (MRI), there has been an increase in detecting CLE during fetal life. Follow-up shows spontaneous resolution in some cases, although postpartum symptoms may occur even in children whose lesions seem to have disappeared before birth.[40] Knowing that CLE can regress spontaneously has led to a more conservative management approach. Previously, it was thought that, once detected, an emphysematous lobe must be removed to relieve respiratory distress and to allow the healthy lobes to grow normally. Surgery remains the treatment of choice for the child with severe respiratory distress; however, it is increasingly apparent that infants with mild to moderate symptoms can be treated medically. Some infants with symptoms at birth do not require surgery.[41]

Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (**Figure 14-10**) is a major congenital defect, and the classic hernia, Bochdalek hernia, is through a posterolateral defect in the diaphragm. Investigators in a 2003 population-based study from Atlanta place the incidence at approximately 2.4 per 10,000 live births,[42] with increased frequency in premature and male neonates. Eighty percent of CDHs



Figure 14-10. Frontal chest radiograph shows indistinct left hemidiaphragm with partial opacification of the left hemithorax by multiple air-filled bowel loops. There is mass effect on the mediastinum, which is shifted towards the right side.

Courtesy of Mariangeles Medina Perez, MD.

are on the left side, and 20% are on the right side. The expected recurrence risk in a first-degree relative is slightly greater than 2%. At present, a genetic cause can be identified in only approximately 30% of cases. The ability to identify more genetic determinants of CDH could have far-reaching implications for prenatal diagnosis and treatment.[43] The incidence of associated abnormalities is about 30%, with skeletal and cardiac abnormalities being the most common.[44,45] Cardiac malformations tend to affect the outflow tracts and include tetralogy of Fallot and transposition of the great vessels. Congenital diaphragmatic hernia occurs in the context of a number of syndromes, including trisomies 21, 18, and 13; Fryns syndrome; Beckwith-Wiedemann syndrome; and Goldenhar syndrome.

The pathophysiological nature of CDH is complex. The diaphragm is formed in 2 stages. The septum transversum forms from the area of the inferior portion of the pericardial cavity. This septum separates the peritoneal and thoracic cavities and ultimately forms the central tendon. However, lateral foramina persist and are called *pleuroperitoneal canals*. Normally, these canals are closed by pleuroperitoneal membranes. It is through these canals that the usual Bochdalek hernia protrudes. The left-sided hernia may contain stomach, small bowel, spleen, and even kidney.

The hernia is covered by a membrane in 10% of cases. The extension of the abdominal viscera into the thoracic cavity results in clinically significant lung hypoplasia by virtue of the space-occupying effect. If the hernia occurs before 16 weeks of gestation, there will be a reduction in the number of bronchial branches. Whether early or late, the hernia decreases acinar development of both the ipsilateral and contralateral lung, and thus gas-exchange surface area is reduced. Vascular abnormalities are striking, with reduced numbers of pulmonary arterial branches and muscular thickening of the arteries. These vascular abnormalities increase the risk of the affected infant having pulmonary hypertension and developing persistent fetal circulation.

The diagnosis of CDH is considered when respiratory distress occurs at birth. The degree of distress depends on the degree of pulmonary hypertension and hypoplasia. In infants in whom a great deal of abdominal viscera is displaced into the thorax, the abdomen is flat (scaphoid) and there is asymmetrical distention of the chest. Respiratory distress may increase as the gastrointestinal

tract fills with swallowed air. The presence of bowel sounds over the thorax and the absence of breath sounds on the affected side are frequently described.

The diagnosis is often determined during a routine prenatal ultrasonographic examination. Ultrasonography can depict CDHs as early as 12 weeks of gestation, but they are usually found at 24 weeks of gestation. The severity of CDH can be estimated prenatally by using observed-to-expected lung–head ratios (at ultrasonography) and total fetal lung volumes (at MRI).[46] Polyhydramnios is reported in 75% of cases. After birth, the diagnosis is confirmed by means of plain chest radiography. Common findings are bowel in the chest cavity and deviation of the mediastinum. The diagnosis is usually obvious, but other diagnoses should be considered, including congenital cystic disease of the lung and agenesis of the lung. Once the diagnosis is confirmed, it is important to screen for associated anomalies by using echocardiography and ultrasonography of the head and kidneys.

Early therapy is directed at improving respiratory status. Although defects in surfactant have been described, a role for prenatal steroid therapy or surfactant administration at birth has not been established.[47,48] Fetal surgery to enhance lung development is no longer used because recent study results demonstrated no benefit.[49] Initial resuscitation should involve endotracheal intubation and placement of a nasogastric tube to abrogate expansion of the stomach and small bowel by swallowed air. Once intubation has been performed, mechanical ventilation is used as a bridge to surgical repair. A number of ventilatory strategies can keep the preductal arterial P_{O_2} greater than 60 mm Hg, including varying from high rates with low positive end-expiratory pressure to lower rates with higher positive end-expiratory pressure. Central to most strategies is the use of pressure-cycled ventilators with strict monitoring of tidal volume and preductal oxygen saturations. The need for extensive support suggests that lung hypoplasia or pulmonary hypertension is substantial. A number of indices have been established to quantify this support and thus help predict ultimate outcome. These indexes include a ventilatory index and an oxygenation index. High-frequency oscillatory ventilation has been used with success, but results from a 2016 study showed similar rates of mortality and morbidity between use of conventional mechanical ventilation and use of high-frequency oscillatory ventilation.[50] This latter therapy should be considered in patients in whom conventional mechanical ventilation fails. Nitric oxide is a successful therapy for pulmonary artery hypertension, but in children with CDH, the results are mixed; however, a therapeutic trial is appropriate when pulmonary artery hypertension is clinically significant.[51] Extracorporeal membrane oxygenation is indicated if conventional or high-frequency oscillatory ventilation and nitric oxide therapies are not beneficial.

Surgery for CDH is no longer considered an emergency intervention. Results from 2 randomized controlled trials did not demonstrate an advantage to either early or late repair.[52,53] With advances in intensive care medicine, surgery can be elective, allowing for appropriate time to look for other congenital abnormalities that may alter the surgical approach. If the diaphragmatic defect is large, it may be closed with a prosthetic patch or a local flap from the chest wall or abdominal wall. The abdominal cavity may be hypoplastic due to relocation of the bowel into the thorax during development. With return of the viscera, it may not be possible to close the abdomen. In these cases, the skin is approximated, and after a few months, the abdominal wall defect can be closed. The minimally invasive surgery approach for CDH repair is gaining acceptance in selective cases. Minimally invasive surgery was associated with decreased length of stay and incidence of small-bowel obstruction but higher recurrence rates.[54]

Outcomes of CDH have improved dramatically in recent years, and survival rates of 80% to 90% are frequently described.[55] Pulmonary function test results are frequently abnormal but improve over time; at long-term follow-up, 50% of patients had normal lung function by 10 years of age.[56] Increased bronchial reactivity, as demonstrated by wheezing with respiratory tract infections, can be a persistent problem. Neurodevelopmental abnormalities are common, particularly when extracorporeal membrane oxygenation has been used. In addition, gastroesophageal reflux is frequently seen and needs to be addressed medically.

The Morgagni hernia is a less common form of CDH. This hernia occurs at either side of the midline just behind the sternum, where the septum transversum joins the chest wall. Occasionally, these hernias are bilateral and give rise to a large central defect. Morgagni hernias are rarely symptomatic and can manifest at any age. These hernias may be associated with other abnormalities, particularly malrotation of the gut. Operative repair is relatively straightforward via a transverse upper abdominal incision, where the diaphragm is attached to the posterior rectal sheath. These hernias may also be manageable with laparoscopic and thoracoscopic approaches.

Eventration of the diaphragm is another frequently seen diaphragmatic defect.[57] In congenital eventration, there is a thin, membranous diaphragm with some protrusion into the thoracic cavity. Although usually benign, a large eventration may manifest with symptoms similar to those of CDH. In the acquired form, the phrenic nerve is paralyzed owing to either birth trauma or surgical trauma. The distribution of the muscle fibers in the diaphragm is normal in the acquired form; however, in the congenital form, the muscle is distributed around the rim of the diaphragm. Generally, eventrations are identified as an incidental finding or because of mild respiratory symptoms during respiratory tract infections. Occasionally, there is intolerance of rigorous exercise.

The diagnosis is confirmed with fluoroscopy of the chest. At fluoroscopy, there is paradoxical movement, with the diaphragm on the affected side rising during inspiration. Most eventrations are small, and surgical repair is not necessary. When the defect is large or symptomatic, plication of the thinned-out diaphragm can optimize lung growth and development.

Pulmonary Sequestration

Of all the lesions discussed in this chapter, pulmonary sequestration is perhaps the most complex, least clear, and most controversial in terminology, origin, and description. Classic extralobar pulmonary sequestration consists of an isolated segment of lung tissue with no connection to the tracheobronchial tree, invested in its own pleura, fed by a systemic artery, and drained via a systemic vein.[58] However, pulmonary sequestration is often associated with multiple variants of this schema and may be seen in combination with other pulmonary anomalies, such as CPAM, bronchogenic cyst, and scimitar syndrome.[59] Intralobar sequestration was initially thought to be an acquired lesion consisting of neovascularization via a systemic artery to an area of chronically inflamed lung parenchyma (generally caused by recurrent infection). However, intralobar sequestration can be a congenital problem unrelated to recurrent infection.

According to the malinosculation classification of Clements and Warner,[1] pulmonary sequestration can be seen as a spectrum of diseases and can involve any or all 4 of the major components of lung tissue: airways, arterial blood supply, venous drainage, and lung parenchyma. Thus, in classic extralobar sequestration, all 4 components are abnormal, whereas in intralobar sequestration, the arterial blood supply may be the only abnormality, although pulmonary disease is generally also present. Given the myriad variations of sequestration, and given the frequent association with other intrapulmonary lesions, some experts believe a more proper name for pulmonary sequestration is *congenital bronchopulmonary foregut malformation*. The more specific term is used with the understanding that each lesion has its own variations and associated anomalies.

Extralobar sequestrations of the lung are predominantly on the left side (65%) and are usually found between the lower lobe and the diaphragm, but they can be located anywhere in the thorax and occasionally even subdiaphragmatically.[57] Blood supply is directly from the thoracic or abdominal aorta in 80% of cases and arises from branches of smaller systemic vessels in the remainder. Venous drainage is generally to the right atrium, creating a left-to-right shunt. On cut sections, the sequestrum contains irregularly formed bronchi, alveolar ducts, and alveoli and may even have cystic elements, confirming the maldevelopment of lung parenchyma in addition to the airway and blood vessel abnormalities.

Extralobar sequestrations appear as triangular opacities and can be seen on chest radiographs in the retrocardiac area. Computed tomography angiography and magnetic resonance angiography allow for much better characterization of the lesions and frequently demonstrate the abnormal systemic blood supply to the area.[60,61] However, feeder vessels may not be visible if their diameter is below the scanning technique's limit of resolution. Resolution is improved in the current generation of CT scanners and postprocessing workstations, which allows visualization of even small aortic branches. Any imaging study should be performed with contrast enhancement to elucidate feeding vessels better.

Extralobar sequestrations may be incidental findings consisting of a retrocardiac mass on a chest radiograph obtained for other reasons, may manifest as respiratory distress in the newborn period, or may become infected at some time after the newborn period. Infection is generally due to hematogenous spread of bacteria unless there is a connection to a bronchus or to the esophagus. Repeat infection or abscess formation may occur and is an indication for surgical resection. Tachypnea in the newborn period may be due to mass effect, high-output cardiac failure, or associated cardiac or pulmonary congenital defects. Treatment for an extralobar sequestration is usually surgical removal, given the need to confirm the lesion histologically, prevent future infection or bleeding, and allow for normal lung growth. Treatment with arterial embolization and recognition of spontaneous involution of some lesions have led to questioning the need for surgery in all cases.[62,63]

Vascular Rings

Vascular rings are a wide spectrum of abnormalities that frequently include the aortic arch, pulmonary arteries, and brachiocephalic vessels. Most infants with vascular rings do not have symptoms, but if symptoms arise they relate to the degree of compression of the respiratory and gastrointestinal tracts. If vascular rings cause symptoms, they manifest in the first few months after birth in most infants. Symptoms can be variable, including stridor, arching of the neck, unusual postures during sleep, a brassy or seal-like cough, and apnea. These symptoms are not unique to vascular rings and, accordingly, infants with rings frequently initially receive a diagnosis of esophageal reflux, laryngotracheomalacia, or reactive airways disease. Dysphagia occurs when the child transitions to solid foods if constriction of the esophagus is severe, and an infant may refuse solid foods. Dysphagia can manifest later in life when the arteries calcify.

The overall incidence of vascular rings is unknown, given that many may remain asymptomatic and go undiagnosed, but they are thought to constitute 1% to 2% of congenital heart defects. Vascular rings are classified into complete rings, incomplete rings, and pulmonary slings. These vascular abnormalities usually occur in isolation, but 10% to 15% are associated with congenital heart disease.[64]

There are a number of types of complete rings, including a double aortic arch and right arch with the ring formed by ligamentum arteriosum, ductus arteriosus, or aberrant left subclavian branching. A double aortic arch occurs when the right dorsal aortic arch does not regress. Thus, the 2 arches encircle the trachea and the esophagus (**Figure 14-11, Figure 14-12**). The right arch is predominant in about 75% of cases. This form usually manifests in infancy and is confirmed by means of echocardiography and CT scanning. Although MRI is superior for vascular imaging, it has a long scanning time and requires sedation, making CT scanning a more appropriate choice for infants. Surgery is indicated when the child has symptoms. Surgery involves ligation of the nondominant arch while preserving brachiocephalic blood flow. There is often associated tracheomalacia from in utero compression of the trachea, and many infants have persistent respiratory symptoms after surgery.

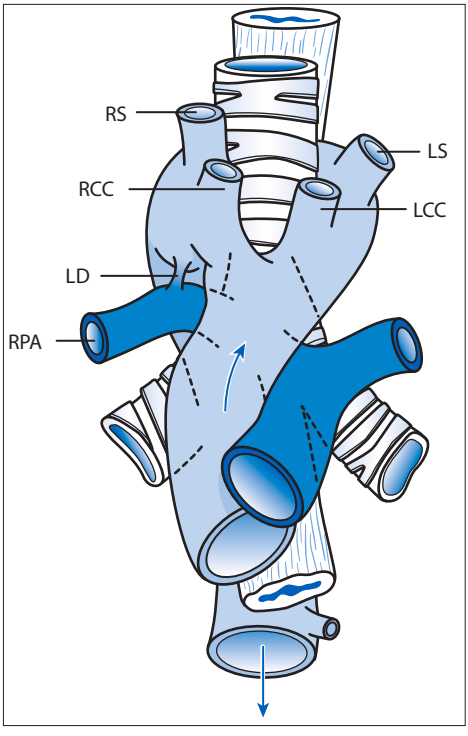


Figure 14-11. Double aortic arch encircling the trachea and esophagus.

Abbreviations: LCC, left common carotid artery; LD, ligamentum arteriosum; LS, left subclavian artery; RPA, right pulmonary artery; RS, right subclavian artery.



Figure 14-12. Axial computed tomography angiography shows symmetric double aortic arch surrounding the trachea and thoracic esophagus.

Courtesy of Mariangeles Medina Perez, MD.

A right-sided aortic arch may occur in isolation or may form part of a ring. In one ring formation (**Figure 14-13**), the right arch traces around the back of the esophagus, and there is an aberrant left subclavian artery from the descending aorta. The ring is closed by the ligamentum arteriosum, which bridges the pulmonary artery and the left subclavian artery. In another form of right-sided arch ring, called *mirror imaging*, an aberrant left innominate artery reaches across the front of the trachea. The arch still traces behind the aorta, and the ring is completed by the ligamentum arteriosum arising from the descending aorta rather than the aberrant subclavian artery to the pulmonary artery. Another form of vascular ring maintains a less complete ring in which the ligamentum arteriosum arises from the mirror image left subclavian or innominate artery to the pulmonary artery. These arches may be complicated by a Kommerell diverticulum at the site where the ligamentum arteriosum joins the aorta. Surgery is generally necessary if the vascular anomaly is causing symptoms such as noisy breathing or dysphagia. It involves ligation of the ligamentum arteriosum. If a Kommerell diverticulum is present, then a resection or aortopexy surgery may be required.

Incomplete vascular rings do not form closed, constricting lesions but may still impinge on the airway or esophagus. Anomalous innominate artery compression is considered to exist if the artery arises from the aortic arch to the left of midline and causes tracheal compression. Usually this causes no or mild symptoms, and no surgery is indicated. Only when symptoms are severe should surgery be considered because, in most untreated cases, symptoms ameliorate over time. Another simple ring involves an aberrant right subclavian artery. It arises from the

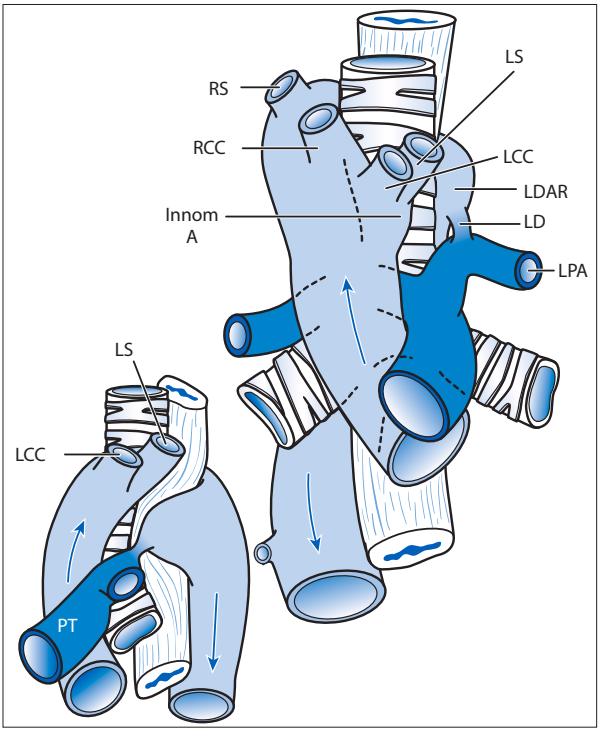


Figure 14-13. Isolated right aortic arch with ductus arteriosus arising from diverticulum of Kommerell.

Abbreviations: Innom A, innominate artery; LCC, left common carotid artery; LD, ligamentum arteriosum; LDAR, left dorsal aortic root (diverticulum of Kommerell); LPA, left pulmonary artery; LS, left subclavian artery; RCC, right common carotid artery; RS, right subclavian artery.

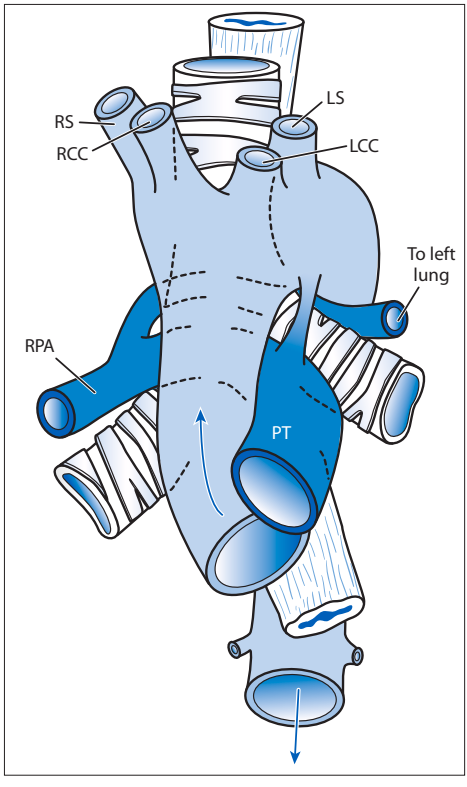


Figure 14-14. Pulmonary sling. The left pulmonary artery arises from the right pulmonary artery and courses behind the trachea and in front of the esophagus.

Abbreviations: LCC, left common carotid artery; LS, left subclavian artery; RCC, right common carotid artery; RPA, right pulmonary artery; RS, right subclavian artery.

descending aorta and traces behind the esophagus. It rarely causes symptoms but can be associated with feeding problems.

Pulmonary slings are an unusual form of vascular compression. In this condition, the left pulmonary artery arises from the right pulmonary artery and travels between the trachea and esophagus (**Figure 14-14**). Pulmonary slings are associated with complete tracheal rings and tracheal stenosis in about one-third of cases.[65] Surgery is usually indicated and may involve tracheal reconstruction. Generally, the long-term prognosis after surgical correction is favorable. However, after surgery, there is usually some tra-cheomalacia that results in a lingering cough and noisy breathing, which should improve in time.

key points

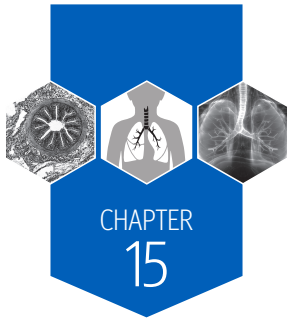
- Pulmonary congenital malformations arise from errors in fetal lung development.
- Pulmonary malformations can involve the airways, pulmonary parenchyma, blood vessels, or any combination of the 3.
- Lung abnormalities that arise from developmental issues before 16 weeks of gestation affect airway development; those that arise after 16 weeks affect acinar development.
- Some pulmonary lesions detected by means of prenatal ultrasonography resolve spontaneously.
- Symptomatic congenital pulmonary abnormalities require surgical intervention.
- Although there have been reports of malignant transformation within some of these lesions, the absolute risk of cancer associated with congenital lung malformations is unknown.

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Chest Wall and Spinal Deformities

Julie L. Fierro, MD, MPH
Oscar Henry Mayer, MD

Mechanics of Breathing

Inspiration Versus Exhalation

The act of breathing is sometimes compared with the movement of a piston because of the cyclical cephalad and caudad motion of the diaphragm, and the chest wall is seen as a passive participant; however, this view is too simplistic. The chest wall is very dynamic during breathing and is critical in maintaining resting lung volume, optimizing lung mechanics, allowing normal respiratory growth, and protecting the thoracic organs.

In healthy children, inspiration begins from functional residual capacity (FRC), which is the point in the respiratory cycle when the outward recoil of the rib cage and the inward recoil of the lungs are equal and opposite. The diaphragm contracts and moves caudally, increasing intra-abdominal pressure and displacing the abdominal contents and the lower edges of the rib cage outward. This caudad motion of the diaphragm, along with outward and cephalad rotation of the ribs, produces increasingly negative intrathoracic pressure and a gradient favoring airflow down the respiratory tract from the mouth to the alveoli (**Figure 15-1A**).

Inspiration is an active process, but exhalation is largely passive. After the muscles of inspiration relax, the inward recoil of the lungs produces positive pressure in the alveoli that favors expiratory flow down the pressure gradient to the mouth, as the lung volume decreases to FRC (**Figure 15-1B**).

Area of Apposition

The extent of the diaphragm's downward excursion depends on the area of apposition of the diaphragm to the rib cage, or the portion of the diaphragm aligned vertically along the inner surface of the chest wall (**Figure 15-2**). As the portion of the diaphragm in the area of apposition contracts, the diaphragm moves caudally. The area of apposition constitutes one-quarter to three-quarters of the total surface area of the rib cage in adults.[1]

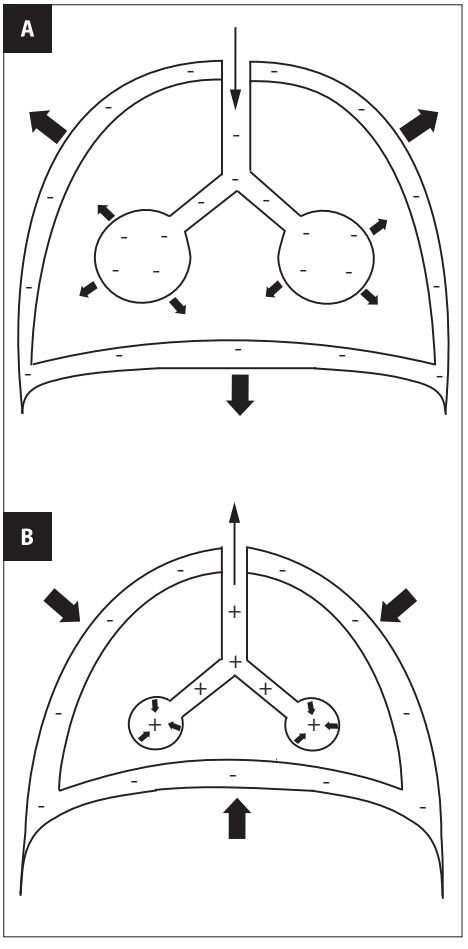


Figure 15-1. Representation of the motion of the alveoli, diaphragm, and chest wall during inspiration (**A**) and exhalation (**B**).
Courtesy of Oscar Henry Mayer, MD.

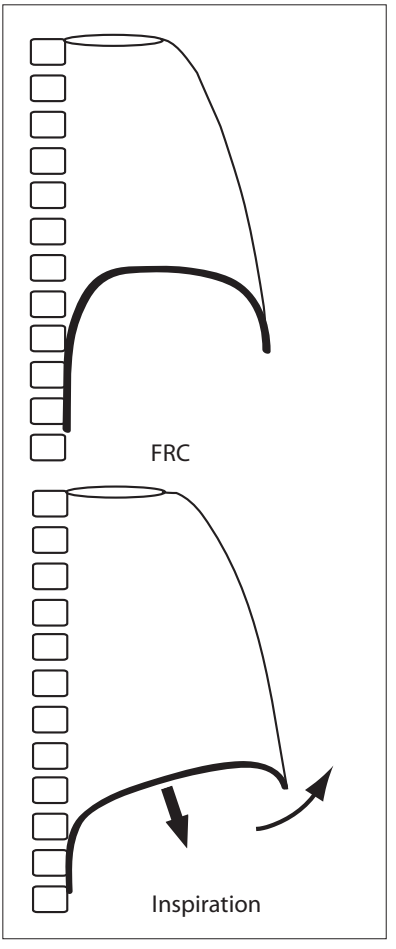


Figure 15-2. Area of apposition at functional residual capacity (FRC) and during inspiration.
Courtesy of Oscar Henry Mayer, MD.

It is somewhat less in children and substantially less in infants. In a child with clinically significant lung disease with hyperinflation, the diaphragm will be positioned in a lower and flatter position, and the area of apposition can be much smaller. Furthermore, with a smaller area of apposition, the diaphragm becomes flatter with a larger radius of curvature (**Figure 15-3**). By the law of Laplace, the force-generating capacity of the diaphragm will be lower with a larger radius of curvature.

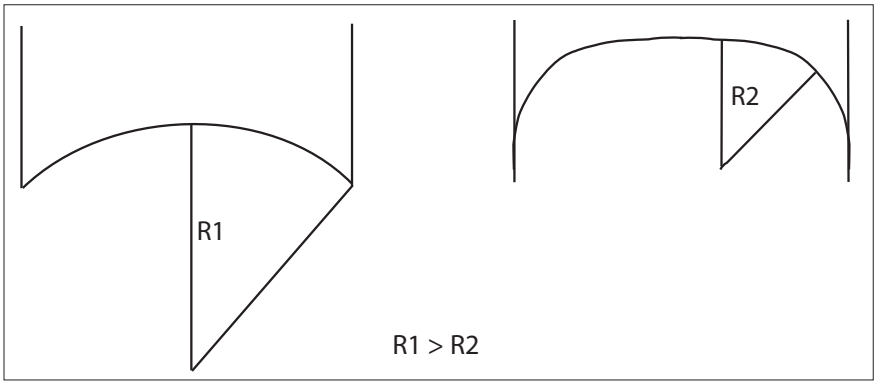


Figure 15-3. Radius of curvature (R) of the diaphragm in 2 different diaphragm orientations with R1 > R2.

Courtesy of Oscar Henry Mayer, MD.

Thoracoabdominal Mechanics

During restful breathing in a healthy child, the abdominal and rib cage excursion are nearly coincident (**Figure 15-4A**). With respiratory disease, such as increased airway resistance or chest wall compliance, the abdominal excursion will lead the chest wall excursion (thoracoabdominal asynchrony). This asynchrony is easily visible during a respiratory examination and can increase to the far end of the spectrum to completely asynchronous or paradoxical respiration, with the abdomen moving outward as the chest wall is moving inward (**Figure 15-4B**).

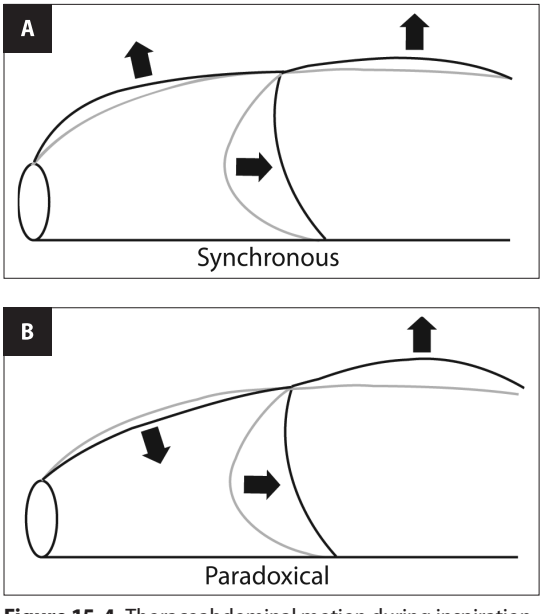


Figure 15-4. Thoracoabdominal motion during inspiration from functional residual capacity with synchronous conditions (**A**) and asynchronous conditions (**B**).

Courtesy of Oscar Henry Mayer, MD.

When airway resistance increases, the pressure gradient needed to overcome the resistance and generate flow is higher, and it takes longer to generate outward chest wall motion. A highly compliant rib cage will move inward while the abdomen moves outward at the onset of inspiration because of the progressively negative intrathoracic pressure (**Figure 15-4B**).

This condition can be seen in some neonates and young infants; children with neuromuscular disease, especially spinal muscular atrophy type 1; and children with chest wall disorders.

To increase inspiration, the diaphragm will contract more caudally, and the scalene and sternocleidomastoid muscles will contract to elevate the superior rib cage further. With forceful exhalation from total lung capacity (TLC), such as coughing, the abdominal muscles contract, pushing the abdominal contents inward and upward elevating the diaphragm, while the internal intercostal muscles contract to augment the inward recoil of the chest wall and lungs.

Pathophysiology

Structural Changes Resulting From Growth and Development

In neonates, lung compliance is low and chest wall compliance is high compared with those in older children and adults.[2–6] In addition, the ribs are more horizontal in infants than in children and adults, in whom the ribs slope more caudally.[7]

Through early childhood, lung compliance increases as the alveoli develop and lung volume increases; however, lung compliance and lung volume increase at roughly the same rate such that when lung compliance is normalized for lung growth it remains constant.[8] Chest wall compliance normalized to lung volume decreases through childhood as the chest stiffens owing to a combination of rib ossification and increasing chest wall muscle mass.[9,10] In adulthood, chest wall compliance decreases further as the costal cartilage also progressively calcifies.[10]

Functional Consequences of Developmental and Structural Changes

A highly compliant chest wall has clear advantages in the birthing process by allowing distortion during the movement through the birth canal. In neonates and infants, this high degree of chest wall compliance creates mechanical disadvantages. First, the negative intrathoracic pressure produced during inspiration can move the highly compliant chest wall inward (**Figure 15-4B**). Second, infants have low *lung* compliance relative to their *chest wall* compliance, which produces a lower FRC relative to that in older children and adults. The lower FRC may be at or below the point when airways close and atelectasis occurs (the closing volume). If closing volume occurs during tidal breathing, before any inspiratory flow can occur, pressure needs to be applied to the respiratory system to raise lung volume above the closing volume to open the closed airways. This increases work of breathing without benefit because the energy used to inflate the lung above closing volume does not produce inspiratory flow.

To compensate for this mechanical inefficiency, infants will often breathe at a higher respiratory rate, allowing for less time to exhale, and use glottic narrowing, ending at an end-expiratory lung volume higher than FRC and above the closing volume.[11,12] Actively maintaining the end-expiratory lung volume above FRC and closing volume minimizes the work of breathing.

Finally, a highly compliant chest wall may move outward during cough owing to the highly positive intrathoracic pressure during a forced exhalation, thereby decreasing cough efficiency.

Under normal circumstances, the outward excursion of the rib cage provides about 35% of the volume of inspiration in a newborn,[13] with the remainder coming from abdominal excursion. The relative rib cage excursion increases to the adult value of 65% of inspiratory volume early in the second year after birth.[13]

Although a chest wall with high compliance may move inward during inspiration (**Figure 15-4B**), a chest wall with low compliance moves very little. To maintain an acceptable tidal volume, the diaphragm will contract further, and the lungs will expand more caudally and less outward, which can cause a number of problems.

First, the inspiratory reserve volume, the volume that can be recruited during a maximal inspiration, will be lower (**Figure 15-5**), as will forced vital capacity (FVC), the volume of air that can move through the lungs during maximal inspiration and expiration. Second, because the diaphragm is contracting more during inspiration, it is working harder and is at risk of fatigue. Third, cough and airway clearance can be compromised because the FVC and inspiratory reserve volume will be lower, which limits how deeply air is inhaled into the lungs and beyond airway secretions.

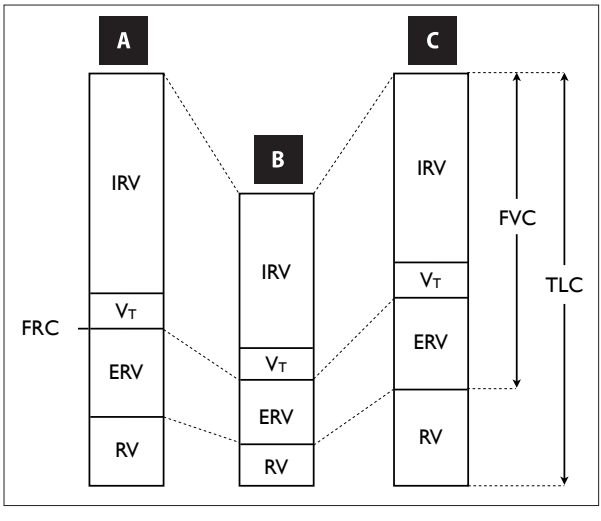


Figure 15-5. Lung volumes in normal condition (**A**), restrictive lung disease (**B**), and obstructive lung disease (**C**).

Abbreviations: ERV, expiratory reserve volume; FRC, functional residual capacity; IRV, inspiratory reserve volume; RV, residual volume; TLC, total lung capacity; VT, tidal volume.

Courtesy of Oscar Henry Mayer, MD.

Methods for Assessing Chest Wall Function

Physical Examination

It is very important to assess chest wall function qualitatively by means of observation.

Spine

Scoliosis is often thought of as a uniplanar defect with a curve that is in the coronal plane on the basis of its radiographic appearance; however, there can also be more complicated multiplanar kyphoscoliosis and rotational scoliosis.

It is important first to assess the back statically and look for gross asymmetry. Scoliosis can often be seen by visually examining the spine and tracing it with a finger while a patient is standing upright. Shoulder asymmetry and unilateral scapular or rib bulging can be a sign of scoliosis with substantial spinal rotation. Examining the spine with the patient bending at the waist and reaching for his or her toes can show more subtle scoliosis and right-to-left asymmetry.

It is then important to evaluate the extent and symmetry of thoracoabdominal excursion. This can be qualitatively assessed using the thumb excursion test[14] by placing the fingers of each hand on the left and right scapula with the thumbs placed on either side of the spine. In a patient without scoliosis, the thumbs should move laterally the same amount. Auscultation of the right and left lungs can be used to discriminate asymmetrical aeration due to airway compression or atelectasis.

Chest Wall

The relative excursion of the convex and concave chest is variable and is based on the mobility of the chest wall and the position and extent of lung compression.[15,16] Thoracoabdominal asynchrony, the difference in timing between chest wall and abdominal excursion, is also important to assess and is a measure of overall respiratory mechanics.[17,18] With a poorly compliant or stiff chest wall, the abdomen moves outward, and there is a delay before outward chest wall movement. It takes more intra-abdominal pressure to move the lower chest wall and more accessory inspiratory muscle contraction to expand the chest wall.

Diaphragm

In unilateral diaphragm dysfunction caused by paralysis or eventration, the contralateral side of the chest should move normally while the ipsilateral side of the chest may move very little, if at all, because of asymmetrical diaphragm motion. In complete unilateral diaphragm paralysis, the epigastric abdominal wall may move upward and toward the side of the lesion during deep inspiration. With a flail chest, there will be a marked asymmetry in chest wall excursion; the unaffected side will move outward during inspiration, and the affected side will move inward.

Diaphragm fatigue, dysfunction, or unilateral paralysis can limit the caudad movement of the diaphragm during inspiration. To compensate, the chest wall excursion is greater, can occur before any abdominal motion, and will be more important in inspiration than typical. Depending on its severity, a patient may have asynchronous respiration with outward chest wall motion coincident with inward abdominal motion, which can occur because of negative intrathoracic pressure pulling the diaphragm cephalad during inspiration.

Abdomen

A highly compliant abdomen will have a greater outward excursion during inspiration but still should lead the thorax on inspiration. On forced expiration, the abdominal contraction can be irregular based on the characteristics of the initial defect (as with gastroschisis and omphalocele), the subsequent repair, and the amount of residual muscle mass.

Quantitative Assessment of Chest Wall Motion

The qualitative assessment of thoracoabdominal motion performed during the observation portion of the physical examination can be quantitated using respiratory inductance plethysmography. During respiratory inductive plethysmography, thoracoabdominal motion is measured by timing the maximal thoracic and abdominal excursion during respiration by using inductance bands that measure the cross-sectional area of the chest wall and abdomen.[17–19] The exact delay between abdominal and thoracic excursion and the relative excursion of each compartment can be measured.[17–19]

Lung Function Testing

Conventional lung function testing can be stratified into 2 different types: (1) forced flow measurements with spirometry to evaluate for obstructive lung disease and (2) static lung volume measurement with plethysmography or gas dilution to evaluate for restrictive respiratory disease (see Chapter 6, Pulmonary Function Testing). In children with obstructive lung disease, the FEV_1, $FEF_{25\%–75\%}$, and FEV_1/FVC can be low. In those with restrictive respiratory disease, however, the FEV_1/FVC is normal, and there is always a low TLC. Although FVC is expected to be low in children with restrictive respiratory disease, it can be low in those with obstructive lung disease because of air trapping due to airway closure during exhalation leading to an increased residual volume. Therefore, a low TLC is needed to diagnose restrictive respiratory disease definitively. Thereafter, FVC can be monitored as an index of severity.

In patients with scoliosis, TLC decreases as the spinal curvature increases; however, TLC can be within the normal range.[20] Patients with more complicated rotational kyphoscoliosis or constrictive scoliosis, such as in thoracic insufficiency syndrome (TIS), can have a marked restrictive defect.[21] When

evaluating the lung function of a patient with scoliosis, it is important to normalize the results by using arm span as a surrogate for height to avoid underrepresenting the restrictive defect (**Figure 15-6A**). There are well-documented tables with normal values for the ratio of the upper body to the lower body.[22] This ratio is abnormal in patients with chest wall or spinal disease, with the upper body being shorter relative to the lower body. Because the height of a patient with scoliosis may be shorter than the idealized height because of the curve and a shorter spine, the use of height to normalize lung volume will give an inappropriate (low) normal value, and lung volume as a percentage of that predicted will then be falsely high (**Figure 15-6B**). Because arm span is not affected by spinal growth, it will more accurately represent the potential, idealized height and metabolic demand. However, lung volume normalized to height can still be useful. This correction will normalize for chest size and, if low, is consistent with an intrinsic restrictive lung disease, separate from any external compression.

Age: 9 **BMI: 11.9** **A**
Gender: Female **Height: 158 cm** **Weight: 29.6 kg**
Race: African American

Note: Height and/or Weight and/or BMI is <3% tile or >97% tile for age.

Spirometry (BTPS) ATS ✓

		Ref	Pre	% Ref	Z-score
FVC	L	2.66	1.37	52	-3.16
FEV_1	L	2.31	1.29	56	-2.92
FEV_1/FVC	%	90	94	104	0.67
FEF_{25-75}	L/s	2.70	2.25	83	-0.57
PEFR	L/s	5.27	3.22	61	-1.78
FET	sec		3.07		
FIF_{50}	L/s		1.92		
FEF_{50}/FIF_{50}			1.36		
FEV.5	L	1.57	1.10	70	
Back Volume			0.05		

Lung Volumes (Box) ATS ✓

		Ref	Pre	% Ref	Z-score
TLC	L	3.51	1.99	57	-3.61
VC	L	2.59	1.37	53	-0.87
FRC	L	1.83	1.00	55	-2.67
ERV	L	0.91	0.38	42	
RV	L	0.92	0.62	67	-1.16
RV/TLC	%	26	31	119	0.36

Figure 15-6. Spirometry and static lung volume measurements in a child with scoliosis with normalization by means of arm span (**A**) or height (**B**).

Age: 9	DOB: 10/11/1999	BMI: 20.6	B
Gender: Female	Height: 120 cm	Weight: 29.6 kg	
Race: African American			

Note: Height and/or Weight and/or BMI is <3% tile or >97% tile for age.

Spirometry (BTPS) ATS ✓

		Ref	Pre	% Ref	Z-score
FVC	L	1.23	1.37	111	0.59
FEV_1	L	1.16	1.29	111	0.65
FEV_1/FVC	%	90	94	104	0.67
FEF_{25-75}	L/s	1.79	2.25	126	1.01
PEFR	L/s	3.19	3.22	101	0.05
FET	sec		3.07		
FIF_{50}	L/s		1.92		
FEF_{50}/FIF_{50}			1.36		
FEV.5	L	0.96	1.10	115	
Back Volume			0.05		

Lung Volumes (Box) ATS ✓

		Ref	Pre	% Ref	Z-score
TLC	L	1.79	1.99	111	0.93
VC	L	1.21	1.37	113	0.24
FRC	L	0.99	1.00	101	0.6
ERV	L	0.41	0.38	93	
RV	L	0.58	0.62	107	0.25
RV/TLC	%	32	31	97	-0.06

Figure 15-6, (*continued*)

Abbreviations: ATS, American Thoracic Society; BTPS, body temperature and pressure, saturated; DOB, date of birth; ERV, expiratory reserve volume; $FEF_{25–75}$, forced expiratory flows between 25% and 75% of the FVC; FEF50 , forced expiratory flow at 50% of FVC; FET, forced expiratory time; FEV.5, forced expiratory volume in 0.5 seconds; $FIF_{50,}$ forced inspiratory flow at 50% of FVC; FRC, functional reserve capacity; FVC, forced vital capacity; PEFR, peak expiratory flow rate; Pre, before; Ref, reference; RV, residual volume; TLC, total lung capacity; VC, vital capacity.

Courtesy of Oscar Henry Mayer, MD.

Respiratory Muscle Strength

Respiratory muscle strength is measured by recording the maximal inspiratory pressure and maximal expiratory pressure by means of manometry. The maximal inspiratory pressure is the maximal sustained pressure that can be maintained for 1 second when inhaling maximally against a closed shutter from residual volume or from FRC. It is critical to measure at the same volume, or the comparisons will not be accurate. The maximal expiratory pressure is the maximal sustained pressure that can be maintained for 1 second when exhaling maximally against a closed shutter from TLC. In

adolescents with scoliosis, inefficient coupling between the muscle and chest wall reduces respiratory muscle strength. The degree of weakness partly depends on the severity of the curve.[23] Children with severe scoliosis have an activation of respiratory muscles similar to that of children with respiratory failure caused by obstructive lung disease.[24]

Structural Abnormalities

A list of structural abnormalities of the chest wall is found in **Box 15-1.**

Box 15-1

Structural Abnormalities of the Chest Wall

Pectus Deformity
- Pectus excavatum
- Pectus carinatum

Scoliosis
- Spinal deformity
- Rib cage deformity
  - Flail chest
  - Rib fusion
  - Neuromuscular disease (eg, spinal muscular atrophy)
- Idiopathic

Thoracic Insufficiency Syndrome
- Congenital constricted chest wall syndrome
  - Progressive congenital scoliosis and spinal disorders
    - Hemivertebrae
    - Wedge vertebrae
    - Bar vertebrae
    - Segmental fusion
    - Fused ribs
  - Hypoplastic chest wall
    - Jeune syndrome
    - Jarcho-Levin syndrome
    - Ellis-van Creveld syndrome
    - Achondroplasia
    - Campomelic dysplasia
    - Osteogenesis imperfecta
    - Hypophosphatemia
- Neuromuscular scoliosis
  - Hypotonic
    - Spinal muscular atrophy
    - Congenital muscular dystrophies
  - Hypertonic
    - Static encephalopathy
    - Flail chest
  - Absent ribs
  - Iatrogenesis or trauma
    - Rib resection

Pectus Excavatum and Carinatum

Clinical Features

Pectus excavatum accounts for about 90% of chest wall defects,[25] with an incidence of between 1 in 400 and 1 in 1,000.[26] Although abnormal lung function is rare in most patients with pectus excavatum, subjective reports of pulmonary difficulty are much more common.[27] Patients with pectus excavatum commonly have cardiac deviation to the left and occasionally have

conduction abnormalities as a result of the distortion.[26] Exercise testing is more effective in diagnosing cardiopulmonary limitation,[26,28] which is still a rare concern. However, when there is exertional limitation, it is typically caused by cardiac limitation as opposed to pulmonary limitation.[29–31] Pectus excavatum is usually sporadic[26] but is associated with connective tissue defects, such as Marfan syndrome, Ehlers-Danlos syndrome, and osteogenesis imperfecta,[32] and progressive neuromuscular defects, such as spinal muscular atrophy. Although pectus excavatum can manifest early in life, it commonly worsens through adolescence.[33]

Pectus carinatum is less common. Pulmonary, cardiac, or exercise limitation is extremely rare, and physical appearance is by far the most common concern.[34] As with pectus excavatum, there are a number of associated disorders that can be present with pectus carinatum, such as Marfan syndrome, Noonan syndrome, and osteogenesis imperfecta.[35]

Diagnostic Evaluation

Computed tomography (CT) scans of the chest can be very helpful in clearly defining the defect and the severity. Haller et al[36] developed criteria for evaluating the severity of pec-tus excavatum via chest CT scanning by using the ratio of the lateral chest diameter to the distance from the sternum to the spine, known as the *Haller index* or the *pectus severity index* (**Figure 15-7**). In pectus excavatum, a pectus severity index of 2.5 or less is considered normal; the higher the pectus severity index, the worse the defect. Patients with an index ratio of 3.25 or higher are likely to undergo corrective surgery.[37] Computed tomography scanning has also been used to define the amount of cardiac distortion from the pectus defect.[38] If there is cardiac distortion, then it is important for the patient to undergo echocardiography and a thorough cardiac evaluation.

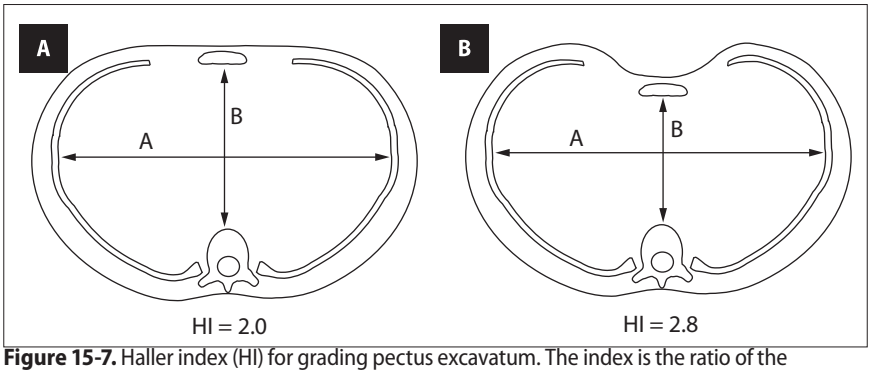


Figure 15-7. Haller index (HI) for grading pectus excavatum. The index is the ratio of the transverse rib-to-rib diameter (**A**) to the distance between the spine and sternum (**B**).

Courtesy of Oscar Henry Mayer, MD.

In pectus carinatum, chest CT scanning is also useful in defining the defect. Conversely to pectus excavatum, the lower the pectus severity index (<2.0), the more severe the disease,[39] given that the defect is one of protrusion rather than invagination.

Pulmonary function testing is indicated to assess for restrictive pulmonary disease in patients with moderate to severe pectus excavatum or those with respiratory symptoms. Although most patients with pectus excavatum may have pulmonary symptoms, pulmonary function abnormalities are found in about one-third of patients.[40] Exercise testing is indicated for patients with moderate to severe pectus excavatum or those with respiratory symptoms.[28]Additional routine testing for patients with pectus carinatum is not typically indicated.

Medical Management

Chest bracing is not used for patients with pectus excavatum, but physical therapy has been used in conjunction with surgery for patients with clinically significant postural abnormalities.[41,42] Part of the challenge in using nonsurgical repair is that the defect is an invagination as opposed to a protuberance, as with pectus carinatum. Alternately, pectus carinatum can respond well to bracing, and this may obviate the need for surgery.[43,44]

Surgical Management

The effect of pectus excavatum on lung function is variable, as is the improvement in lung function after surgical correction. There are 2 main surgical procedures for correcting pectus excavatum—the modified Ravitch procedure and the Nuss procedure.

In the modified Ravitch procedure, a number of cartilage segments are resected, leaving the perichondrium in place.[26] A sternal support, usually a metallic strut, is placed between the anterior edges of the rib cage and through the sternum, with the sternum repositioned normally. After 2 to 3 years, the strut is removed. In the past, aggressive and extensive cartilage resection and sternal remodeling were performed. This practice has since been substantially modified owing to cases of severe asphyxiating thoracic dystrophy, believed to be caused by the disruption of sternum and cartilage growth, thereby limiting future chest wall growth.[44] However, limiting cartilage resection and performing the procedure in children older than 8 years have largely eliminated this concern.

The Nuss procedure, or minimally invasive pectus excavatum repair, involves using a titanium rod that is bent to the corrected contour of the chest wall. It is inserted into the pleural space through a small axillary thoracotomy, passed through the retrosternal space anterior to the heart, and through the contralateral chest at the same level as the entry point. It is then rotated anteriorly

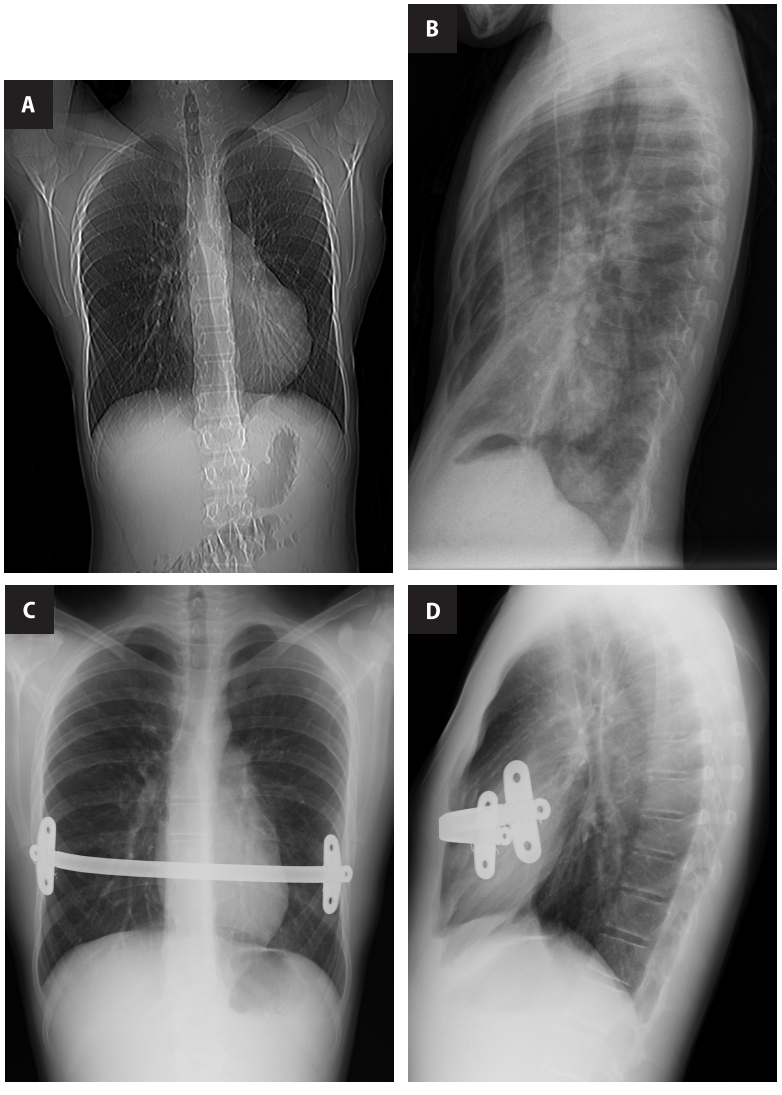


Figure 15-8. Pectus excavatum repair by means of the Nuss procedure with anteroposterior (**A**) and lateral (**B**) chest radiographs before insertion and anteroposterior (**C**) and lateral (**D**) chest radiographs after insertion.
Courtesy of Oscar Henry Mayer, MD.

to press the sternum outward at the level of the maximal invagination and is sutured in place on the outside of the chest wall (**Figure 15-8**).[45] The rod is kept in place as a brace until the sternum has remolded and usually is removed after 2 years, usually with a permanent repair.

Although data from some centers demonstrate a modest increase in lung function after pectus repair, the results are quite variable.[28–31,39,45] For patients not deemed to be surgical candidates, periodic physical examinations and imaging should be performed, particularly during periods of rapid growth, because the deformity and associated symptoms may progress.[46]

Scoliosis

Clinical Features

Scoliosis can decrease chest wall compliance and lung compliance in the concave chest, thereby worsening respiratory mechanics. As scoliosis progresses, the convex chest can become hyperexpanded because of the lateral rotation of the chest and stretching of the intercostal muscles (**Figure 15-9**), further limiting chest wall excursion and worsening chest wall compliance.

More complex scoliosis with clinically significant transverse chest wall rotation (**Figure 15-10**) can substantially distort the chest wall in the transverse plane. In doing so, the diaphragm can rotate radially and flatten and increase the radius of curvature; however, the clinical significance of this has not been

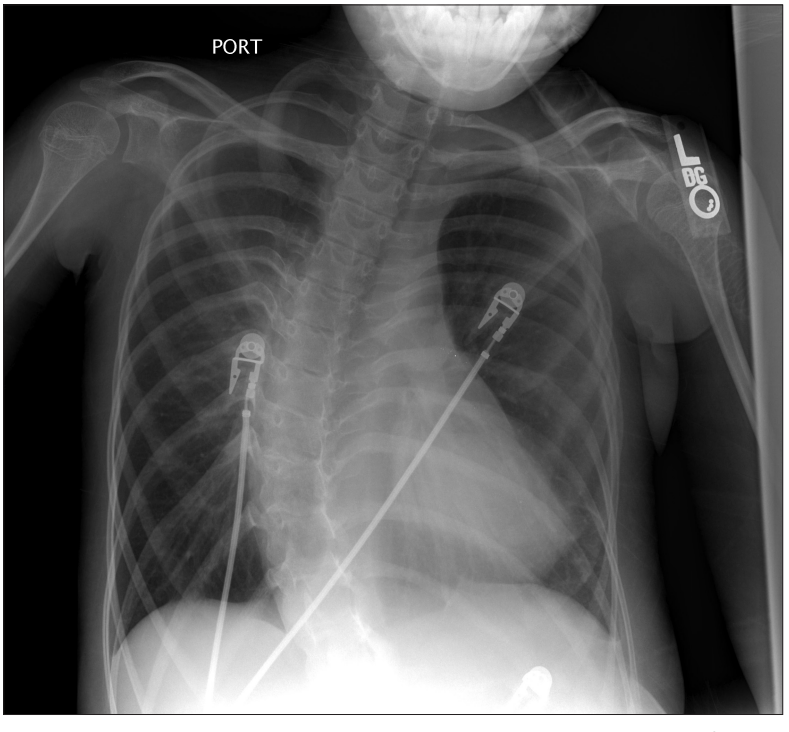


Figure 15-9. Scoliosis. Anteroposterior radiograph showing the compression of the lung and chest wall on the concave side of the chest and the hyperexpansion of the chest on the convex side in a teenager with spinal muscular atrophy type 2.

Courtesy of Oscar Henry Mayer, MD.

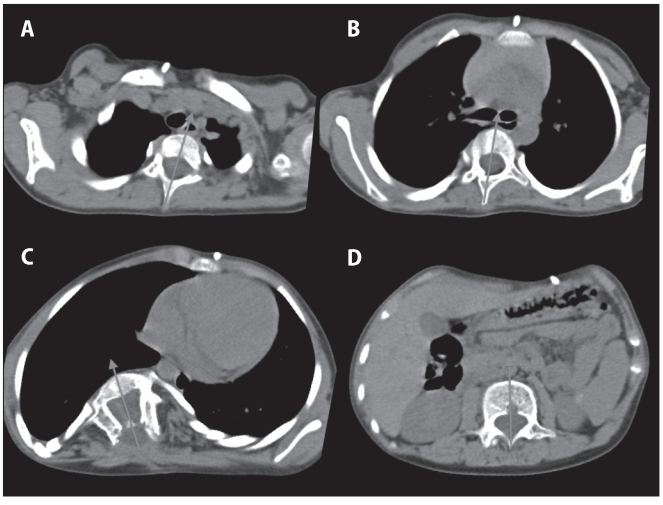


Figure 15-10. Transverse computed tomography scans showing the rotation of the spine and diaphragm in complicated scoliosis from the level of the apex of the lung (**A**), the carina (**B**), the lower thorax (**C**), and the lower edge of the liver (**D**). Gray arrows indicate the rotational axis of the spine.

Courtesy of Oscar Henry Mayer, MD.

demonstrated. Bronchial compression can also occur because of compression by the rotated anterior edge of the vertebral body.[47]

The cause of scoliosis can be described in 1 of 3 ways (1) spinal instability or abnormality with asymmetrical growth; (2) rib cage deformity with absence of ribs, rib fusion, or general lateral instability from muscle weakness; or (3) idiopathic scoliosis, in which there is no clear cause.

In children with hemivertebrae or asymmetrical vertebrae, such as wedge or bar vertebrae, scoliosis will serve as a nidus for the curve because spinal integrity is disrupted at that point (**Figure 15-11**). A bar vertebra or unilateral fusion provides a tethering point around which vertical spinal growth is asymmetrical and produces scoliosis (**Figure 15-11**). In children with absent ribs, lateral chest wall support will be deficient, and the lateral chest wall will collapse, creating an ipsilateral scoliosis (**Figure 15-12A**). Rib fusion that causes a tethering point around which the spine will grow asymmetrically can cause scoliosis (**Figure 15-12B**). In children with neuromuscular disease, the biomechanics of the thorax are abnormal, often with weak rib-to-rib support and eventual unilateral or bilateral collapse, with severe caudad rotation of the ribs in the convex chest, as is often seen in spinal muscular atrophy type 1 (**Figure 15-13**). Finally, idiopathic scoliosis can occur in children with no clear underlying musculoskeletal abnormality. Often the scoliosis is asymptomatic and noticed incidentally as part of a health supervision visit or on a chest radiograph.

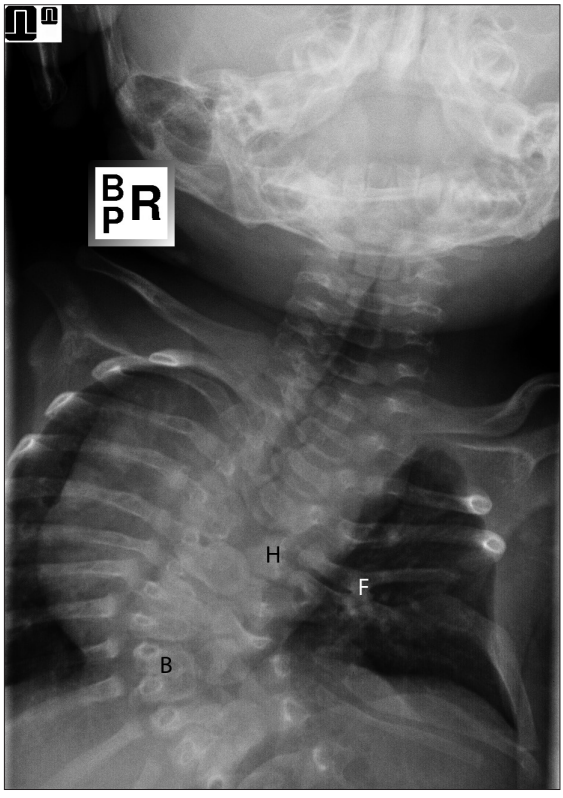


Figure 15-11. Anteroposterior chest radiograph demonstrating scoliosis caused by an underlying spinal disorder with hemivertebrae (H), bar vertebra (B), and rib fusion (F).

Courtesy of Oscar Henry Mayer, MD.

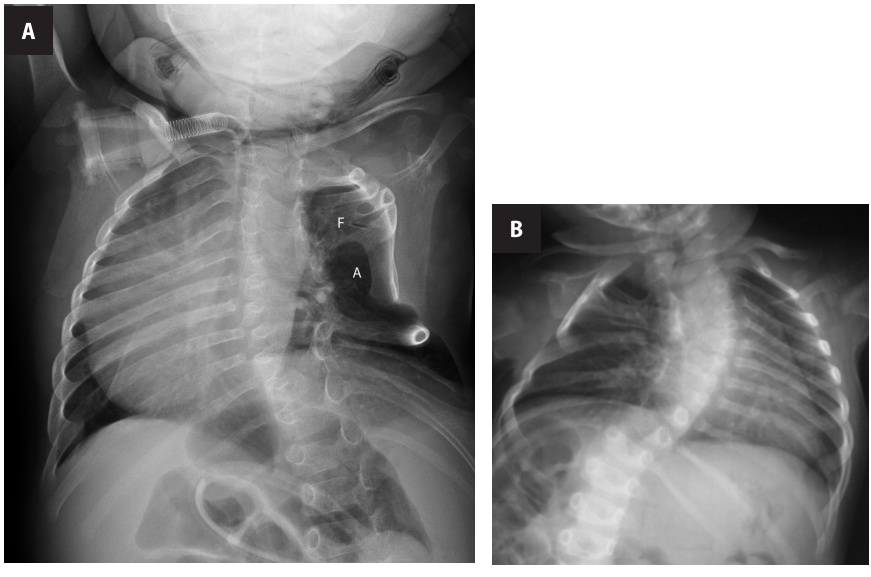


Figure 15-12. A, Anteroposterior radiograph showing scoliosis caused by rib fusion (F) and rib absence (A). **B,** Anteroposterior radiograph showing scoliosis caused by rib fusion.

Courtesy of Oscar Henry Mayer, MD.

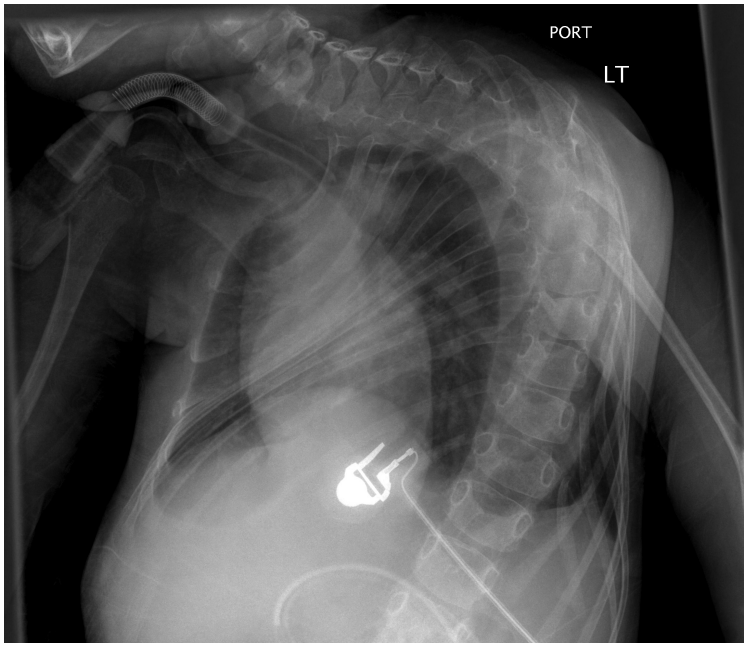


Figure 15–13. Anteroposterior radiograph showing neuromuscular scoliosis caused by spinal muscular atrophy type 1 with caudad rotation of the ribs in the right side of the chest.
Courtesy of Oscar Henry Mayer, MD.

Medical Management

Before surgery is considered, bracing can be used to align the spine in a more favorable midline position, or as close to it as possible. Although in many situations bracing is seen as a temporizing procedure and not a cure,[48] it can be successful in preventing scoliosis curve progression in patients who are skeletally immature and have curves of less than 40°[48,49] and occasionally may obviate the need for surgery.[48]

Surgical Management

The decision to treat scoliosis is made on the basis of clinical symptoms, severity of scoliosis, and rapidity of progression, with 50° of curve being the point at which surgical intervention is often considered.[48] The definitive surgical treatment is placement of spinal fusion rods along each edge of the spine with use of metal suture material to connect to the spinal laminae (**Figure 15-14**), pedicle screws placed into the vertebral bodies, or laminar hooks over the spinal laminae. Although this treatment provides mechanical stability, it prevents further spine growth within the fused region and limits FVC commensurate with both the length of the fusion and the height of the superior fusion point.[50] This growth prevention clearly limits the usefulness of the procedure in younger children. In these children, growth can be maintained with nonsurgical interventions, such as bracing the abdomen and part of the thorax intermittently to keep the spine aligned properly.

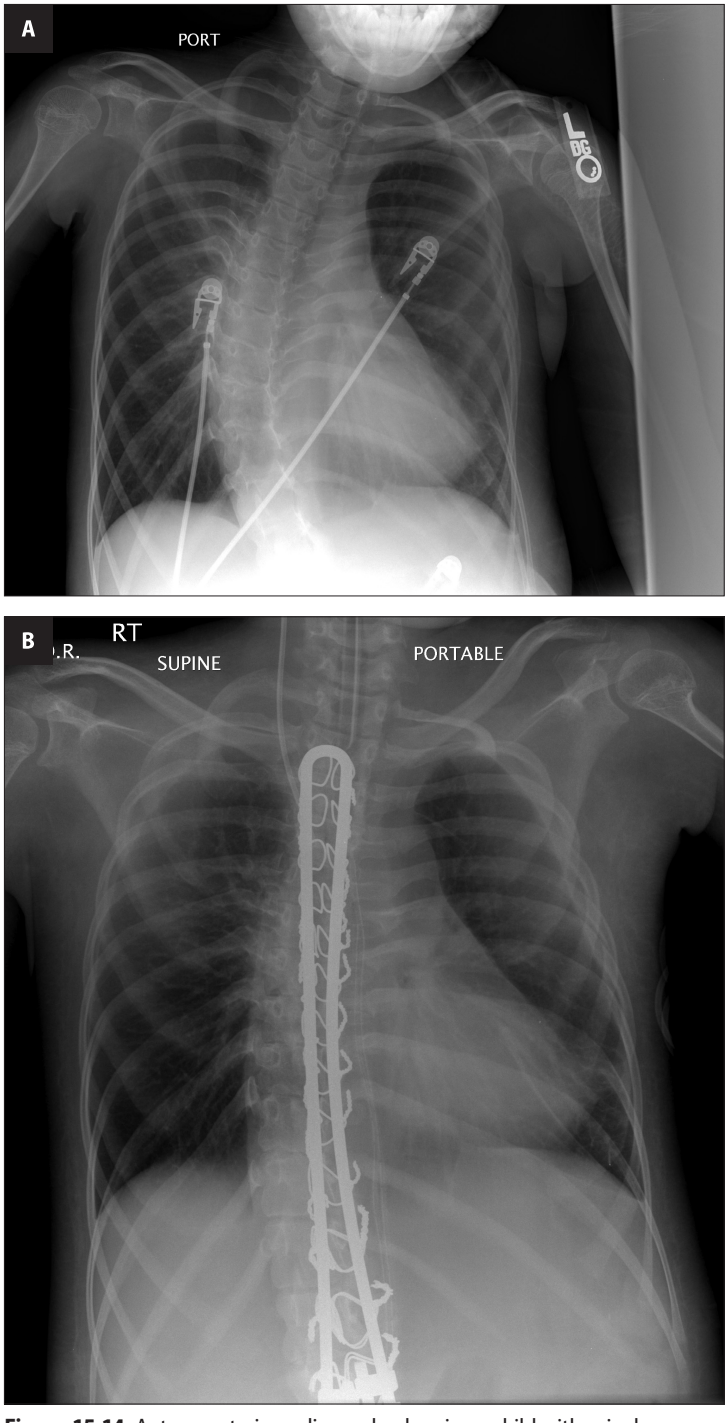


Figure 15-14. Anteroposterior radiographs showing a child with spinal muscular atrophy type 2 before (**A**) and after (**B**) spinal fusion.

Courtesy of Oscar Henry Mayer, MD.

The longitudinal pulmonary outcome of scoliosis surgery is determined chiefly by the preoperative FVC and, to a lesser extent, by the surgical approach, with the posterior approach without thoracotomy being more favorable than the anterior approach via thoracotomy.[20] Among a number of potential complicating factors is the potential for a secondary lordosis, or "crankshaft" abnormality, with posterior-only spinal fusion because of continued anterior spinal growth and arrested posterior spinal growth. The alternative of a thoracotomy and anterior fusion has been associated with a decrease in lung function.[38]

It is hard to make a definitive statement about the usefulness of spinal fusion in correcting lung function because lung function is not the only outcome measure. In addition, there should not be an expectation of substantial improvement in vital capacity as a percentage of that predicted after scoliosis surgery because the act of fusion limits further spine growth and worsening of scoliosis at the expense of lung growth and, in some situations, loss of lung function.[38,51] Therefore, the decision to perform spinal fusion is a balance between supporting growth and minimizing the further loss of lung function.

A separate approach is to use growing rods (**Figure 15-15**) along the spine to support the spine, as is done with spinal fusion, but with serial lengthening of the rods commensurate with expected spine growth.[52] Although spine growth can be kept in the normal range,[52] the effect on future lung function is not yet known. These rods must be transitioned to a static rod to fuse the spine after growth is complete. Definitive spinal fusion may be more challenging in this approach because of residual perispinal scarring from the growing rods.

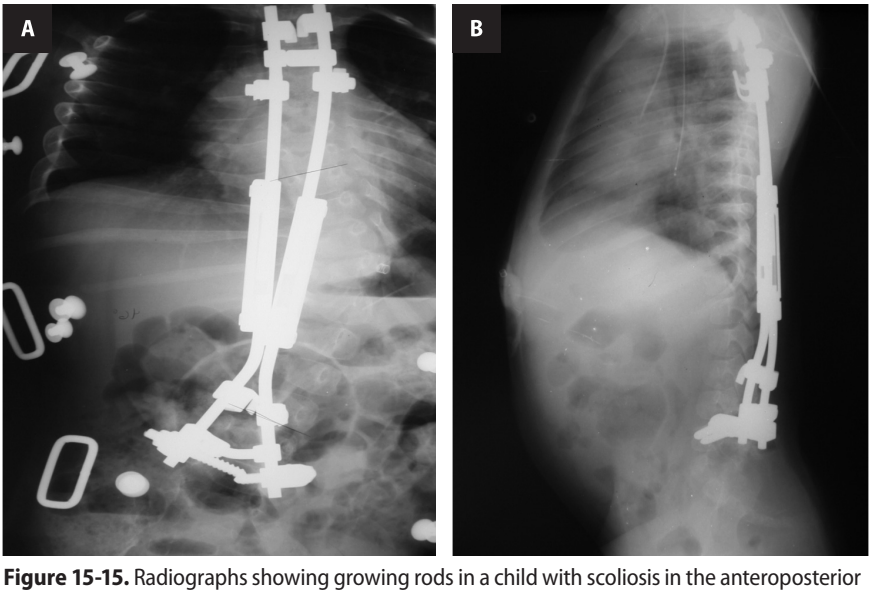


Figure 15-15. Radiographs showing growing rods in a child with scoliosis in the anteroposterior (**A**) and lateral (**B**) projections.

Courtesy of Robert Campbell, MD.

Thoracic Insufficiency Syndrome

Clinical Features

Thoracic insufficiency syndrome encompasses a wide range of complex thoracospinal disorders in which the chest wall and spine cannot support normal respiration and lung growth.[14] Thoracic insufficiency syndrome is different from idiopathic scoliosis in that patients with TIS typically have a more rapid loss of lung function that can cause severe pulmonary morbidity or respiratory failure if untreated. Although TIS encompasses a number of disparate conditions, there are 3 phenotypic categories of TIS—congenital constricted chest wall syndrome, progressive spinal deformity, and flail chest.[53]

Congenital constricted chest wall syndrome has 2 subtypes—progressive congenital thoracic scoliosis and hypoplastic thorax disorders.[14,53] Progressive congenital thoracic scoliosis can result from abnormal rib segmentation, or rib fusion (**Figure 15-12B**), with or without a skeletal abnormality.[14,53] In congenital cases, clinical symptoms can occur quite early and may be severe. Primary rib defects, such as rib fusion, can also occur.

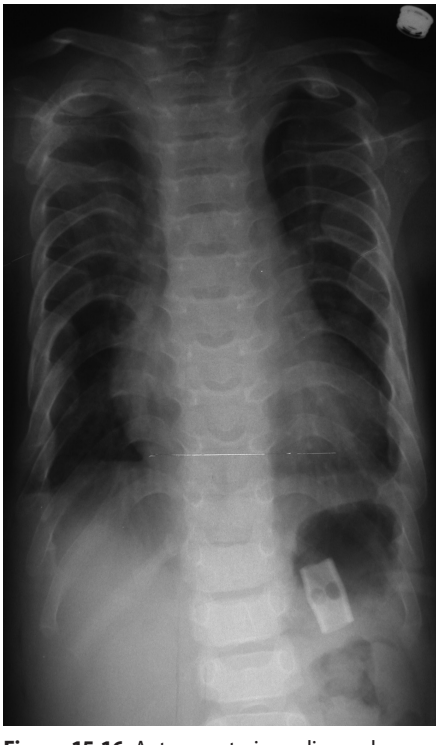


Figure 15-16. Anteroposterior radiograph showing hypoplastic thorax in Jeune syndrome.
Courtesy of Robert Campbell, MD.

Hypoplastic thorax disorders can occur owing to defects in cartilage (achondroplasia, campomelic dysplasia), costal growth abnormalities (Ellis-van Creveld syndrome, Jeune syndrome [**Figure 15-16**]), or spinal growth abnormalities (Jarcho-Levin syndrome [**Figure 15-17**]).[14,53] Similarly, the thorax can be hypoplastic with osteogenesis imperfecta type 2 and with hypophosphatemia owing to undermineralized bone causing easy fracture, disrupted healing, and poor thoracic growth. Over time, the chest does not grow with the rest of the body and the increasing metabolic need.



Figure 15-17. Anteroposterior radiograph showing Jarcho-Levin syndrome.
Courtesy of Robert Campbell, MD.

Progressive spinal deformity is progressive scoliosis caused by neuromuscular disease (**Figure 15-13**) or a primary vertebral abnormality, such as bar vertebrae, segmental fusion, hemivertebrae, or wedge vertebrae (**Figure 15-11**),[14,53] without rib abnormalities. In congenital cases, clinical symptoms can occur quite early and may be severe.

Flail chest can occur because of a congenital defect with absent ribs (**Figure 15-12A**) and may also be associated with a variety of different spinal defects. It can also occur as a result of chest wall surgery to remove a portion of the chest wall or as a result of trauma.

Medical Management

Although there is no medical therapy that can effectively treat TIS, nutritional support and noninvasive or invasive ventilation can be critical in helping a patient grow to the point at which surgery would be most feasible. With chest wall expansion and spinal straightening, as described in the next section, proper soft-tissue mass is needed to close the newly expanded chest wall and cover the inserted supportive hardware.[53] If this is not done, there can be a higher risk for complications, such as skin and soft-tissue breakdown at the site of the repair.

Surgical Management

Thoracic insufficiency syndrome poses surgical challenges that go well beyond stabilizing the spine, and with the early age at which many patients with TIS present, fusion is not a viable option. The combination of early onset of thoracospinal disease with TIS spurred the development of the vertical expandable prosthetic titanium rib (VEPTR). This model provides spinal support and is expandable to allow normal longitudinal growth, as with the growing rod model. However, the VEPTR has the additional advantage of

lateral support in a variety of different ways based on the placement of the devices (**Figure 15-18**).[14] It can also be used to correct rotational scoliosis and a variety of types of complicated thoracospinal disorders,[53] such as flail chest; scoliosis with fused ribs or with absent ribs; and scoliosis with major vertebral abnormalities that destabilize the spine, such as bar vertebrae, hemivertebrae, or wedge vertebrae. The expansions are typically performed every 6 to 8 months during a day- surgery procedure to maintain a normal spinal growth velocity while providing spinal and thoracic stability.[52] A magnetically controlled growing rod inserts similarly to the VEPTR but lengthens nonsurgically and during an outpatient visit. It uses telescoping rods containing an internal magnet that are lengthened from an external actuator, thereby eliminating the need for anesthesia.[54,55] Long-term data comparing outcomes among the main growth-sparing procedures are not yet available.

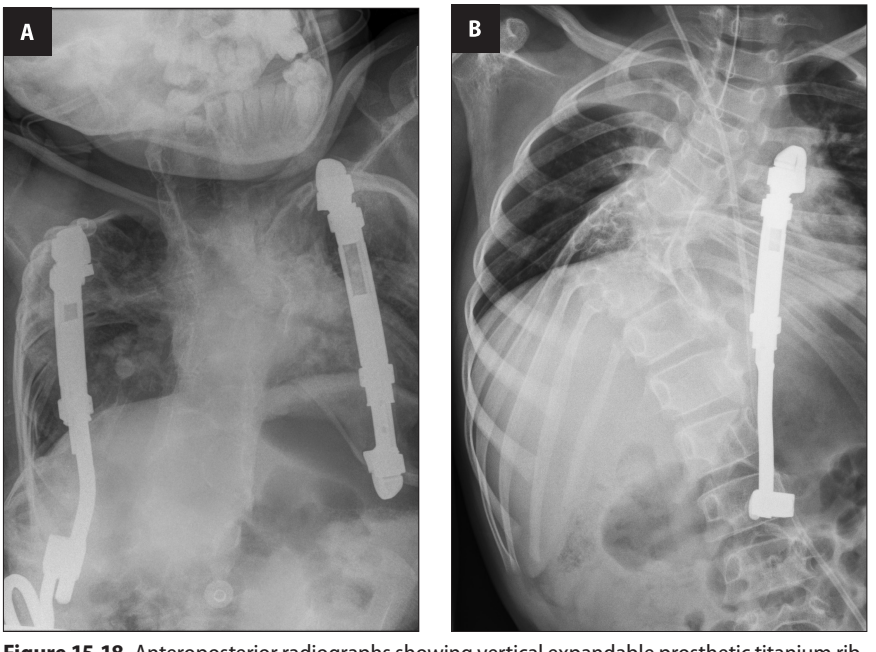


Figure 15-18. Anteroposterior radiographs showing vertical expandable prosthetic titanium rib placement in the rib-to-rib (right) and rib-to–iliac crest (left) (**A**) and rib-to-spine (**B**) orientations.
Courtesy of Robert Campbell, MD.

Because TIS is a constellation of heterogeneous conditions that have similar morbidity, optimal timing for correction is based on a combination of the severity of the underlying thoracospinal defect and the associated respiratory morbidity. Thus, the ideal insertion time of the VEPTR is variable and individualized to the patient. Although there is clearly a benefit in surgically treating TIS early to minimize progression, there are no data that give a clear link between age of surgery and long-term prognosis.

The VEPTR can be used in patients with a hypoplastic chest, such as with Jarcho-Levin syndrome and Jeune syndrome. With Jarcho-Levin syndrome, the VEPTR supports the spine and places a longitudinal traction force to encourage growth (**Figure 15-19**). In Jeune syndrome, the VEPTR pro-vides a lateral tethering point for the rib cage to expand after a series of rib osteotomies and outward traction leaving the periosteum in place (**Figure 15-20**). There is also

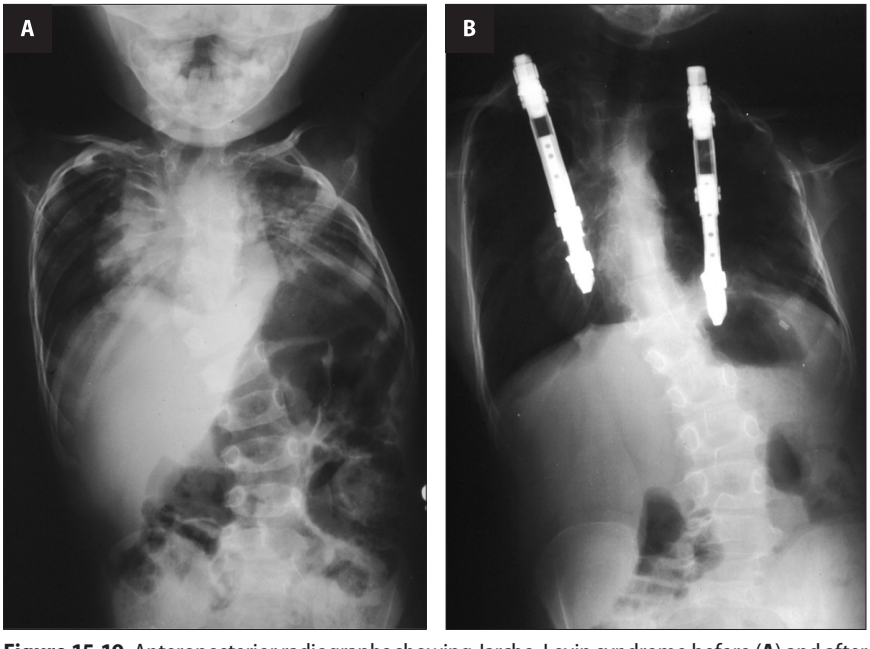


Figure 15-19. Anteroposterior radiographs showing Jarcho-Levin syndrome before (**A**) and after (**B**) repair with the vertical expandable prosthetic titanium rib.

Courtesy of Robert Campbell, MD.

an alternative approach, a lateral thoracic expansion technique, in which there are a series of staggered rib osteotomies with fusion of the alternating longer lengths of rib to expand the chest wall circumference (**Figure 15-21**).[56] Unlike the VEPTR, in which the device is lengthened about every 6 months, the lateral thoracic expansion technique is a single procedure that is not repeated and does not allow for growth over time.

There are substantial challenges in obtaining reliable pulmonary function testing results given the young age of the patient at the time of surgery. In a cohort of older patients with TIS, pulmonary function testing showed that VEPTR insertion does not result in an improvement in lung function but rather in a decrease in FVC and an increase in residual volume, which suggest that the role of surgical correction is to prevent further decline in pulmonary function.[21] However, advanced imaging techniques, including dynamic magnetic resonance imaging, have shown increases in lung volume and diaphragm excursion after VEPTR placement.[57]

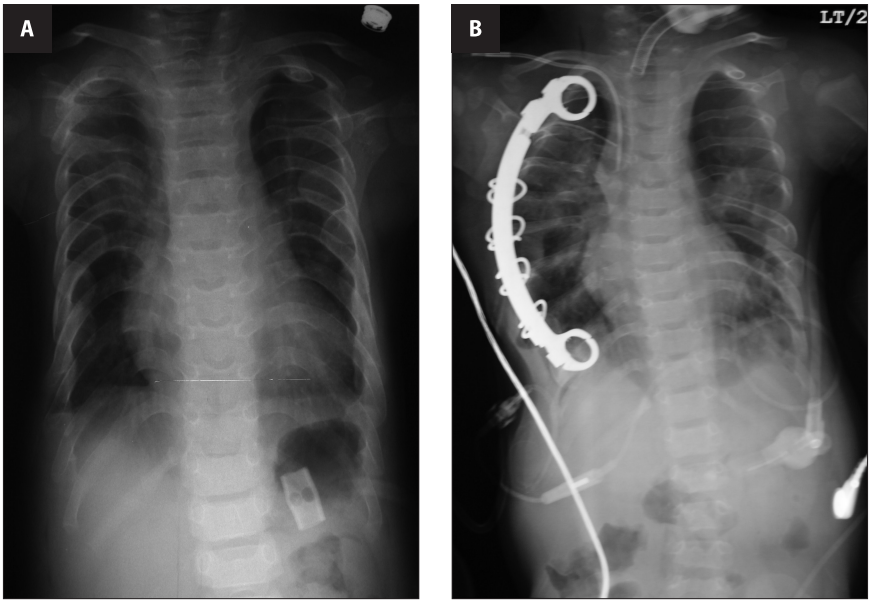


Figure 15-20. Anteroposterior radiographs showing Jeune syndrome before (**A**) and after (**B**) vertical expandable prosthetic titanium rib insertion.
Courtesy of Robert Campbell, MD.

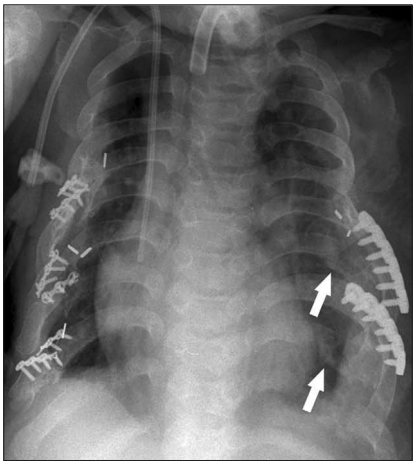


Figure 15-21. Anteroposterior radiograph showing Jeune syndrome repair by means of the lateral thoracic expansion technique, with arrows pointing to the free rib segments with growth of new bone.

Courtesy of Robert Campbell, MD.

Muscular Abnormalities

A list of muscular abnormalities is found in **Box 15-2**. Diaphragm weakness is common in Duchenne muscular dystrophy. Chest wall weakness and abnormal mechanics are prominent in both spinal muscular atrophy and Duchenne muscular dystrophy, can be seen in the congenital muscular dystrophies, and can lead to clinically significant thoracospinal disease. These conditions are discussed in Chapter 54, Pulmonary Complications of Neuromuscular Disorders.

Box 15-2

Muscular Abnormalities

- Congenital diaphragmatic hernia
- Abdominal wall defects
- Gastroschisis
- Omphalocele
- Prune belly syndrome (Eagle-Barrett syndrome)

Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) occurs when the pleuroperitoneal canal fails to close during early fetal development. The primary morbidity from CDH is related to pulmonary hypoplasia or other organ system defects.[58–60] Diaphragm function and muscle strength, on the basis of maximal inspiratory pressures,[61] are directly related to the size of the diaphragm defect and synthetic patch needed for the repair. However, in a cohort of 25 patients with CDH, diaphragm function was adequate for unsupported respiration, even considering the associated pulmonary hypoplasia and airway disease.[61]

Abdominal wall defects and CDHs are repaired surgically; however, the chronic respiratory failure and pulmonary hypertension that are often seen coincidently can require substantial medical therapy, both before and after definitive surgical repair.

Gastroschisis and Omphalocele

Gastroschisis and omphalocele cause lateral and midline defects, respectively, in the abdominal musculature; after successful closure, the abdomen is devoid of muscle and highly compliant. Prune belly syndrome, also known as Eagle-Barrett syndrome, has a similar outcome but is associated with urinary tract obstruction and massive dilatation of the urinary tract and abdomen, affecting mesenchymal development and abdominal muscle structure. These defects can affect respiration in 2 ways. First, the high abdominal compliance means that caudad diaphragm movement during inspiration will displace the abdominal contents outward more, with less resistance from the abdominal wall. As a result, there will be a smaller increase in intra-abdominal pressure and less outward excursion of the lower rib cage. Second, the paucity of abdominal muscle limits forceful exhalation and reduces cough effectiveness.

key points

- Normal respiration involves coordination between diaphragm contraction and abdominal and chest wall motion. Chest wall abnormalities can substantially compromise respiratory system function by interfering with these functions.
- The central tenet of treating thoracospinal defects is to prevent their progression, stabilize the chest and spine, and support normal growth. Although the likelihood of a clinically significant improvement in lung function remains low, it is possible to prevent or minimize further decline in lung function.

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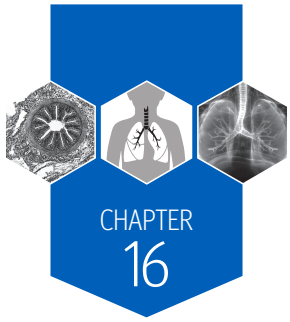
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PART
4

Upper Airway Infections

Chapter 16. Croup, Epiglottitis, and Bacterial Tracheitis 311
Girish D. Sharma, MD, FAAP, FCCP



Croup, Epiglottitis, and Bacterial Tracheitis

Girish D. Sharma, MD, FAAP, FCCP

Croup

CASE REPORT 16-1

A 2-year-old boy with a history of mild upper respiratory symptoms for 2 days develops sudden onset of a barky, croupy cough at 2:00 am. His voice is hoarse. When taken to the emergency department (ED), he develops intermittent inspiratory stridor when agitated. He is afebrile and tachycardic. His oxyhemoglobin saturation in room air is normal, and he has minimal retractions and no cyanosis. Lung auscultation reveals good and equal air exchange bilaterally, with coarse sounds but no wheeze or crackles. There is a history of similar symptoms 2 months ago, and, as his parents prepared to take to him to the ED, there was sudden resolution of symptoms during the car trip. That time, he was observed for a short time in the ED before being discharged. A diagnosis of croup is suspected.

Introduction

Croup, or acute laryngotracheobronchitis, is an early childhood viral syndrome characterized by acute laryngeal and subglottic swelling resulting in the sudden onset of a barky cough, inspiratory stridor, hoarse voice, and respiratory distress. Onset of these symptoms in a young child with acute worsening, usually in the early hours of the morning, and associated disruption of family routine may lead to substantial anxiety in both the child and the caretaker.

Causes

The cause of croup is primarily parainfluenza type 1.[1] Other viruses implicated in the cause are parainfluenza types 2 and 3; influenza A and B; adenovirus; respiratory syncytial virus; rhinovirus; measles; human metapneumovirus; and coronavirus, including SARS-CoV-2, the virus causing COVID-19.[2,3] Most patients presenting with mild symptoms and mild fever have acute laryngotracheitis. Presence of a high-grade fever, substantial respiratory distress, and toxemia point to a bacterial cause, such as bacterial tracheitis or laryngotracheobronchitis.[4]

Pathophysiology

Mild cases involve noninflammatory edema in the subglottic region. More severe cases (acute laryngotracheitis) involve inflammation and edema of the subglottic area and lateral wall of the trachea, which is characterized by cellular infiltration with lymphocytes, neutrophils, histiocytes, and plasma cells. The inflammation and edema of the subglottic region result in narrowing and clinical presentation of barky, brassy cough; hoarse voice; stridor; and respiratory distress with retractions. Subglottic and upper tracheal narrowing is responsible for the typical steeple sign on radiographs (**Figure 16-1**). The fluctuation in symptom severity, nocturnal worsening, and tendency of some children to develop severe and recurrent episodes of croup may be related to whether the child is agitated or calm,[5] low levels of endogenous cortisol,[6] and tendency of some children for having an intrinsically narrower subglottic space.[7] Host factors, such as allergies, may play a role in recurrent croup.[8]



Figure 16-1. Frontal radiograph of the airway of a patient presenting with croup. Note the typical steeple sign due to upper tracheal and subglottic narrowing.

Courtesy of Mariangeles Medina Perez, MD.

Epidemiology

Most patients with viral croup are younger than 6 years and more typically are between 3 months and 3 years of age. The incidence in boys is 1.5 times higher, and the disease tends to occur most commonly from September to December in the northern hemisphere. The incidence has been reported to correlate with parainfluenza virus prevalence.[9] Up to 6% of children with croup may require hospitalization.[10] CD14 gene polymorphism (C/C variant of CD14 [C-159T]) has been reported to be associated with reduced prevalence of croup.[11]

Clinical Features

Typically, the child with croup has mild upper respiratory symptoms for 12 to 48 hours before the abrupt onset of the characteristic barky cough, respiratory distress, stridor, and hoarse voice. The onset of these symptoms is usually during the early hours of the morning. The symptoms are generally short-lived, and most children have resolution of the barky cough within 48 hours. The symptoms are worse if the child is agitated. There may be diminished breath sounds, rhonchi, and scattered crackles.

Differential Diagnosis

The differential diagnosis of croup includes retropharyngeal or peritonsillar abscess, which is identified by a typical swelling of the local area. Other

diagnoses to rule out include angioneurotic edema, allergic reaction, and foreign body, which are identified by a corroborative history and sudden onset. Tracheitis and epiglottitis, though rare, should be considered in the presence of toxic appearance, fever, and rapidly worsening course.

Unlike viral croup, spasmodic croup (laryngismus stridulus) usually involves the croup-like cough that occurs in an older age group, tends to be recurrent, and is thought to be allergic in origin. It is treated with corticosteroids and tends to be benign even though it can be persistent. Recurrent croup is diagnosed in patients with tracheomalacia who present with prominent cough with each upper respiratory infection episode that results in a visit to urgent care or the emergency department. Investigators in a retrospective study of recurrent croup reported a 47% incidence of gastroesophageal reflux.[12]

Modern vaccination practices have resulted in a drastic reduction in the prevalence of laryngeal diphtheria, a highly contagious infection that should be considered in patients with possible exposure who are unimmunized. It can affect all ages. There is usually a prodromal phase of pharyngitis, and the illness is characterized by hoarseness, barking cough, usually dysphagia, minimal to severe inspiratory stridor, fever, and membranous pharyngitis. *Corynebacterium diphtheriae* is identified on smear and culture of the membrane.

Assessment of Severity

Table 16-1 summarizes the classification of clinical features in mild, moderate, and severe croup.

Table 16-1. Classification of Croup Severity

Clinical Feature	Severity		
	Mild	**Moderate**	**Severe**
Cough	Occasional barking	Frequent barking	Frequent barking
Stridor	None at rest	Audible at rest	Prominent inspiratory
Retractions	None or mild	Suprasternal	Marked sternal
Agitation	None	None or little	Substantial with distress

Investigations

Radiography is not usually indicated because the clinical picture is straightforward and there is appropriate response to treatment. Moreover, the child may be more agitated during a visit to the radiology department, resulting in further worsening of clinical condition. In the event that there is an atypical clinical picture and the diagnosis is uncertain, anteroposterior and lateral soft-tissue neck radiographs show a typical steeple sign that is consistent with the diagnosis of croup (**Figure 16-1**) or that differentiates it from an alternative diagnosis, such as epiglottitis.[13] Soft-tissue neck radiographs are not routinely used in

patients with croup; however, if performed to exclude other causes of upper airway obstruction, they will show tracheal narrowing, which has been correlated with the severity and outcome in patients with croup.[14]

Management

General

Effort should be taken to make the child comfortable and to reduce agitation because agitation can substantially worsen the condition. Sitting the child comfortably in the lap of a parent or caregiver is usually the best way to examine the child.

Figure 16-2 shows an algorithm to treat croup in pediatric practice. Children who have a compromised airway, such as a subglottic stenosis, may experience worse symptoms and may require endotracheal intubation or tracheotomy.

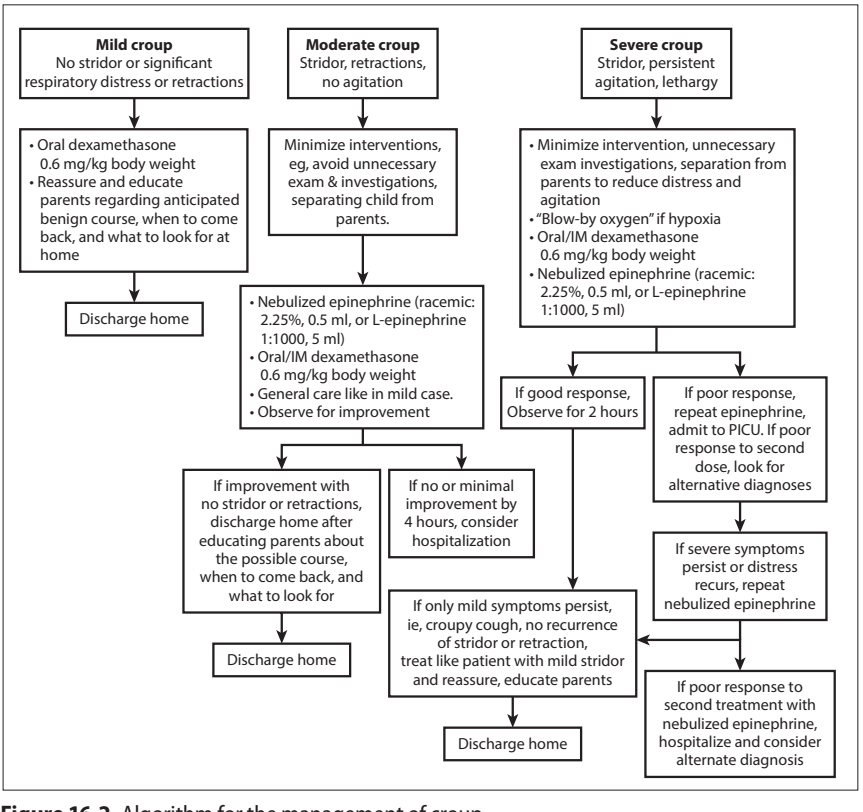


Figure 16-2. Algorithm for the management of croup.

Corticosteroids

Corticosteroids are routinely used in the treatment of croup. Investigators in a meta-analysis of 24 studies in which corticosteroids were used to treat croup concluded that dexamethasone and budesonide are effective in relieving the symptoms of croup as early as 6 hours after treatment; fewer co-interventions were used, and the length of hospital stay was reduced in patients treated with corticosteroids.[15] A recent Cochrane Database review reported the glucocorticoids improved symptoms at 2 hours, reduced length of stay, and led to fewer return visits.[16]

In children with mild croup, oral dexamethasone in a dose of 0.6 mg per kilogram of body weight results in consistent, small, but clinically significant improvement.[17] If the child is vomiting, intramuscular dexamethasone is indicated.

In moderately severe cases of croup, a single dose of intramuscular dexamethasone of 0.6 mg per kilogram of body weight or nebulized budesonide 4 mg resulted in statistically significant reduction in hospitalization. Dexamethasone was associated with greater clinical improvement at 5 hours.[18]

Results from a systematic review of 43 studies in which investigators used dexamethasone (0.6 mg/kg administered orally) or nebulized budesonide (2–4 mg) involving more than 4,500 children from North America, Europe, Asia, and Australia showed that glucocorticoids reduced croup symptoms at 2 hours, shortened hospital stays, and reduced the rate of return visits.[16] A lower dose of dexamethasone, 0.15 mg/kg, has had a similar effect and is gaining wider acceptance.[19]Administration of a single dose of dexamethasone to treat croup does not affect endogenous corticosteroid levels.[20]

Epinephrine

Although nebulized racemic epinephrine traditionally has been used to treat croup, nebulized epinephrine 1/1,000 is as effective and safe.[21] The usual dose is 0.05 mL/kg of 2.25% racemic epinephrine or 5 mL (or 0.5 mL/kg) of 1/1,000 epinephrine via nebulizer. Authors of a systematic review of 8 studies (225 subjects), with the limitation of the number of relevant studies and subjects, reported statistically significant, albeit transient, improvement in croup symptoms within 30 minutes of epinephrine administration.[22] Therefore, children with croup who have received epinephrine should continue to be monitored for recurrence of symptoms and can be discharged home if the symptoms do not recur within 2 to 4 hours after treatment.[23,24] Symptoms that occur once the epinephrine wears off are not likely a rebound phenomenon but a recurrence of the original symptoms. If more than 2 doses of epinephrine are needed, the child likely should be hospitalized. Over-the-counter epinephrine metered-dose inhalers have been used for home treatment of recurrent croup; however, oral dexamethasone or nebulized

budesonide (see Corticosteroids earlier in this chapter) are gaining wider acceptance and obviate epinephrine use–related adverse effects.

Oxygen Supplementation

Oxygen supplementation may be used in the unlikely situation of hypoxia. Because croup is caused by airway obstruction rather than ventilation/perfusion mismatch, a patient with croup who is hypoxic is probably also hypercarbic. The clinical practice guidelines developed by the Alberta Clinical Practice Guideline Working Group recommend blow-by oxygen in children with respiratory distress.[13]

Humidified Air

Although it has been used for a long time, there is no published evidence to suggest that administration of humidified air results in substantial improvement. Authors of a systematic review and meta-analysis of 3 studies[25] concluded that there is no statistically significant improvement in the croup score of children with mild to moderate croup treated in an emergency setting and that evidence is insufficient to exclude either a small beneficial or a harmful effect with its use. Severe burns due to steam inhalation used for respiratory infection have been reported.[26,27]

Heliox

Heliox is a combination of inert gas helium with oxygen. Because low-density helium (as opposed to the nitrogen present in the air) converts turbulent flow into laminar flow through a narrow airway, some have advocated its use. Heliox was reported to provide no benefit compared with results with standard treatment in older studies,[7,28] especially in patients with moderate to severe croup, but more recent research has shown that heliox may be beneficial in the short term for children with moderate to severe croup treated with dexamethasone. The effect may be similar to 100% oxygen administered with 1 or 2 doses of adrenaline.[29]

Other Medications

Other medications, such as decongestants, short-acting β_2 agonists, antitussives, and analgesics, have no physiological basis for their use. Sedatives should not be prescribed.

When to Refer

- Cases of croup associated with excessive tachycardia may be associated with impending respiratory failure.
- In addition, persistence of symptoms for several days may merit referral for ear, nose, and throat specialist or pediatric pulmonologist evaluation and to rule out underlying structural airway abnormality. Similarly, patients with recurrent croup or croup in children with a history of airway manipulation or facial hemangioma warrant a referral.

When to Admit

- Severe respiratory distress, particularly if there is hypoxia (hypoxia is unusual in benign croup)
- Inability to eat or drink
- Acute care requiring 2 or more nebulizations of epinephrine

Epiglottitis

CASE REPORT 16-2

A 4-year-old boy who was previously healthy and received all immunizations expected for his age is brought into the emergency department for evaluation of fever and sore throat. He refuses to eat or talk. He has a temperature of 39.5°C (103.1°F) and oxygen saturation of 94% while breathing room air. He appears ill, is drooling, and prefers to sit alone and prop himself up and forward onto his hands in a tripod position. The examination reveals inspiratory stridor and suprasternal retractions.

The differential diagnosis is short, and clinical suspicion for impending respiratory failure due to acute epiglottitis should be quite high. In this case, consultation with the otolaryngology and anesthesiology teams should be initiated, and the child should be taken to the operating room for endotracheal intubation. Ideally, a protocol for team mobilization for this situation should be determined in advance and standardized as an interdisciplinary policy.

Introduction

Acute epiglottitis, also known as *supraglottitis*, is a potentially life-threatening infection of the supraglottic structures that can lead to sudden, fatal airway obstruction if treatment is delayed. Classically, the disease does not involve the subglottic or tracheal mucosa. If treatment is delayed, it may rapidly progress to complete airway obstruction with cardiorespiratory arrest.

Epidemiology

Historically, acute epiglottitis was described as a disease of adults, but in the 1960s it was recognized primarily as a pediatric disease. Since the introduction of the *Haemophilus* vaccination, the incidence has decreased significantly to 0.63 cases per 100,000 per year in the United States.[30] Invasive disease due to *Haemophilus influenzae* occurred at a rate of 116 cases per 100,000 children in 1986, and this is the organism most often cultured in children with epiglottitis. After the introduction of the conjugate vaccine against *H influenzae* type b (Hib) in 1985, the incidence of invasive disease due to *H influenzae* decreased dramatically,[31] and there was a concomitant and dramatic decline in the incidence of acute epiglottitis in children.[32–34] Epiglottitis is now more frequently seen in adults than in children, and respiratory pathogens other than *H influenzae* are typically implicated.[35]

Causative Organisms

As the frequency of Hib disease has decreased, the cause of epiglottitis has shifted toward other causative organisms. Today, most cases are thought to be caused by other bacteria, such as *Streptococcus pneumoniae* and other *Streptococcus* species, *Staphylococcus aureus*, *Moraxella catarrhalis, Pseudomonas* species, *Candida albicans, Klebsiella pneumoniae, Pasteurella multocida,* and *Neisseria* species.[33,36] Bacterial superinfection of viral infections also occurs, particularly with herpes simplex, parainfluenza, varicella zoster, and Epstein-Barr.[34,36]

Epiglottitis tends to occur throughout the year but mainly during the 6-month period from December to May in the northern hemisphere. It previously occurred equally in male and female patients, with a slight male predominance between the ages of 2 and 6 years,[37] but more recently has shifted toward substantially older patients[38] and should be a consideration at any age.

Clinical Presentation

The onset of epiglottitis is usually abrupt, preceded by a minor upper respiratory infection in some cases. The onset is characterized by high fever, toxic appearance, and sore throat that progresses over a few hours to dysphagia, drooling, and respiratory distress. The patient appears anxious and irritable. Stridor is a late finding. Breathing becomes noisy, and the voice and cry are muffled as swelling of the aryepiglottic folds and supralaryngeal mucosa obstructs the glottic inlet. The patient tends to sit forward in the sniffing position with the neck hyperextended to increase airway patency. Complete airway obstruction may occur at any time without any preceding deterioration in clinical signs.

Diagnosis

A very high index of suspicion must be maintained, and epiglottitis should be considered in every child with apparent acute upper airway obstruction who has a high fever and sore throat, especially when those signs have developed over a few hours. A lateral neck radiograph can be helpful, though it should be attempted only if the patient is stable and the diagnosis is in doubt, because the disease can progress rapidly. Therapeutic trials of inhaled medicines, such as corticosteroids or racemic epinephrine, should not be initiated because time is wasted and it may irritate the child, leading to complete obstruction of the airway. In addition, direct visualization of the epiglottis should not be performed until the child is undergoing tracheal intubation.

Epiglottitis must be differentiated from other causes of acute upper airway obstruction, including viral croup (laryngotracheobronchitis), spasmodic croup, and bacterial tracheitis. Any patient with stridor, sore throat, and fever should be referred to a specialist for confirmation of the diagnosis. Trauma and accidental causes are easily ruled out by the history. Foreign body aspiration should be considered as well, and this diagnosis may be suggested by a history of choking while eating or of playing with small objects in the mouth, the absence of fever, or visualization of an object in the airway on inspection.

Management

Most fatalities occur within the first few hours after the patient has arrived at the hospital. All deaths result from complete airway obstruction. Once the diagnosis is determined, there should be no delay in establishing an artificial airway. If there is time, the child should undergo intubation in the operating room under general anesthesia by personnel who can perform emergency tracheostomy in case intubation fails. Corticosteroids and epinephrine have been used in the past; however, there is no solid evidence that these medications are helpful in cases of epiglottitis.

Approximately 10% to 25% of cases may be managed by observation, though these are older patients with larger airways, and mortality is a risk. **Box 16-1** describes an appropriate treatment protocol.

Box 16-1

Management When Epiglottitis Is Suspected

- **Avoid disturbance until an airway is secured. Allow the child to sit up and stay in a parent's arms to avoid agitation.**
- **Provide 100% oxygen via blow-by administration.**
- **Perform a radiological lateral neck study *only* if the child appears stable and the diagnosis of epiglottitis is in doubt.**
- **Notify and assemble the epiglottitis team (eg, intensivist; ear, nose, and throat specialist; anesthetist; and pediatric pulmonologist).**
- **Perform intubation in the operating room or tracheotomy if intubation is not possible.**
- **Provide sedation (after intubation) or critical care (if tracheostomy is required).**
- **Administer intravenous antibiotics, which may effectively control inflammation and infection. Antibiotics are usually prescribed to treat the most common types of bacteria. Blood cultures are usually obtained with the premise that any organism found growing in the blood can be attributed as the cause of the epiglottitis, even though *Hemophilus influenzae* (which has a recovery rate of 80%–100% from the blood) is now a very uncommon cause of epiglottitis.**

When to Refer

As soon as epiglottitis is suspected, the child should be referred to the nearest pediatric emergency department with surgical and anesthesia expertise available.

When to Admit

All children suspected of having epiglottitis should be admitted to the hospital for intravenous antibiotic treatment and intensive care monitoring. The surgical specialist (eg, pediatric ear, nose, and throat specialist; pediatric surgeon) and anesthesiologist should be contacted immediately. In some institutions, rapid responders may include a skilled flexible bronchoscopist. The medical and surgical team should be ready to place an endotracheal tube emergently and also be ready for emergent tracheotomy. It is best for the surgeons to visualize the airway when in the operating room.

Bacterial Tracheitis

CASE REPORT 16-3

A 4-year-old-boy arrives in the emergency department with cyanosis and a very productive cough. His history reveals a mild case of croup 1 week prior. The previous day, he developed a high fever with rapidly progressive symptoms of cough and respiratory distress. Respiratory failure is diagnosed. He undergoes intubation, and purulent secretions are aspirated from the airway. A diagnosis of bacterial tracheitis is assigned.

Introduction

Bacterial tracheitis is a serious and potentially life-threatening cause of acute upper airway obstruction. Bacterial tracheitis has also been referred to as *membranous croup, bacterial croup,* and *pseudomembranous croup.*

Epidemiology

Until recently, viral croup and epiglottitis have been considered the main causes of infectious upper airway obstruction.[39] Immunization against *H influenzae*[40] and treatment of viral croup with nebulized or systemic corticosteroids[15–18] have changed the incidence, morbidity, and mortality of upper airway obstruction. Bacterial tracheitis has assumed predominance over epiglottitis as the most common cause of acute upper airway obstruction in children older than 2 years. However, it is still uncommon, the estimated annual incidence being 0.1 in 100,000 children. The manifestation may vary between a mild upper respiratory infection and a typical bacterial tracheitis.[41] The authors of an

article published in 2020 reported a higher incidence of tracheitis in patients with tracheostomy.[42]

Bacterial tracheitis generally affects children between 4 weeks and 13 years of age, with a mean age of 4 years. The number of cases increases during the fall and winter when viral croup is more prevalent.

Causative Organisms

The pathogenesis of bacterial tracheitis remains controversial. It often occurs as a secondary bacterial infection complicating a preexisting viral infection, including parainfluenza, adenovirus, and influenza A or B. Bacteria can gain access to the tracheal epithelium after a viral infection compromises epithelial integrity. Tracheal epithelial inflammation causes mucosal damage and predisposes the patient to bacterial adherence to the compromised epithelial cells of the trachea. The usual protective and defensive response of the epithelial cells is weakened and results in mucous hypersecretion as well as inflammatory cell chemotaxis, allowing for thick mucopurulent secretions to accumulate, sometimes forming a pseudomembrane. Thick secretions and sloughed mucosa may result in tracheal obstruction, which may also involve mainstem bronchi.[43] Before 1985, when the Hib conjugate vaccine was introduced, *H influenzae* was one of the primary causative organisms, but since 1997, the most commonly implicated organism has been *S aureus,* followed by *M catarrhalis, Streptococcus* species, and oral anaerobes.[44] In patients admitted to a pediatric intensive care unit, ventilator-associated tracheobronchitis has been associated with an increase in the length of stay and mortality,[45] and a reduction in the incidence has been reported when an evidence-based approach for prevention is used.[46]

Presentation

Bacterial tracheitis can be distinguished from croup by patient age and symptom severity (**Table 16-2**).[47] Children with bacterial tracheitis tend to be older (preschoolers) than are those with viral croup (toddlers). A sign more characteristic of bacterial tracheitis is toxic appearance and high fever. Patients with both bacterial tracheitis and viral croup can present with a prodrome of fever, barky cough, and stridor. In contrast to croup symptoms, bacterial tracheitis symptoms worsen over time. The presenting symptoms are shown in **Box 16-2.**

Table 16-2. Comparison of Epiglottitis, Viral Croup, and Bacterial Tracheitis

Factor	Epiglottitis	Viral Croup	Bacterial Tracheitis
Age	2–6 years	3 months–3 years	4 weeks–13 years
Organism	Various	Parainfluenza 1, 3	*Staphylococcus aureus* *Streptococcus* species *Moraxella catarrhalis*
Season	All year	Late spring, late fall	All year
Clinical presentation	Child sitting Toxic appearance Drooling Dysphagia Muffled voice	Child lying down Nontoxic appearance Barking cough Hoarseness	Toxic appearance Barking cough
Onset prodrome	Rapid; over a few hours	Variable; a few hours to 4 days	Variable; a few hours to 5 days
Stridor	Less common	Common	Common
Fever	High	Low	High
Chest retractions	Less common	Common	Common
Lateral neck radiograph	Swollen epiglottis	Subglottic narrowing	Pseudomembrane
Progression	Rapid	Usually slow	Usually slow
Recurrence	Rare	Common	Rare

Box 16-2

Presentation of a Patient With Bacterial Tracheitis

- **Fever, which may be high**
- **Stridor, inspiratory; may also be expiratory**
- **Seal-like brassy cough**
- **Hoarseness**
- **Dyspnea with retractions, nasal flaring**
- **Cyanosis**
- **May progress rapidly to respiratory failure**

Tracheostomy and Tracheitis

Patients with tracheostomy are more likely to have other complex issues[48,49] and bacterial colonization of the trachea and contiguous airways. Such patients tend to have a higher incidence of tracheitis,[42,50] which is diagnosed and treated early because there is likely to be a low threshold for direct visualization of the trachea with use of a bronchoscope. Viral coinfection is associated with poorer outcome.

Diagnosis

Lateral and anteroposterior radiographs of the neck and chest may be helpful in diagnosis. Findings on plain-film radiographs include subglottic narrowing, a ragged edge to the usually smooth tracheal air column, and a hazy shadow within the tracheal lumen. The epiglottis and supraglottic structures appear normal on neck radiographs. The steeple sign characteristically seen in croup may also be evident.

The most definitive procedure is to visualize the trachea endoscopically. The supraglottic structures will appear normal, but subglottic edema is the prominent feature, and ulcerations and copious purulent secretions will be present. These secretions should be cultured so that the causative agent may be treated effectively with antibiotics.

Management

Children with bacterial tracheitis must be monitored very closely; often, tracheal intubation with mechanical ventilation is necessary in the event of respiratory failure or an inability to mobilize secretions effectively. Using an endotracheal tube 1 size smaller than usual can reduce trauma to the subglottic area. Careful attention to the suctioning and mobilization of secretions is essential. Occlusion of the endotracheal tube has been reported as the most frequent cause of death in children with bacterial tracheitis who have undergone intubation and mechanical ventilation. Some otolaryngologists have advocated for expectant placement of tracheotomy tubes in children with bacterial tracheitis for this reason. Humidification of the inspired air helps prevent mucous plugging of the endotracheal tube. Antibiotics and supportive care are essential for full recovery. Antibiotics should be initiated with nafcillin or oxacillin (200 mg/kg per day divided every 6 hours for either agent) in conjunction with a third-generation cephalosporin, such as ceftriaxone (50 mg/kg daily). The addition of vancomycin should be considered if resistant organisms are present in the local community or if there is multisystem involvement.

Complications

Complications associated with bacterial tracheitis include toxic shock syndrome, septic shock, postintubation pulmonary edema, acute respiratory distress syndrome, and subglottic stenosis.[51] Most children recover, and there is no reason to suspect an underlying immunodeficiency. It is rare for a child to have a second episode of bacterial tracheitis.

key points

- The differential diagnosis for children who have stridulous breathing should include croup, epiglottitis, and bacterial tracheitis.
- Most patients with croup can be treated as outpatients.
- When symptoms are severe, croup should be differentiated from alternative causes, such as epiglottitis or bacterial tracheitis.
- Corticosteroids are the established treatment of choice for croup.
- If epiglottitis is suspected, the child should be admitted to the hospital. A pediatric otolaryngologist or anesthesiologist should be contacted immediately and should be the only physician to attempt to visualize the airway.
- Children who have croup tend to have a sudden onset of hoarseness and barking cough, but do not appear toxic, as do those who have epiglottitis or bacterial tracheitis.
- Children with bacterial tracheitis have high fever and typically require endotracheal intubation and mechanical ventilation.

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PART 5

Lower Airway Infections

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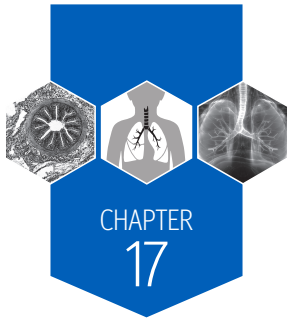
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Bronchiectasis

Jordana E. Hoppe, MD, MSCS
Paul C. Stillwell, MD, FAAP

Introduction

Bronchiectasis is the dilatation of bronchi and bronchioles associated with airway wall thickening.[1,2] The most common cause among children in North America is cystic fibrosis (CF), but there are numerous other potential underlying causes (**Table 17-1**). The most commonly identified causes have considerable geographic variability based on the risk of serious infections and the particular diagnostic expertise of regional medical centers.[3] A 2014 study demonstrated that in most, but not all, children a cause of non-CF bronchiectasis can be identified, with infection, primary immunodeficiency, aspiration, and primary ciliary dyskinesia being the most common causes.[4] The end result of airway injury that is associated with both acute and chronic inflammation, bronchiectasis perpetuates ongoing airway injury. It can occur in 1 or a few lung segments, or it can be generalized throughout all segments. If the airway injury is severe or recurrent, the airway damage becomes irreversible and self-sustaining.

Clinical Manifestations

The child with bronchiectasis has a chronic "wet" or productive cough and recurrent chest infections. Some children may have recurrent wheezing. A small percentage may have hemoptysis.[2,3] Recurrent or persistent pneumonia can also be a presenting feature of bronchiectasis. The results of the chest examination in the child with bronchiectasis may be normal until significant airway abnormalities are present. As the disease advances, the intensity of breath sounds may be decreased and inspiratory crackles may be present. Expiratory wheezing may be present when severe airway damage has occurred. The examination findings may be more prominently abnormal during acute exacerbations of the bronchiectasis, and less so after resolution. The abnormal findings may be localized if the bronchiectasis is segmental. Other examination findings may be present depending on the underlying cause of the bronchiectasis (eg, failure to thrive in patients with CF; ear, nose, and throat abnormalities in patients with primary ciliary dyskinesia

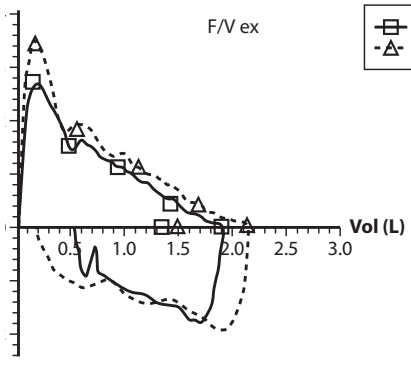
Table 17-1. Disease Processes Associated With Bronchiectasis and Potential Evaluations

Disease Process	Possible Diagnosis	Evaluation
Impaired mucociliary clearance	Cystic fibrosis	Sweat test, DNA analysis
	Primary ciliary dyskinesia	Ciliary biopsy (electron microscopy), DNA analysis, nasal nitric oxide
Infections	*Mycobacterium tuberculosis*	Skin test, acid-fast stain and culture, interferon-γ release assay
	Atypical mycobacteria	Acid-fast stain and culture
	Measles	Serology
	Pertussis	Direct fluorescent-antibody serology
	Mycoplasma	Polymerase chain reaction (PCR), serology
	HIV	PCR, serology
	Varicella	PCR, serology
	Adenovirus	PCR, serology
	Severe bacterial pneumonia	Cultures
	Necrotizing pneumonia	Cultures
Immunodeficiency	Humoral or cellular immunodeficiency	Immunoglobulins, complement levels, cell-mediated immunity tests, genetic testing
	Neutrophil dysfunction	Dihydrorhodamine or nitroblue tetrazolium tests, genetics
Airway injury or toxin	Dysphagia with aspiration	Video-assisted swallow study, functional endoscopic evaluation of swallowing
	Esophageal reflux	Contrast esophagram, pH/impedance probe, milk scan
	Inhalational injury	History
Immunologic	Allergic bronchopulmonary aspergillosis	Specific immunoglobulin (Ig) E and IgG, total IgE
	Connective tissue disease	Various (see Chapter 26)
	Inflammatory bowel disease	Gastrointestinal endoscopy, bronchoscopy

Disease Process	Possible Diagnosis	Evaluation
Congenital/connective tissue abnormality	Tracheobronchomegaly	Computed tomographic (CT) scan, bronchoscopy
	Airway cartilage deficiency	CT scan, bronchoscopy
	Marfan syndrome	Clinical criteria, genetic testing
	Yellow nail syndrome	Clinical criteria
	Young syndrome	Sperm count, negative cystic fibrosis test results
	Alpha-1 antitrypsin deficiency	Alpha-1 antitrypsin levels; Pi type
Obstructed airways	Retained foreign body	Imaging, bronchoscopy
	Endobronchial tumor	Imaging, bronchoscopy
	Extrinsic compression	CT scan, bronchoscopy
	Severe asthma	Pulmonary function testing, history

or primary immunodeficiency). Digital clubbing can occur with moderate and severe bronchiectasis regardless of the etiology.

Pulmonary function testing (PFT) performed in children old enough to cooperate may show an obstructive pattern, a restrictive pattern, or a combination of both.[5] The spirometric abnormalities in children with bronchiectasis due to CF are generally correlated with disease severity and progression,[6] but the utility of spirometry in monitoring non-CF bronchiectasis is less certain.[7] Because of ready availability and absence of risk, PFT is commonly used to monitor the airway function in children with bronchiectasis. However, the abnormalities that may be present with bronchiectasis are not specific to this diagnosis. An evaluation for bronchiectasis should be considered for children with persistent or progressive PFT abnormalities. **Figure 17-1** shows an example of flow-volume loops in a child with severe non-CF bronchiectasis.



	Reference	Pre-Bronchodilator	% Predicted	z score	Post-Bronchodilator	% Predicted	z score	% change
FVC (L)	2.18	1.91	88	–1.08	2.16	99	–0.08	+13
FEV_1 (L)	1.89	1.34	71	–2.54	1.49	79	–1.86	+11
FEV_1/FVC	87	70	—	–2.34	69	—	–2.49	—
$FEF_{25–75}$ (L/s)	2.24	0.99	44	–2.95	1.05	47	–2.76	+6
PEFR (L/min)	248.2	1.62	66	–2.45	2.04	82	–1.27	+25

Figure 17-1. Example of a flow-volume loop in bronchiectasis (with volume on the horizontal axis and flow on the vertical axis). Expiratory flow is above the volume axis and inspiratory flow is below the volume axis. The expiratory loop is concave with regard to the volume axis, indicating an airflow obstruction, without a significant bronchodilator improvement. When such an obstructive abnormality occurs in a child with chronic cough, the differential diagnosis should be expanded beyond asthma. A bronchodilator response of ≥ 12% in FEV_1 would be more typical of asthma.

Abbreviations: $FEF_{25–75}$, forced expiratory flow between 25% and 75% of the vital capacity; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PEFR, peak expiratory flow rate.

The chest radiograph (**Figure 17-2**) may show increased interstitial markings but may also appear normal until the bronchiectasis is extensive. A definitive diagnosis of bronchiectasis is established using high-resolution computed tomography (HRCT), which has supplanted bronchograms as a diagnostic tool.[1] The radiographic findings on chest radiography and HRCT are outlined in **Box 17-1.**[8] Airway changes used to diagnose bronchiectasis on HRCT include an airway diameter that is larger than the diameter of the accompanying pulmonary artery (signet ring sign), lack of normal bronchial tapering, and visualization of peripheral airways (within 1 cm of the pleura).[9,10] The

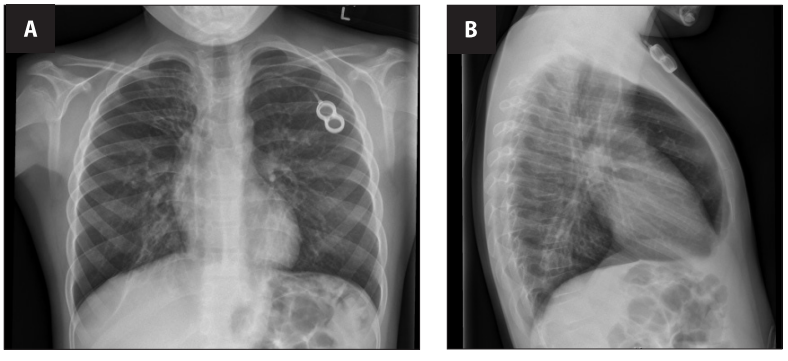


Figure 17-2. Chest radiograph, frontal (**A**) and lateral (**B**), in a 13-year-old with severe bronchiectasis from an underlying immunodeficiency (T and B cell). There are diffuse increased interstitial markings, multiple thin-walled cavitary lesions, and overinflation.

Box 17-1

Radiographic Findings in Bronchiectasis

Chest Radiographic Findings

Increased interstitial markings
Thickened airway walls
Dilated airway lumen
Hyperinflation

High-resolution Chest Computed Tomographic Findings

Airway lumen greater than adjacent blood vessel ("signet ring")
Tram-track markings
Extension of airway markings to periphery
Lack of tapering of airways toward periphery
Mucus plugging and centrilobular opacities ("tree in bud")
Mosaic pattern of perfusion
Focal air-trapping (best seen on expiratory views)
Mucus plugging

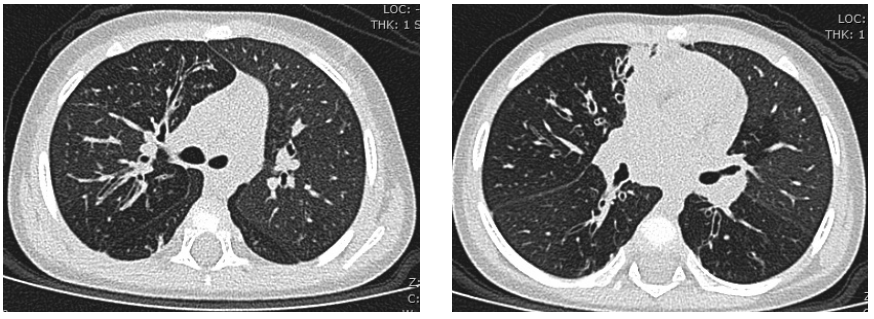


Figure 17-3. High-resolution computed tomographic scans showing cylindrical bronchiectasis. The patient is a 2-year-old with neutrophil dysfunction.

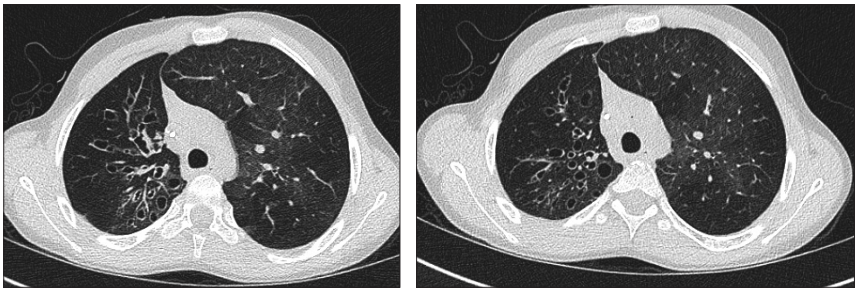


Figure 17-4. High-resolution computed tomographic scans demonstrating cystic bronchiectasis. The patient is a 10-year-old boy with an immunodeficiency resulting in bronchiectasis.



Figure 17-5. High-resolution computed tomographic scan of a cystic (saccular) bronchiectasis. The patient is a 13-year-old with saccular bronchiectasis due to an underlying immunodeficiency and chronic aspiration.

3 types of bronchiectasis—cylindrical, varicose, and cystic—are also defined by their appearance on HRCT.[9] Cylindrical bronchiectasis (**Figure 17-3**) has a tubular appearance with smooth walls, is the least severe form, and may be reversible.[9] In varicose bronchiectasis, the airway has an irregular appearance, with alternating portions of more dilated airway next to more narrowed portions.[9] Finally, cystic bronchiectasis is the most severe form, with larger, saccular dilatation of the airways (**Figure 17-4**, **Figure 17-5**).[9]

A chest CT scan should be considered to evaluate for bronchiectasis in children with persistent productive cough, persistently abnormal chest radiographic findings, persistently abnormal chest auscultation findings, or persistent PFT abnormalities. Additionally, children with severe asthma can be at risk for the development of bronchiectasis.[11]

Pathophysiology

The initial airway injury leading to bronchiectasis can result from a variety of causes, but the most common is an infection.[1] A mucosal injury, severely impaired mucociliary clearance, or an underlying immunodeficiency allows an initial infection, and perpetuation of the host inflammatory response eventually leads to airway damage. The cellular response is predominantly neutrophilic, and ongoing inflammation produces increased mucus secretion, thickened mucus, and airway edema. Higher levels of neutrophil elastase are associated with greater disease severity and an increased risk of exacerbations in patients with bronchiectasis.[1] It is unclear in most cases why the enhanced host response persists (unlike acute bronchitis, which resolves), unless there is repeated injury such as that which may occur with repeated chronic aspiration or repeated airway infections. The combination of dilated airway walls, mucosal inflammation, and thickened secretions impairs mucociliary clearance, which impairs clearance of the infection and increases the risk of subsequent infection. Eventually, the airway damage becomes irreversible and self-perpetuating.[1,2]

Microscopic examination of the bronchiectatic airway reveals thickened airway walls, mucosal gland enlargement, cellular (usually neutrophilic) infiltration, dilated cross-sectional airway lumen, and excessive secretions.[1] If the infection has not been treated with antibiotics, bacteria may be evident on special stains. Excessive proinflammatory mediators are present in bronchoalveolar lavage (BAL) fluids.[1]

Evaluation

Once bronchiectasis is documented, an underlying cause should be sought (**Table 17-1**). If the history or examination findings suggest a specific cause, the initial evaluation can be targeted toward that cause (eg, sweat test if steatorrhea is present). More commonly, several tests are necessary and are usually performed from least invasive to most invasive. All children with bronchiectasis should undergo a sweat chloride test to assess for CF (even if newborn screening results were negative). Screening for immunodeficiency should include quantitative immunoglobulins, white blood cell counts with differential, and measurement of total complement levels. More advanced immune studies include assessment of response to immunizations, evaluation of cell-mediated immunity, neutrophil function tests, and genetic testing.

Allergic bronchopulmonary aspergillosis and connective tissue diseases can be assessed by means of specific immunologic studies. *Mycobacterium tuberculosis* infection can be assessed with a skin test, an interferon-γ release assay in those older than 5 years, and stains and culture at the time of bronchoscopy. A video-assisted swallow study can be conducted to assess swallowing coordination and risk of aspiration. An upper gastrointestinal barium contrast study can assess for gastroesophageal reflux. Other tests to evaluate the risks for aspiration include the functional endoscopic evaluation of swallowing, esophageal pH/impedance probe, and radionuclide milk scans. Primary ciliary dyskinesia can be evaluated by means of electron microscopy of ciliary ultrastructure, DNA analysis, nasal nitric oxide measurement, and ciliary wave form analysis; these tests are usually performed at a referral center. Flexible bronchoscopy allows assessment of airway anatomy and obstruction, visual inspection of the airway mucosa, and collection of airway secretions and BAL fluid. The BAL fluid can be analyzed with stains and cultures for a variety of infections, as well as cell counts with differential and other specialized stains.

Management

Once the clinical suspicion of bronchiectasis is confirmed by HRCT scan, an evaluation for the specific underlying disease should be undertaken (**Table 17-1**). If a specific disease can be identified, therapy directed at that process should be initiated or intensified. Therapeutic options for CF have undergone sophisticated evaluation to help direct appropriate management choices[12] (see Chapter 45, Cystic Fibrosis), but randomized clinical prospective studies of non-CF bronchiectasis in children are just beginning. Much of the treatment offered for non-CF bronchiectasis is extrapolated from data acquired in patients with CF.[13]

Antibiotics targeting bacteria isolated from sputum or bronchoscopy samples are likely beneficial in treating exacerbations of bronchiectasis,[14] similar to treatment for CF airway infections. The most common bacteria isolated in non-CF bronchiectasis include *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis,* and *Staphylococcus aureus.* However, less is known about the microbiome of bronchiectasis, and its impact on disease severity and exacerbations, in patients who do not have CF compared with those who do.[15] Patients with CF have a greater risk of developing *Pseudomonas aeruginosa* airway infection than patients with non-CF bronchiectasis. Antibiotic treatment for acute exacerbations of bronchiectasis is documented to help reverse the acute illness.[1,13] The role of long-term antibiotic therapy for non-CF bronchiectasis is not well established.[1,13] Inhaled antibiotics have documented benefit for patients with CF and may have benefit in non-CF bronchiectasis as well, depending on the organisms in the airway.[1,12,13] Airway clearance therapy using a variety of techniques is commonly prescribed, with

perceived anecdotal benefit (see Chapter 55, Airway Clearance Techniques). Some individuals may respond to inhaled bronchodilators, and even if there is no documented increase in airflow on PFT, the bronchodilator may have a positive effect on mucociliary clearance.[1,13] Inhaled corticosteroids have shown some benefit in adults with non-CF bronchiectasis,[1,13] but their role in CF has been challenged, with conflicting evidence.[12] Despite limited evidence of the benefits of inhaled corticosteroids, high rates of use are observed in patients with bronchiectasis.[16] Other anti-inflammatory treatments show promise in CF, but there is limited evidence of benefit in non-CF bronchiectasis, particularly in children.[13] Several studies have suggested that oral macrolide therapy, used as an anti-inflammatory rather than as an antibiotic, has reduced the frequency of exacerbations in non-CF bronchiectasis.[17]

Mucolytic treatments with rhDNase have had documented benefit for patients with CF,[12] but they may have a detrimental effect in patients with non-CF bronchiectasis (based on a single adult study).[18] Nebulized hypertonic saline has been shown to benefit patients with CF.[12] Although less is known regarding the benefits of hypertonic saline in non-CF bronchiectasis, studies have suggested that it decreases the viscosity of sputum, leading to an increase in expectorated sputum, and may decrease hospitalizations and improve lung function.[19]

Hospitalization to intensify antibiotic therapy and airway clearance might be indicated for an exacerbation in patients with non-CF bronchiectasis, an approach that has documented benefit for patients with CF. Anecdotal evidence suggests that the same benefit can be achieved for children with non-CF bronchiectasis. Patients with large volumes of hemoptysis, hypoxia, or rapidly declining pulmonary function require hospitalization.

Surgical resection of limited or segmental bronchiectasis may be necessary if massive hemoptysis occurs, but recent evidence suggests that, in the absence of hemoptysis, aggressive medical management can result in similar improvement to that of surgical intervention in non-CF bronchiectasis.[20] Double lung transplantation may be an option for patients with severe progressive bronchiectasis that does not respond well to medical management.[13] Lung transplantation has commonly been offered as an option for end-stage bronchiectatic lung disease due to CF, with short- and long-term outcomes similar to those in other diseases for which transplantation is often performed.[21]

Prognosis

The prognosis for non-CF bronchiectasis is not as well studied as that for CF, but generally survival has been longer for patients with non-CF bronchiectasis than for those with CF.[22] This may change as improved understanding of CF lung disease and new treatment options have steadily increased the median

age of survival.[12,23] The rate of progression of non-CF bronchiectasis and prognosis for survival are likely primarily related to the underlying cause and treatment options.[1,13] However, persons with bronchiectasis have a high rate of health care utilization and disease burden,[24] which likely has an adverse effect on their quality of life. The presence of chronic *P aeruginosa* airway infection negatively affects the survival of patients with both CF and non-CF bronchiectasis.[1,13]

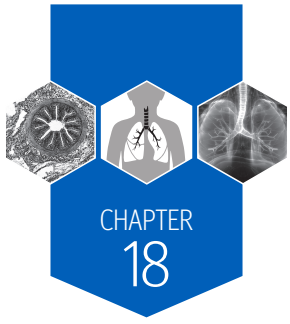
key points

- Bronchiectasis in children can be the result of a wide variety of underlying causes.
- When no cause is found, these cases are considered idiopathic.
- Bronchiectasis should be suspected if a child has a chronic wet cough and recurrent chest infections.
- An HRCT scan should be performed to definitively establish the diagnosis of bronchiectasis.
- Once bronchiectasis is confirmed, an underlying cause should be sought.
- The management of patients with non-CF bronchiectasis has largely been determined by expert opinion and data extrapolated from CF studies.

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CHAPTER 18

Bronchiolitis

Girish D. Sharma, MD, FAAP, FCCP

Introduction

Bronchiolitis usually manifests as an isolated episode, mostly a viral lower respiratory tract infection in an infant with symptomatic airway obstruction. Most patients are younger than 1 year; however, bronchiolitis can occur beyond infancy. It is characterized by acute inflammation, edema and necrosis of the epithelial lining of small airways, and mucus production. An infant with bronchiolitis typically presents with increased work of breathing manifested by retractions and associated with polyphonic wheeze, which may be heard without a stethoscope.

Epidemiology

As many as 3% of all US infants are hospitalized annually for bronchiolitis, making this clinical problem the leading cause of hospitalization during the first year after birth.[1] Although respiratory syncytial virus (RSV types A and B) predominates (50%–80%) as a cause of bronchiolitis, many other respiratory viruses have been detected in the nasopharyngeal secretions of children hospitalized with bronchiolitis. These include, in descending order of frequency, human rhinovirus (groups A, B, and C) (5%–25%),[2] parainfluenza virus (most commonly type 3), human metapneumovirus (subgroups A and B), coronavirus, adenovirus, influenza (A and B) virus, and enterovirus (echovirus and coxsackievirus).[3]

Authors of a systematic review and remodeling study estimated 33.1 million episodes of RSV caused acute lower respiratory infections globally in 2015, resulting in 3.2 million hospitalizations and 27,300 in-hospital deaths.[4] Regardless of the viral cause, a predictable seasonal pattern occurs for bronchiolitis, although there is some variability from year to year[5,6] and by region.[7]

Clinical Presentation

The prodrome of bronchiolitis is a typical-appearing upper respiratory tract infection, with mild rhinorrhea and occasionally a low-grade fever. Progression then occurs over 1 to 2 days to cough, retractions (**Figure 18-1**), tachypnea, and prolonged expiratory phase with wheezing and inspiratory crackles.

The tachypnea and increased work of breathing can result in poor feeding. The extent of poor feeding is related to the degree of respiratory distress. In a mild case, the infant is able to finish the usual amount of food but takes longer to finish because of interruptions. More severe respiratory distress results in reduced quantities of food taken along with an increase in time to finish. Finally, the infant may not be interested in feeding owing to severe respiratory distress. Reduced feeding with increasing respiratory distress may result in dehydration manifested by poor tearing, dry mucous membranes, and poor skin turgor.

A varying degree of hypoxemia can occur, and hypercapnia may be found in severe cases.

Crackles and wheezing may be present at auscultation. Wheezing may be audible without a stethoscope.

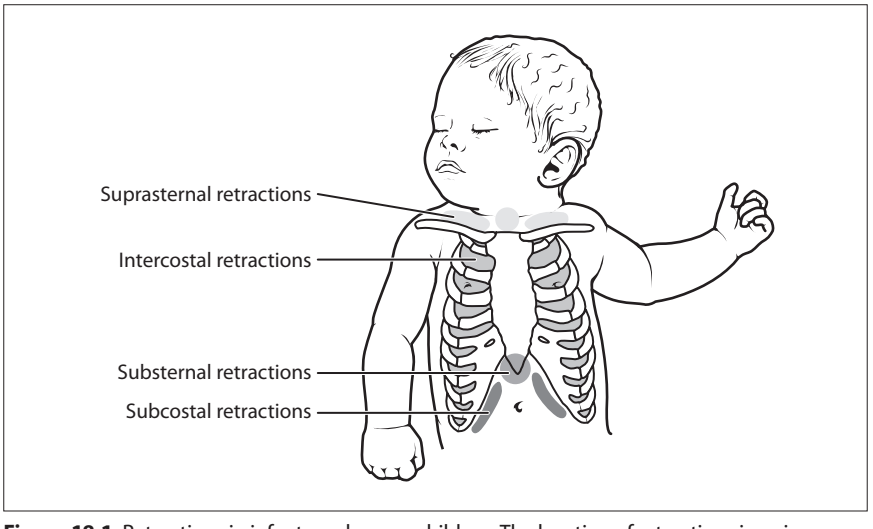


Figure 18-1. Retractions in infants and young children. The location of retractions is an important clue to the cause and severity of respiratory distress. Suprasternal retractions predominate when infants have extrathoracic obstruction. Subcostal and substernal retractions usually result from lower respiratory tract disorders. Suprasternal retractions occur in upper respiratory tract disorders. Alone, mild intercostal retractions may be normal. However, intercostal retractions accompanied by subcostal and substernal retractions may indicate moderate respiratory distress. Deep suprasternal retractions typically indicate severe distress.

Differential Diagnosis

The term *bronchiolitis* should not be applied to repeated episodes of wheezing. The following conditions, manifesting as nonisolated or repeated wheezing, should be differentiated from a typical case of bronchiolitis.

Asthma

Authors of a 2020 article have attempted to differentiate bronchiolitis with its neutrophil-mediated airway inflammation, secretions, and associated airway obstruction from asthmatic airway obstruction with bronchoconstriction and airway inflammation.[8] An asthmatic episode may mimic bronchiolitis; however, a history of recurrent of bronchospastic symptoms, presence of triggers such as physical activity, typical nocturnal asthmatic symptoms and eczema, allergic rhinitis symptoms, and family history should help. Asthma can manifest as clinically nondiscernible from bronchiolitis, even in infants. The future course and follow-up may help to differentiate bronchiolitis from asthma.

Conditions Causing Focal Wheeze

Lobar pneumonia, congenital lung anomalies such as congenital pulmonary airway malformations, sequestration, and focal airway obstruction due to lobar emphysema may mimic bronchiolitis; however, the presence of focal clinical signs, corroborative findings on investigations, and other features such as high persistent fever in pneumonia may help differentiate these from typical bronchiolitis. Foreign body aspiration may cause focal or generalized wheeze. However, in a child who is previously healthy and without symptoms who presents with sudden respiratory distress, a typical history (if witnessed) and clinical and radiological findings may help differentiate.

Recurrent Wheeze With Other Causes

Children with chronic conditions such as bronchomalacia, craniofacial malformations, upper airway obstruction due to such causes as a vascular ring, gastroesophageal reflux, oropharyngeal incompetence, and dysphagia (extreme prematurity) may develop recurrent wheeze with upper respiratory infections and may have bronchiolitis diagnosed. However, the diagnosis of an associated condition and history of recurrent wheeze with an upper respiratory tract infection may help differentiate the diseases. Conditions such as congestive heart failure and interstitial lung disease may manifest with persistent crackles, tachypnea, and low oxygen saturation. However, the presence of clinical features specific to the disorder and the absence of the typical bronchiolitis picture may help differentiate these conditions from bronchiolitis.

Pathophysiology

The virus initially replicates in the epithelium of the upper respiratory tract, but in the susceptible young infant, it spreads rapidly to the lower airways. The pathological findings in bronchiolitis are primarily in the respiratory epithelium with generalized involvement. Inflammatory changes of variable severity are observed in most small bronchi and bronchioles. Peribronchiolar infiltration, mostly with mononuclear cells, and edema of the submucosa and adventitia occur. Necrosis and sloughing of the bronchiolar epithelium occur with gradual recovery. Plugs of necrotic material and fibrin may completely or partially obstruct the small airways. Smooth muscle constriction does not appear to be important in the obstruction.

Infants are particularly vulnerable to obstruction because mucosal inflammation causes relatively greater compromise of their small-lumen airways, and changes in resistance are proportional to the cube of changes in the radius of the airway (the Poiseuille law). Therefore, small airway obstruction in an infant with bronchiolitis results in a larger increase in work of breathing. In areas peripheral to sites of partial obstruction, air becomes trapped by a process similar to a ball-valve mechanism. The negative intrapleural pressure exerted during inspiration allows air to flow beyond the point of partial obstruction. However, during expiration, the size of the lumen decreases with the positive intrathoracic pressure, thereby resulting in increased obstruction and hyperinflation. Thus, although airflow is impeded during both inspiration and expiration, the latter is more affected and prolonged. In areas peripheral to complete obstruction, the trapped air eventually becomes absorbed, which results in multiple areas of atelectasis. This absorptive atelectasis is greatly accelerated when the infant is breathing a high concentration of oxygen. A presumed reason why infants have increased susceptibility to the development of atelectasis or hyperinflation is that collateral channels that maintain alveolar expansion in the presence of airway obstruction are not well developed early in life.

Natural History

Viral bronchiolitis is most commonly caused by RSV. Virtually all infants contract RSV during the first 2 years after birth, most during the first year. An estimated 20% develop bronchiolitis from an RSV infection, whereas others develop upper respiratory symptoms, coryza, or the symptoms of a common cold. Of those with bronchiolitis, most do not require hospitalization. Nonetheless, bronchiolitis is the leading cause of hospitalization during the first year beyond the neonatal period.

An estimated 25% to 50% of patients with bronchiolitis have subsequent recurrence of similar symptoms triggered by viral respiratory infections, as in the case of patients with asthma developing bronchospastic symptoms

triggered by viral respiratory infections.[9,10] Those who develop bronchiolitis appear to differ from those who do not in genetic factors that involve innate immunity.[11–13] Thus, although all children get viral respiratory infections, it is primarily genetic susceptibility that contributes to both bronchiolitis and recurrent symptoms of asthma exacerbations from viral respiratory infections. Exposure to tobacco smoke during pregnancy and after birth appears to be an environmental contributing factor that increases the risk of bronchiolitis.[14–16]

Laboratory and Radiological Findings

Bronchiolitis is a clinical diagnosis. Investigations apart from antigen tests, pulse oximetry, and, in a patient with severe hypoxia, blood gas measurements are not valuable.

Antigen tests of nasal washings provide rapid (usually within 30 minutes) and accurate (sensitivity, 87%–91%; specificity, 96%–100%) detection of RSV during the peak season. Respiratory viral panels, cultures for RSV or other viruses, or detection by means of direct fluorescent antibody or polymerase chain reaction may be useful for epidemiological and educational purposes. However, they add to the cost and provide no useful information for patient care.

Pulse oximetry can be used to identify the presence of sufficient hypoxemia to warrant supplemental oxygen. Blood gas measurements can indicate the P_{CO_2}, which is essential to distinguish hypoxia caused by ventilation/perfusion mismatching from that caused by hypoventilation and hypercarbic respiratory failure.

A complete blood cell count is seldom useful because the white blood cell count is usually within normal limits. Urine specific gravity testing may provide useful information regarding fluid balance and possible dehydration. Serum chemistry is not affected directly by the infection but may aid in assessing and managing dehydration.

Radiological findings are nonspecific and typically demonstrate hyperinflation with flattened diaphragms and increased anteroposterior diameter with precordial air from air trapping. Patchy infiltrates and focal atelectasis may also be present. None of those findings alters therapy. Consequently, chest radiography is not routinely necessary when the clinical presentation is typical of bronchiolitis.[17] However, it may be considered if complications such as secondary bacterial infection are suspected.

Management

American Academy of Pediatrics (AAP) clinical practice guidelines do not recommend use of inhaled bronchodilators for a patient with typical viral bronchiolitis.[18] Nebulized hypertonic saline may be tried in patients who are

hospitalized; however, AAP clinical practice guidelines do not recommend its regular use in the emergency department.[18] The AAP guidelines also recommend using supplemental oxygen when oxygen saturation is less than 90%.[18] Supportive management to maintain adequate hydration, by using nasogastric or intravenous fluids when oral hydration is not possible, is recommended in AAP clinical practice guidelines.[18] Current study results do not support the use of antibiotics to treat persistent cough or wheeze after acute bronchiolitis.[19]

Prophylaxis

Passive immunity is used for at least partial prophylaxis of bronchiolitis in infants at high risk of developing the disease. Results of double-blind studies of palivizumab have shown reduction in severe RSV infections by 55% and reduction in hospitalizations by about 50% for infants at high risk because of prematurity, chronic lung disease, or congenital heart disease. The AAP clinical practice guidelines recommend 5 monthly doses of palivizumab (15 mg/kg per dose) during the RSV bronchiolitis season in the appropriate high-risk population—those with a gestational age less than 29 weeks, during the first year in infants with hemodynamically significant heart disease, or those with chronic lung disease of prematurity (premature babies <32 weeks requiring supplemental oxygen for more than 28 days after birth).[18]

Palivizumab is a humanized monoclonal immunoglobulin G1 antibody that recognizes the RSV F protein. Agents targeting different proteins within the RSV virion, such as SH protein, which causes inhibition of cell apoptosis through inhibition of the tumor necrosis factor-α pathway; M2–2 protein, which mediates the transition from transcription to RNA replication; NS2 protein, which inhibits host cellular antiviral type 1 interferon induction and interferon response; and N protein, are undergoing clinical trials. A phase 3 clinical trial of motavizumab for the prevention of RSV disease in healthy Navajo and Apache infants showed an 87% relative reduction in the proportion of infants admitted with RSV[20]; however, because it lacks greater clinical efficacy compared with that of palivizumab and because of reports of cutaneous hypersensitivity in some treated infants, it did not receive US Food and Drug Administration approval.

Hospitalization

Because bronchiolitis is generally a self-limited illness for which specific treatments are of unclear effectiveness, the primary reasons for admission are poor oral intake, dehydration, and concern that the degree of respiratory distress may result in respiratory failure and the need for assisted ventilation. If the caretakers are unable to assess the severity of illness or there is concern about their reliability to monitor the infant, then hospitalization may

be indicated. Assessing the degree of feeding difficulty, described in the Clinical Presentation section, may help in deciding which patients need hospitalization. The frequent use of pulse oximetry in the office or emergency department assessment has been associated with an increase in the frequency of hospitalization for bronchiolitis because of the perceived need for supplemental oxygen.

If there is a concern regarding the potential for respiratory failure, a facility with a pediatric intensive care unit is the preferred site for hospitalization. The potential for respiratory failure can be assessed by means of the presence of hypoxemia detected with pulse oximetry and a blood gas (capillary or venous) measurement indicating an increased P_{CO_2}. Assessing P_{CO_2} is essential to distinguish ventilation/perfusion mismatching from respiratory failure that may require assisted ventilation.

In-Hospital Management

Because there is little documented evidence that pharmacological measures have any clinically important effect on symptoms, length of stay, or duration of symptoms, treatment is mainly supportive.[21,22] Treatment includes oxygenation, hydration, and ventilation if needed. Nebulized hypertonic saline may be tried in patients who are hospitalized.[18]

Use of a high-flow nasal cannula in children with bronchiolitis is reported to be safe[23,24] and may decrease the rate of treatment failure compared with use of only supplemental oxygen. However, no statistically significant benefit is seen compared with results with standard therapy using supplemental oxygen and continuous positive airway pressure (CPAP),[24] and a higher failure rate of the high-flow nasal cannula compared with that of CPAP or bilevel positive airway pressure has been reported in infants admitted to the pediatric intensive care unit.[25] Using CPAP may reduce the respiratory rate in children with acute bronchiolitis more than does standard therapy but has no effect on length of hospital stay.[26] Furthermore, investigators in a large, multicenter database study of infants with acute bronchiolitis reported that the infants initially receiving noninvasive positive pressure ventilation required invasive ventilation at a higher rate than did infants initially receiving respiratory support with a high-flow nasal cannula.[27] Authors of a 2021 meta-analysis of the comparative efficacy of bronchiolitis interventions concluded, with low confidence, that nebulized hypertonic saline and nebulized hypertonic saline plus epinephrine reduced hospital length of stay but that treatment with a high-flow nasal cannula did not.[28]

Routine chest radiography results do not influence treatment and are unnecessary. Testing for RSV antigen is also unnecessary because the clinical course and treatment are independent of which respiratory virus is causing the bronchiolitis.[18,29]

Evaluation for bacterial infection is rarely indicated but may be considered in select situations, such as in patients with a temperature greater than 38°C (100.4°F), particularly in infants younger than 2 months. Some study investigators have reported clinical benefits with use of chest physiotherapy.[30] However, authors of a Cochrane review[31] concluded that these techniques cannot be used as standard clinical practice, in line with AAP clinical practice guidelines.[18] Use of cool mist is not indicated. The scheduled use of bronchodilators, routine use of antibiotics, routine use of corticosteroids via any route, antihistamines, and decongestants are not indicated. Cardiorespiratory monitoring should be considered for all patients during the acute stage. Monitoring, including continuous pulse oximetry, may help in decisions about the use of supplemental oxygen[18] and may be discontinued as status improves because excessive monitoring does not improve outcome and can prolong hospitalization.[32] Respiratory and contact isolation should be routine to prevent nosocomial spread of infection.

Discharge

Infants may be discharged when they are sufficiently comfortable with improved respiratory distress, do not require frequent suctioning, are able to take full oral feedings for at least 12 hours, have oxygenation of at least 90% when checked with pulse oximetry, and have a social situation that raises no concerns about care. Family members and caregivers should be educated about the adverse effects of smoke exposure; smoking cessation; and the importance of hand hygiene before and after direct contact with the patient, objects in contact with the patient, and even after taking off gloves.[18] Discharge instructions should include advice regarding tobacco smoke exposure and the risk of recurrent similar respiratory symptoms, especially if there is a family history of asthma or recurrent episodes of prolonged lower respiratory symptoms, cough, or labored breathing in the parents or siblings during preschool-age years.

key points

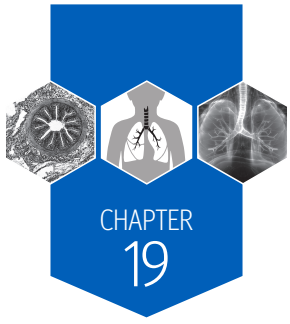
- Bronchiolitis may manifest with respiratory distress in the form of tachypnea, retractions, and cyanosis.
- The decision to hospitalize an infant with bronchiolitis is based on the presence of severe respiratory distress, hypoxemia, and poor oral intake, as well as social situation.
- Treatment and monitoring
  - Measure pulse oximetry until clinically stable, followed by spot checks with vital signs.
  - Bronchodilators, if administered, may be albuterol or racemic epinephrine as a trial, but only with physician assessment of respiratory distress level before and after; if there is improvement, the bronchodilator can be repeated as needed.
  - Routine scheduled bronchodilators are not indicated.
  - Hydration and nutrition should be provided as needed.
- Criteria for discharge
  - Oxygen saturation stable with breathing room air of at least 90% with normal to low P_{CO_2}
  - Good oral intake
  - No social contraindications (distance from medical care and parental capability may delay discharge)
- Discharge planning should include
  - Counseling regarding smoking cessation if needed
  - Counseling regarding risk for recurrent episodes (influenced by family history)

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CHAPTER
19

Viral Pneumonia (Including COVID-19)

Michael J. Light, MD
Paul C. Stillwell, MD, FAAP
Nanda Ramchandar, MD, MPH, FAAP
Mark H. Sawyer, MD

In a prospective, multisite comprehensive evaluation of children hospitalized with radiographically documented community-acquired pneumonia, 1 or more viruses alone were responsible for 66% of the pneumonia.[1] The most common viruses were respiratory syncytial virus (RSV; 28%), human rhinovirus/enterovirus (27%), human metapneumovirus (13%), adenovirus (11%), human parainfluenza virus (7%), influenza A and B (7%), and seasonal coronavirus (5%). Coinfection with 2 or more viruses was common. The isolation of RSV was most common in those 4 years or younger, as was human metapneumovirus. Influenza, human rhinovirus/enterovirus, and coronavirus were present in similar percentages in all age groups. Although each virus tends to have a seasonal pattern, the pattern is most pronounced for RSV, human metapneumovirus, influenza, and coronavirus. Similar findings were identified in a large study in Africa and Asia.[2]

Viral infections are the most common cause of symptomatic disease in children. The number of respiratory infections per year may be 5 to 10 or even more, with most being upper respiratory infections. Most cases of pneumonia are diagnosed clinically, but there is an increasing ability to find a causative agent as new biotechnology facilitates the diagnosis of viral infections. As noted in Chapter 20, Nonviral Pneumonia, depending on the age of the child and viral pathogen responsible, secondary bacterial infection occurs in about one-third of cases of viral pneumonia.[3,4] Although children who are immunocompromised are at higher risk of opportunistic infections, such as cytomegalovirus and varicella-zoster virus, they are also at risk of seasonal pneumonias, including RSV, influenza, and parainfluenza. The symptoms of viral pneumonia are similar to those of bacterial pneumonia, although there is less in terms of chest pain or rigors with viral pneumonia.

Coronavirus

Coronavirus made headlines in 2003 when the severe acute respiratory distress syndrome (SARS) was a cause of life-threatening pneumonia. The virus (SARS-CoV) quickly spread from China to the rest of the world, affecting 8,000 patients in 29 countries, and caused 774 deaths. As a result of intensive infection control measures, the global transmission was halted in 2003. It was speculated that subsequent variant strains of coronavirus would likely cause increased cases of pneumonia in the future. There are 7 coronaviruses, of which 4 typically only cause mild upper respiratory illness. The others are SARS-CoV from China; Middle East respiratory syndrome from the Middle East; and SARS-CoV-2, which was responsible for the COVID-19 pandemic.

COVID-19

The COVID-19 pandemic originated in December 2019 in Wuhan, China, and spread throughout the world. The virus was named *SARS-CoV-2*, which is the causative agent; COVID-19 is the disease. Mutations of viruses are typical, and the changes may affect the course of the disease. Variants of concern of SARS-CoV-2 have resulted in spikes of cases, including (as of publication) beta, delta, and omicron, with anticipation of future mutations.

The pulmonary complications, although variable, are overall less serious in children than adults. Although the incubation period may vary from 1 to 15 days, the average is 3 to 7 days. The clinical classification of severity is shown in **Box 19-1**, and the symptoms are shown in **Box 19-2**.

SARS-CoV-2 results in an acute viral infection of both the upper and lower respiratory tract. The virus is transmitted primarily via droplets. Close proximity with both children and adults who are infected permits rapid spread.

When SARS-CoV-2 reaches the lower airway, the viral spike protein binds with high affinity to the angiotensin-converting enzyme 2 cellular transmembrane receptor principally found on the apical membrane of type II pneumocytes. The receptor and virus are transported inside the cell and subsequently replicate. The immune response has 2 phases. Initially, an immunoreactive phase is characterized by activation of a cytokine storm. The second phase depends on the immune system, and subsequent progression may result in cell damage with release of cytokines and chemokines (IL-6, IL-10, and interferon) and recruitment of inflammatory cells, which mediate lung damage.

Box 19-1

Classification of COVID-19 Severity in Children

Asymptomatic: Positivity of the RT-PCR buffer to SARS-CoV-2 or positive serology in the absence of any symptoms of illness.

Mild: Symptoms are mild and mainly affect the upper airways (nasal obstruction, sneezing), sometimes associated with fever, cough, and gastrointestinal symptoms.

Moderate: Symptoms are more critical, and fever and cough (mainly dry) are almost always present and are associated with breathing difficulties. It is characterized radiologically by lung anomalies compatible with interstitial pneumonia.

Severe: It is characterized by the presence of hypoxemia ($SpO_2 < 92\%$) with signs of respiratory distress (tachypnea, groaning, wing flaps, sags), cyanosis, neurological signs and symptoms, refusal to eat, and signs of dehydration.

Critical: Disease progression to ARDS with onset of respiratory failure requiring mechanical ventilation, signs of shock, or multiorgan failure.

Abbreviations: ARDS, acute respiratory distress syndrome; RT-PCR, reverse transcriptase–polymerase chain reaction; SpO_2, oxygen saturation as measured by pulse oximetry.

Derived from Miao H, Li H, Yao Y, et al. Update on recommendations for the diagnosis and treatment of SARS-CoV-2 infection in children. *Eur J Clin Microbiol Infect Dis.* 2020;39(12):2211–2223.

Box 19-2

Symptoms of COVID-19 in Children

- Fever or chills
- Nasal congestion or runny nose
- Cough
- Sore throat
- Loss of smell or taste
- Shortness of breath or difficulty breathing
- Fatigue
- Headache
- Muscle aches or body aches
- Nausea or vomiting
- Diarrhea

Clinical Features

In children, there is considerable variation in symptoms; they tend to be less severe than in adults. Absence of symptoms is not uncommon.

The pulmonary features of COVID-19 in children vary from asymptomatic to respiratory failure. Respiratory management dominates the clinical picture of children who are hospitalized. Hospital admission is decided based on symptoms and pulse oximetry results. Deterioration of the clinical picture with increasing dyspnea, cyanosis, and the onset of acute respiratory distress syndrome occurs 8 to 10 days after onset of infection, which potentially may lead to multiple organ failure and death.[5]

Chest Imaging

If COVID-19 is diagnosed and symptoms are mild, chest radiography is not necessarily indicated. If there are moderate or severe symptoms, chest radiography may assist in characterizing the extent of disease. Computed tomography is indicated if the symptoms are worsening or if there is suspicion for pulmonary embolus.[6] Findings may be unilateral or bilateral (55% and 45%, respectively) and include peribronchial thickening and ground-glass opacities. These findings are seen in adults and are milder in children than in adults. One finding that is present in children but not in adults is the halo sign that appears early. There is a central opacity that blocks out underlying lung structure with a ringlike, surrounding hazy area (ground-glass opacities) (**Figure 19-1A**). The halo sign has also been reported in infectious aspergillosis and other fungal infections.

Authors from Boston Children's Hospital[7] developed recommendations on when to conduct imaging studies for COVID-19 in children. They do not recommend imaging as a screening tool or when symptoms are mild. The decision depends on symptom severity, and chest radiography or computed tomography is indicated if results may affect patient care. The decision to order imaging is affected by the conditions shown in **Box 19-3**.

As the disease progresses, so do the radiological findings. **Figure 19-1** shows the progression that can be expected if there is worsening.

Ultrasonography has the advantage of portability and no radiation. Findings in children with COVID-19 have shown the ability to follow the progress of pulmonary findings. Musolino et al[7] reported 10 children with COVID-19 showing B lines (70%), pleural irregularities (60%), white lung (10%), and subpleural thickening (10%).

Box 19-3

Imaging Considerations for COVID-19 in Children

- **Disease severity: mild or moderate/severe**
- **Disease prevalence: low or high**
- **Presence of underlying health conditions like:**
  - **Asthma**
  - **Cystic fibrosis**
  - **Congenital heart disease**
  - **Cancer**
  - **Prematurity-related lung disease**
  - **Chronic infection (eg, tuberculosis or HIV)**
- **Travel history to area of known high COVID-19 prevalence**
- **Constrained health resources**

Derived from Foust AM, Phillips GS, Chu WC, et al. International expert consensus statement on chest imaging in pediatric COVID-19 patient management: imaging findings, imaging study reporting, and imaging study recommendations. *Radiol Cardiothorac Imaging.* 2020;2(2):e200214.

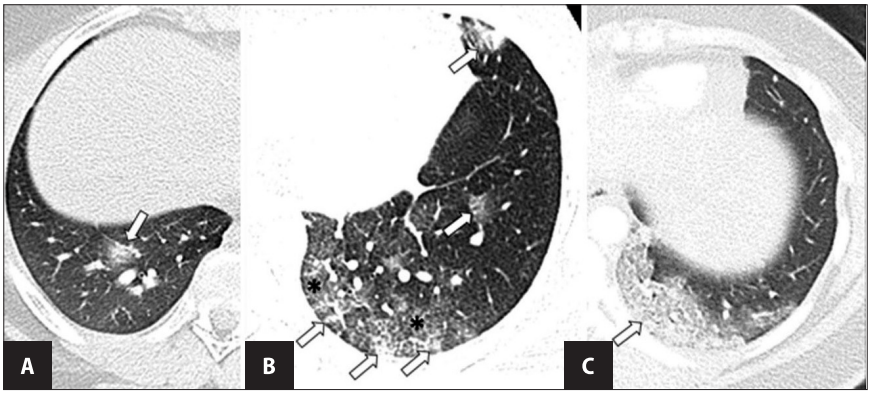


Figure 19–1. Axial lung window computed tomography images showing 3 phases (early, progressive, and developed) of COVID-19 pneumonia in 3 pediatric patients. **A,** Early phase of pediatric COVID-19 pneumonia in a 14-year-old female adolescent with Hodgkin lymphoma and a positive COVID-19 RT-PCR (reverse transcriptase–polymerase chain reaction) test result who presented with fever and cough. The image shows a rounded ground-glass opacity (arrow) with a subtle area of central consolidation in keeping with the halo sign that is often seen in the early phase of pediatric COVID-19 pneumonia. **B,** Progressive phase of pediatric COVID-19 pneumonia in a 15-year-old female adolescent with traveling history in an endemic area in Europe and a positive COVID-19 RT-PCR test result who presented with increasing cough and shortness of breath. The image shows rounded ground-glass opacities (arrows) with a subtle area of central consolidation. Between these areas, ground-glass opacities (*) have started to fill the lung parenchyma. **C,** Developed phase of pediatric COVID-19 pneumonia in a 16-year-old female adolescent with a positive COVID-19 RT-PCR test result who presented with severe shortness of breath. The image shows predominantly confluent consolidation (arrow) in the posterior left lower lobe.

From Foust AM, Phillips GS, Chu WC, et al. International expert consensus statement on chest imaging in pediatric COVID-19 patient management: imaging findings, imaging study reporting, and imaging study recommendations. *Radiol Cardiothorac Imaging.* 2020;2(2):e200214. Published online April 23, 2020. DOI: 10.1148/ryct.2020200214. © Radiological Society of North America.

Persistence of Pulmonary Symptoms

Long COVID-19

Long COVID-19 or long-haul COVID-19 is when symptoms persist for a period of months. Most children have symptoms for only a short time. Symptoms that may last more than 4 weeks include fatigue, fever in children aged 5 to 11 years, headache, and sore throat in adolescents aged 12 to 17 years. Other symptoms that have been reported include brain fog or difficulty thinking or concentrating, chest pain, cough, depression or anxiety, and loss of smell or taste. There is no specific test for long COVID-19, and it can be expected to improve over time.

Pediatric Inflammatory Multisystem Syndrome and Multisystem Inflammatory Syndrome in Children

The inflammatory response to SARS-CoV-2 may be exaggerated, resulting in pediatric inflammatory multisystem syndrome (PIMS) or multisystem inflammatory syndrome in children (MIS-C). The 2 conditions are essentially the

same but have different criteria for diagnosis. Multisystem inflammatory syndrome in children is a postinfectious exaggerated inflammatory response that is rare but can occur 2 to 6 weeks after the acute infection. Criteria include confirmation of SARS-CoV-2 infection and evidence of inflammation with involvement of multiple systems with an illness that manifests like Kawasaki disease. Evidence of inflammation may include an elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, ferritin, d-dimer, elevated neutrophils, and reduced lymphocytes. This inflammation may progress to more severe illness with multisystem involvement, including cardiac involvement and shock. Treatment of MIS-C is primarily with anti-inflammatory or immunomodulatory medications such as corticosteroids and intravenous immunoglobulin.

Management

Isolation is necessary, as is adequate fluid and calorie intake. Fever is managed preferably with acetaminophen rather than ibuprofen. Children hospitalized with hypoxemia require administration of oxygen via nasal cannula or mask to keep the saturation at 92% or higher and should be monitored closely for clinical worsening. High-flow nasal oxygen or continuous positive airway pressure may be indicated in such cases. High-flow nasal oxygen should be administered in single or negative pressure rooms to protect health care workers.

The National Institutes of Health recommendations for treating COVID-19 in children are that steroids should be used when the patient requires supplemental oxygen, high-flow oxygen, nonmechanical ventilation, mechanical ventilation, or extracorporeal membrane oxygenation. The effectiveness of other treatments, including antibiotics, is unclear.

Remdesivir, a nucleoside antiviral, previously used to treat Ebola, has been approved for children 28 days or older and adults hospitalized with COVID-19. At one point in the pandemic, several monoclonal antibody combinations showed a benefit as therapy, particularly in mild infection in individuals at high risk of severe disease; however, they are no longer authorized as currently the overall prevalence of non-susceptible variants is high. This is a rapidly evolving area of investigation; for the most up to date recommendations, see https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/outpatient-covid-19-management-strategies-in-children-and-adolescents/.

In December 2021, nirmatrelvir and ritonavir (Paxlovid, Pfizer) received emergency use authorization from the US Food and Drug Administration (FDA) for use in patients 12 years or older with COVID-19 who are at risk of progression to severe disease.

Respiratory Syncytial Virus

Respiratory syncytial virus is the most important cause of lower respiratory infection in children younger than 2 years. By age 2 years, more than 94% of children will have serological evidence of RSV infection. During the RSV season, RSV is the cause of hospitalization in more than 90% of infants hospitalized with bronchiolitis. The differentiation between bronchiolitis and pneumonia can be difficult, so the designation of lower respiratory tract infection due to RSV may be easier than trying to define whether there is one or both diagnoses. Infants with RSV pneumonia tend to have less wheezing, less hyperinflation, and more crackles.

The clinical scenario of pneumonia is similar to that of bronchiolitis (see Chapter 18, Bronchiolitis), with an upper respiratory prodrome followed by worsening cough and increasing respiratory distress. As noted, wheezing tends to be less prominent, and there may be crackles during examination. The radiographic appearance of lobar consolidation (especially in the right upper lobe) or a bronchopneumonia pattern supports the diagnosis of pneumonia.

Most infants with RSV pneumonia recover in a few days, but a small percentage progress to respiratory failure. Infants younger than 2 months and those with clinically significant respiratory distress or apnea should be hospitalized. Severe lower respiratory tract infection is a concern for former preterm infants with bronchopulmonary dysplasia and cyanotic heart disease and also for infants with pulmonary hypertension.

Influenza Virus

The influenza virus is a single-stranded RNA virus that is a common cause of pneumonia, especially in the very young and very old. It occurs in epidemic form in the winter months, and children who are chronically ill are at more risk for serious illness. Pandemics in the past 110 years include the 1918–1919 Spanish pandemic (influenza virus subtype H1), the 1957 pandemic (subtype H2N2), the 1968–1969 pandemic (Hong Kong subtype H3N2), and the novel influenza A (H1N1) pandemic of 2009–2010. The incubation period is 1 to 5 days after exposure to the virus.

The manifestation of influenza is characteristic with high fever, chills, muscle aches, and headache, although young children may have more nonspecific symptoms. The illness starts as an upper respiratory infection with rhinitis, pharyngitis, and initially nonproductive cough. Young children may also have conjunctivitis and gastrointestinal symptoms. Pneumonia is associated with increasing respiratory symptoms and hypoxemia. Secondary bacterial infection is common after influenza pneumonia.

Positivity for A or B influenza virus can be determined by means of immunofluorescence or hemagglutination techniques, although during the 2009–2010 H1N1 pandemic, these tests were not very helpful in diagnosis. A polymerase chain reaction assay of respiratory specimens has both high sensitivity and high specificity for detection of influenza virus.

Symptoms last for several days and are treated with over-the-counter medications. Aspirin should be avoided because of the association with Reye syndrome.

Oral oseltamivir may be used in persons 2 weeks or older with influenza A or B who have had symptoms for no more than 2 days. Oseltamivir may also be used for prophylaxis of influenza infection for patients older than 3 months who have been exposed.[7,8] Baloxavir marboxil is approved by the FDA for uncomplicated influenza in persons 12 years or older and is administered as a single dose orally within 48 hours of symptom onset. Study results have shown safe use of baloxavir marboxil in children as young as 1 year of age.

Human Parainfluenza Virus

Human parainfluenza virus (HPIV) 1, HPIV-2, and HPIV-3 cause croup; HPIV-1 and HPIV-3 cause lower respiratory tract infection, including bronchiolitis, bronchitis, and pneumonia. Outbreaks of HPIV-3 occur during spring and summer. Almost all children have been infected, and, because immunity is short-lived, repeated infections occur. Human parainfluenza virus is spread via droplet and fomite exposure.

Morbidity and mortality from HPIV lower respiratory tract infection is uncommon in the United States. It is a substantial cause of mortality in under-resourced countries, especially after secondary bacterial infection in children who are malnourished.

Adenovirus

Adenovirus is an enveloped DNA virus that causes both upper and lower respiratory infection. Most cases are mild, self-limited upper respiratory infections. The population at risk for severe disease is the immunocompromised, including patients who have received transplants, especially patients who have received hematopoietic stem cell as well as solid organ transplants. Treatment is to relieve symptoms. Cidofovir has been used in patients who are severely ill and immunocompromised. There is a small risk of developing bronchiectasis after adenovirus lower respiratory tract infection.

Human Metapneumovirus

Human metapneumovirus was first described in the Netherlands in 2001. It is in the same family as RSV and HPIV (the *Paramyxoviridae* family). In the pediatric population, the infections are similar to those with RSV, although

the illness tends to be milder and the children tend to be older. The symptoms include rhinorrhea, cough, tachypnea, and wheeze. The signs include retractions, crackles, and wheeze. The clinical manifestations are similar to those of RSV bronchiolitis, but pneumonia and respiratory failure may occur.

Varicella-zoster Virus

Varicella-zoster virus is a herpesvirus that causes chicken pox and has the potential to reactivate as shingles. Risk factors for varicella pneumonia include high-dose steroids (1–2 mg/kg/day for>2 weeks), malignancy (including leukemia), and other immunocompromised states (including HIV infection). Varicella pneumonia causes substantial mortality and is associated with severe invasive group A streptococcal disease. The viremia is treated with acyclovir, and children with varicella pneumonia should be hospitalized. Varicella-zoster immune globulin is indicated for immunocompromised patients without evidence of immunity and newborn infants whose mothers have signs of varicella 5 days before and 2 days after delivery.

Measles Virus

Measles virus is another member of the *Paramyxoviridae* family. It causes a febrile illness with morbilliform rash; pneumonia can occur. Children who are unvaccinated, malnourished, or immunocompromised are at risk for severe lower respiratory tract infection.

Cytomegalovirus

Cytomegalovirus is a virus in the herpes group. Cytomegalovirus pneumonia is a major cause of pneumonia in children who are immunocompromised, including those with transplant, HIV, and malignancy. The typical scenario is that 2 to 3 months after transplant, there is cough and fever; severe dyspnea and hypoxia result. The symptoms are nonspecific, and the lung involvement is an interstitial pneumonia. The chest radiograph shows bilateral interstitial infiltrates. Pulmonary symptoms may be accompanied by gastrointestinal disease, especially hepatitis and diarrhea, and chorioretinitis.

Ganciclovir is used as prophylaxis in patients at risk after transplant (eg, when the donor is seropositive and the recipient is seronegative). It is also beneficial for patients with pneumonia who have symptoms.

Supportive Care

For most patients with viral pneumonia, supportive care is all that is required to make sure they have satisfactory oxygenation and hydration. Hospitalization may be necessary for more severe illness and is most common in children younger than 2 years. If influenza is identified, then appropriate antiviral therapy might shorten the duration of the illness. Oseltamivir is commonly

selected because it is usually effective for both A and B strains. The Centers for Disease Control and Prevention (CDC) regularly checks for resistance to the recommended antiviral drugs, and amantadine is no longer recommended because of lack of effectiveness for influenza B and a high percentage of resistance with influenza A. Inhaled zanamivir may be used for children 5 years or older provided they can use the device correctly and are not at risk for bronchospasm. Intravenous peramivir is available for children 2 years or older, and baloxavir is available for children 12 years or older.

Prevention of Viral Pneumonia

The CDC recommends that all individuals 6 months or older get a seasonal flu vaccine. The seasonal flu vaccine protects against influenza viruses that research indicates will be most common during the upcoming season. The CDC also recommends that people in contact with certain groups of children get a seasonal flu vaccine the better to protect the child (or children) in their lives from the flu.

The CDC recommends that the following contacts of children receive seasonal influenza vaccination:

- Close contacts of children younger than 5 years (people who live with them), especially those younger than 6 months
- Out-of-home caregivers (nannies, child care providers, etc) of children younger than 5 years
- People who live with or have other close contact with a child or children of any age with a chronic health problem (asthma, diabetes, etc)
- All health care workers, to keep from spreading the flu to their patients

When to Refer

Most children with viral pneumonia will not require consultation. If there are complications, such as pleural effusion, acute respiratory failure, or prolonged hypoxia, consultation with a pulmonologist may be indicated. If the child has a chronic illness, consultation with the specialist who is involved in the child's long-term care may be helpful. Consultation with infectious diseases or allergy specialists is indicated if patients have allergies, comorbid conditions, or unresponsiveness to antibiotics.

When to Admit

Children with pneumonia and a chronic illness, for example if they are immunocompromised, may require hospitalization. If the degree of respiratory distress is clinically significant, if there is hypoxia, and if they appear septic, they may require hospitalization. Currently, validated screening

systems do not exist to help predict which children with pneumonia should be hospitalized. Hospitalization is indicated with the following:

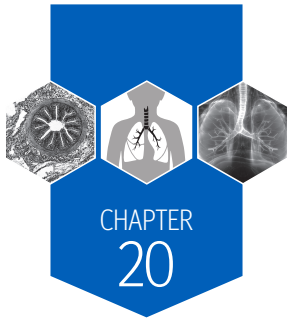
- Oxygen saturation consistently less than 90%
- Moderate or severe respiratory distress
- Severe dehydration
- A home circumstance or social situation that raises concerns

key points

- The cause of pneumonia is closely related to the age of the child.
- Imaging studies do not help differentiate viral from bacterial lower respiratory tract infections.
- Chest radiography is not necessary to establish the diagnosis of pneumonia.
- Computed tomography is indicated for evaluating complications of pneumonia.
- Ultrasonography is useful to characterize pleural effusion or empyema.
- Treatment depends on the age of the child and the likely diagnosis and severity of illness.

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CHAPTER
20

Nonviral Pneumonia

Michael J. Light, MD
Paul C. Stillwell, MD, FAAP
Nanda Ramchandar, MD, MPH, FAAP
Mark H. Sawyer, MD

Introduction

Pneumonia is a serious global health issue. It is the second leading cause of death in children younger than 5 years and the leading cause of death in this age group in certain geographic areas.[1,2] Death from pneumonia is closely linked to poverty, with the highest mortality occurring in the most economically disadvantaged areas.[3] The story is quite different in resource-rich counties: the incidence of community-acquired pneumonia (CAP) in the United States is about 35 to 40 per 1,000 children 4 years or younger and decreases to 10 per 1,000 in teenagers and adolescents; less than 1% die.[4]

There are several different ways pneumonia may be classified to identify the suspected organism, determine the best management, and predict the outcome. There are multiple causative agents, both nonviral and viral. These include gram-positive and gram-negative bacteria, atypical bacteria, and fungal, parasitic, and chemical agents. Classification based on the clinical scenario includes CAP or health care–related (including ventilator-associated pneumonia), immunocompromised versus immunocompetent host, patient age, and geographic and exposure risks.[5,6] Classification based on the appearance of radiographic images includes bronchopneumonia, lobar (or multilobar) pneumonia, and interstitial pneumonia.[6] *Complicated pneumonia* is defined as a pulmonary parenchymal infection complicated by parapneumonic effusions, multilobar disease, abscesses or cavities, necrotizing pneumonia, empyema, pneumothorax, or bronchopleural fistula or as pneumonia that is a complication of bacteremic disease that includes other sites of infection (see Chapter 21, Complications of Pneumonia).[7] Not one of these classifications has a strong predictive value as to the specific cause. Despite various classification schemes, the specific microorganisms responsible for the pneumonia may be difficult to determine.[7] Therefore, it is common practice to prescribe antibiotic therapy, despite lack of a documented bacterial infection, "just in case."[8]

Common Clinical Presentations

Children with pneumonia, regardless of the cause, may have a constellation of symptoms, including fever, cough, chest pain, and dyspnea. Other systemic symptoms such as nausea and vomiting are also common.[2] The findings at auscultation vary with the extent of the pneumonia but commonly include tachypnea, inspiratory crackles, and decreased intensity of breath sounds.[8] Expiratory wheezing suggests a viral or atypical bacterial cause. If a pleural effusion is present, there may be dullness to percussion over the affected area. Small children with compliant chest walls often have retractions. The oxygen saturation is commonly reduced, although cyanosis may be evident only with severe levels of desaturation (**Table 20-1**).

Table 20-1. Findings Suggestive of Pneumonia

Finding Method	≤2 months	2–12 months	1–5 years	>5 years
Respiratory rate WHO threshold	≥60/min	≥50/min	≥40/min	≥30/min
Symptoms and signs	Cough Poor feeding Apnea Tachypnea Grunting Nasal flaring Retractions	Cough Fever Poor feeding Tachypnea Grunting Rhinorrhea Nasal flaring Retractions	Cough Fever Rhinorrhea Chest pain Tachypnea Retractions	Cough Fever Headache Pleuritic pain Abdominal pain Tachypnea Retractions
Auscultation	Crackles Wheeze	Wheeze Crackles	Crackles Wheeze Pleural rub	Crackles Wheeze Pleural rub

Abbreviation: WHO, World Health Organization.

Evaluation of Suspected Pneumonia

Imaging

Pneumonia can be diagnosed on clinical grounds without documentation with a chest radiograph (CXR).[2,5,9–12] In countries with limited resources, identifying children with fever and elevated respiratory rate as needing a higher level of care and antibiotics has reduced the mortality from pneumonia. However, results from a study in which the investigators compared pneumonia diagnosed simply by means of World Health Organization clinical criteria, especially elevated respiratory rate, showed that a majority of the children who were considered as having pneumonia actually had a normal CXR.[13]

In resource-rich areas, a CXR is commonly obtained to help diagnose pneumonia for children with fever, cough, and adventitious pulmonary sounds aside from wheezing.[10] This is particularly true for children taken to the emergency department or admitted to the hospital. Although it is possible to have pneumonia without abnormal radiographic findings, an abnormal CXR is usually the gold standard for diagnosing pneumonia. A negative CXR has a high predictive value of the patient not having pneumonia and not developing pneumonia in the near future, unless it is obtained very early in the illness.[9,10] Standard practice is to obtain a posteroanterior CXR (or anteroposterior if the patient is younger than 4 years). A lateral view is also advisable for children who are hospitalized.

Chest computed tomography is seldom required for CAP and is reserved for helping evaluate and define complicated pneumonias (see Chapter 21, Complications of Pneumonia). Ultrasonography is useful with pleural effusions, and there is interest in its use for CAP as well, which may be important in resource-limited areas when chest radiography and computed tomography are not readily available.[2,5]

Laboratory Evaluation of Pneumonia

Which laboratory tests are ordered for a child with pneumonia often depends on the severity of the illness and whether hospitalization is being considered.[2] For a child with mild CAP who was previously healthy, perhaps no laboratory studies are indicated. For a child who is more seriously ill who will be admitted to the hospital, a complete blood cell count (CBC) with a white blood cell (WBC) differential count and inflammatory markers (C-reactive protein [CRP] level, erythrocyte sedimentation rate, procalcitonin [PCT] level) and a basic metabolic panel are commonly ordered.[14,15] Certain patterns of results may suggest a specific type of organism, but the predictive value is not high. If the WBC count is higher than 15,000/μL (15.00×10^9/L) with a shift toward immature neutrophils, bacterial infection may be suspected.[14,15] The CRP and PCT levels are more sensitive and specific for bacterial infections.[16–19] If the WBC count is normal or low and there is a lymphocyte predominance, viral infection is suspected, especially if accompanied by a modestly elevated or normal CRP or PCT level. In infants, if the WBC count is high with a marked lymphocyte predominance, *Bordetella pertussis* is suspected. If the WBC differential count has excessive eosinophils, parasitic or fungal infection is suspected. In infants, peripheral eosinophilia may suggest *Chlamydia trachomatis* pneumonia. Another benefit of the CBC is checking the hemoglobin level to make sure there is satisfactory oxygen-carrying capacity for oxygen delivery to the tissues. Electrolyte disturbance such as hyponatremia may raise concern for inappropriate antidiuretic hormone secretion. Elevated liver enzyme levels may be found with adenovirus or *Mycoplasma* infections.

Microbiology

Advances in laboratory techniques have increased the ability to make a specific microbiological diagnosis in many cases of pneumonia.[7] Polymerase chain reaction (PCR) detection with a rapid turnaround time is now available for a wide range of viruses and some bacteria from the upper respiratory tract.[16] Studies using this technology in children hospitalized with pneumonia in the United States identified a viral cause in 66%, a bacterial cause in 8%, and mixed bacterial and viral causes in 7% of the 81% in which a specific cause was identified.[4] A similar study in younger children hospitalized with pneumonia in Africa and Asia identified a viral cause in 61%, a bacterial cause in 27.3%, and *Mycobacterium tuberculosis* in nearly 6%; bacterial infection was more common in these children with "very severe" pneumonia compared with "severe" pneumonia.[17] The multiplex PCR technology has largely supplanted other testing modes such as direct fluorescent antibody testing and serial serological testing; some types of rapid influenza detection tests use immunofluorescence but are less sensitive and less specific than molecular tests.[7]

Although multiplex PCR testing has greatly improved the ability to identify evidence of specific organisms, it has also created concern whether some of these organisms are the source of the pneumonia or found incidentally in the patient's nasal and oral secretions.[18] According to a comparison of patients with CAP versus control subjects without symptoms, detection of influenza, respiratory syncytial virus (RSV), and human metapneumovirus is probably indicative of cause, whereas the detection of parainfluenza, coronavirus, rhinovirus, and adenovirus is less clearly indicative of cause. A positive PCR result for rhinovirus may occur for several weeks after an infection. These concerns also apply to more recently discovered potential pathogens such as bocavirus among others.[18]

A sputum sample for Gram stain and culture is not usually indicated in CAP but may be valuable, provided the sample is good quality and not predominantly upper airway secretions and squamous epithelial cells. Predominance of a single type of bacteria in large numbers suggests this is the pathogen responsible for the pneumonia.[14,15] Mixed flora in lower density usually does not correctly identify the pathogen. Blood cultures in patients with simple CAP are infrequently positive and are not cost-effective; they are more likely to be positive in patients hospitalized with complicated pneumonia.[19] When a pleural effusion is present, sampling the pleural fluid to find a specific pathogen may be helpful; however, the result is often negative, particularly if the patient has already received antibiotics.[8,15] Recent development of metagenomic next-generation sequencing rapid tests is likely to greatly improve the ability to identify bacterial infections and resistance patterns of bacterial pathogens.[20]

Indirect tests such as urinary antigen testing are useful in some causes of pneumonia such as histoplasmosis but have had less use with bacterial pneumonia such as *Streptococcus pneumoniae*. Serum antibody testing is very helpful in patients who are immunocompromised and have fungal pneumonia for which culturing an organism in the laboratory can be slow and challenging. Markers of fungal cell wall elements such a β-D-glucan and galactomannan can be helpful if present in blood or bronchoalveolar lavage specimens, especially in a patient who is immunocompromised.

Pathology

The pathology of pneumonia is described as follows:

- Lobar
- Bronchopneumonia
- Interstitial
- Miliary

Lobar pneumonia has 4 stages. The initial stage is congestion, when the alveoli are filled with fibrinous fluid, neutrophils, and bacteria. This stage occurs within 24 hours of infection. The second stage usually occurs on days 2 to 3 and is called *red hepatization*. The lung reddens and is of the consistency of liver. The alveoli are filled with fibrinous inflammatory exudates with increased numbers of neutrophils and red blood cells that contribute to the color. The consolidated lobe is airless and evident on a CXR. The pleura is usually thickened, and a pleural rub may be heard. The next stage is called *gray hepatization*, when the alveoli are filled with fibrin threads and neutrophils and the red blood cells are much fewer in number. The lung is still stiff, and the alveolar walls are thickened and fibrosed. The fourth stage is that of resolution as the inflammatory exudates are resorbed.

Bronchopneumonia is patchier, and, as the name suggests, there is suppurative inflammation of the bronchi and surrounding alveoli. The exudates fill bronchi and bronchioles and affect the adjacent alveoli, while the distant alveoli may be free of exudates. The patchy consolidation may affect one or several lobes and is usually bilateral. The lobes more involved include the dependent lung zones and the bases.

Interstitial pneumonia results from inflammation within the alveolar wall rather than in the alveolar airspace. The infiltrate tends to be lymphocytes and macrophages, and hyaline membranes may line the alveolar spaces.

Miliary pneumonia occurs with hematogenous spread to the lung, which leads to multiple discrete lesions, often throughout both lungs.

Bacterial pneumonia often follows a viral upper respiratory infection (URI). Lobar pneumonia is most commonly bacterial, including atypical bacteria.

Bronchopneumonia may be bacterial, atypical, or viral. Interstitial pneumonia may result from HIV, measles, and pertussis, as well as from noninfectious causes, including aspiration. Miliary pulmonary infection is most commonly seen in tuberculosis, histoplasmosis, and coccidioidomycosis. Patients who are immunocompromised are at risk for cytomegalovirus or varicella-zoster virus and other opportunistic infections.

Diagnosis

The microbiological diagnosis of pneumonia is difficult to prove in many cases without extensive investigation. The age of the child will suggest the most likely cause, and it is also helpful to be aware of which organisms are in the community at the time. Pneumonia in the pediatric population is most common in infants and toddlers and least common in adolescents.

Box 20-1 lists the more likely causes of pneumonia on the basis of age.

Box 20-1

Age-Related Causes of Pneumonia in the Child Who Is Immunocompetent

≤ 2 Months
- Group B *Streptococcus*
- Pneumococcus
- *Staphylococcus aureus*
- *Chlamydia trachomatis*
- *Listeria monocytogenes*

2–12 Months
- Pneumococcus
- RSV
- Parainfluenza
- Influenza
- Adenovirus
- hMPV
- *C trachomatis*
- Pertussis

1–4 Years
- Pneumococcus
- Parainfluenza
- Influenza
- Adenovirus
- RSV
- hMPV
- *Mycoplasma*

5–12 Years
- *Mycoplasma*
- Pneumococcus
- Group A *Streptococcus*
- Viruses

≥ 12 Years
- *Mycoplasma*
- *Chlamydia pneumoniae*
- Pneumococcus
- Group A *Streptococcus*
- Viruses

Abbreviations: hMPV, human metapneumovirus; RSV, respiratory syncytial virus.

Infants to School Age (1 Month–4 Years)

After children reach 1 month of age, cough is the most common manifestation of pneumonia. A viral upper respiratory illness commonly precedes the pneumonia. If the pneumonia is bacterial, a clinically significant fever is usually present, whereas in viral or atypical infections, the fever may be low-grade. Generally, the height of the fever is a poor indicator of cause. Most cases of pneumonia are viral, and RSV is the most common pathogen. Although RSV principally causes bronchiolitis, it is also a common cause of pneumonia. After children reach 2 years of age, RSV does not typically cause lower respiratory tract infection except in patients who are immunocompromised (especially transplant recipients). Human parainfluenza type 3 occurs year-round, with peaks in the spring, and types 1 and 2 are typically seen in the fall.

From 5 Years of Age to Adolescence

The most common cause of bacterial pneumonia is *S pneumoniae*, but *Mycoplasma* is increasingly being diagnosed as the cause of CAP. Group A *Streptococcus* is also increasingly being diagnosed. Various viruses cause pneumonia, including adenovirus, influenza, parainfluenza, and RSV (in patients who are immunocompromised or have received transplants).

Bacterial Pneumonia

In one study, bacteria were isolated as a cause of CAP in less than 10% of children hospitalized for pneumonia, and an additional 7% had mixed bacterial and viral infections.[4] A bacterial pathogen alone was infrequent in children younger than 2 years, and the incidence increased through childhood and adolescence.[4] *S pneumoniae* was the most common typical bacteria identified and only in less than 5% of the patients. Other bacteria identified in lower frequency included *Staphylococcus aureus* (both methicillin resistant and methicillin sensitive), *Streptococcus pyogenes*, viridans streptococci, and *Haemophilus influenzae*. Only a very small number of gram-negative organisms were identified. Atypical bacteria (*Mycoplasma* and *Chlamydia*) are discussed separately later.

Bacterial pneumonia is an important cause of death if untreated, especially in underresourced countries. Although most children with bacterial pneumonia improve without sequelae, children with a preexisting condition may be at increased risk for morbidity, including subsequent infections because of scarring in the lungs. The immune status of the child also affects the risk of mortality and morbidity.

Gram-Positive Bacteria

Pneumococcus

S pneumoniae was the most common bacterial cause of lower respiratory infection before the institution of the pneumococcal vaccine in 2000. Since 2000, there has been a reduction of invasive pneumococcal disease by 80% for children younger than 2 years, and this finding may increase since the 13-valent pneumococcal conjugate vaccine (PCV13) replaced PCV7 in the routine childhood immunization schedule and became available in 2010.[6] Surveillance is also indicated for nonvaccine serotypes. Although invasive pneumococcal disease has decreased, complicated pneumonia has increased significantly across the United States,[7] and these cases tend to be due to nonvaccine serotypes.

Pneumococci are gram-positive diplococci, and the upper respiratory tract is colonized in many people. Transmission is by droplet, and the incubation period is short (sometimes 1–3 days). Populations at more risk for invasive pneumococcal disease (pneumonia, meningitis, and sepsis) are shown in **Box 20-2**.

Pneumococcal pneumonia may be preceded by a mild URI. Infants may present with a sudden increase in fever, possibly a seizure, and diarrhea and vomiting. Cough may be absent, but evidence of respiratory distress includes tachypnea, nasal flaring, and perioral cyanosis. Older children usually present with fever, chills, dyspnea, and pleuritic chest pain. Older children may have sputum production, and streaks of blood may be apparent in the sputum.

Chest examination results may not be abnormal in infants and small children. Older children will usually have crackles and dullness to percussion with bronchial breathing over the involved lobe. Friction rub is not often elicited. Abdominal pain is a common symptom in an older child.

Box 20-2

Children at Increased Risk of Invasive Pneumococcal Disease

- **Children younger than 36 months**
- **Children with sickle cell disease**
- **Children with asplenia**
- **Children with HIV**
- **Children with cochlear implants**
- **Children with chronic disease including asthma, immune deficiency (including transplants), cardiac disease, pulmonary disease, renal insufficiency, and diabetes mellitus are at presumed high risk, but the data are insufficient to calculate rates.**

Laboratory findings also are not consistent. Although not usually obtained in the outpatient setting, a WBC count higher than 15,000/μL (15.00×10^9/L) with the clinical picture of pneumonia is certainly suggestive of pneumococcal disease. The yield from blood culture is low, but, when an adequate specimen is obtained, the sputum findings of many polymorphonuclear leukocytes with gram-positive diplococci are almost diagnostic. Young age is a barrier to sputum collection. Antigen detection is not considered useful for diagnosis except for pleural fluid.

Chest radiography in children with pneumococcal pneumonia may initially demonstrate a lobar pattern and then extend beyond the lobar boundaries. It is the most common cause of the round pneumonia pattern. On occasion, the markings may be patchy or interstitial. As discussed in Chapter 7, Pulmonary Imaging, chest radiography is not consistently able to help confirm the diagnosis of a bacterial or viral pneumonia because of overlap between findings.

The clinical course of pneumococcal pneumonia is usually rapid, with response to antibiotics causing reduction of fever within a few hours. For outpatient treatment in children with CAP that has been proven to be or is suspected to be of bacterial origin, amoxicillin or amoxicillin-clavulanate is the therapy of choice. In school-aged children (>5 years), the addition of a macrolide for coverage of atypical organisms may be warranted. In children ill enough to warrant hospitalization, the empirical use of penicillin or ampicillin and the addition of a macrolide may be appropriate, and decisions for therapy should take into account local resistance patterns and immunization history. Use of third-generation cephalosporins is reserved for infants and children who are hospitalized and not fully immunized in areas with a higher incidence of invasive pneumococcal strains and high-level penicillin resistance or in children with severe infection. Empirical therapy with a third-generation parenteral cephalosporin (ceftriaxone or cefotaxime) should be prescribed for infants and children who are hospitalized and not fully immunized; in regions where local epidemiology of invasive pneumococcal strains documents high-level penicillin resistance; or for infants and children with life-threatening infection, including those with empyema. Complications may be systemic, with meningitis, carditis, peritonitis, and septic arthritis resulting from bacteremia. Pulmonary complications include pleural effusion and empyema. Inappropriate secretion of antidiuretic hormone is common and may cause a clinically significant reduction of serum sodium.

Group A *Streptococcus*

Also known as *S pyogenes*, Group A β-hemolytic *Streptococcus* is an uncommon cause of pneumonia. It is important because the clinical course is aggressive and may result in necrotizing pneumonia. The clinical appearance of the child includes fever, chills, lethargy, cough, and dyspnea. The most common radiographic pattern is a patchy bronchopneumonia, but in a

minority of cases there is lobar consolidation. Cavitation may occur, as well as pleural effusion with progression to fibrinopurulent empyema.

The response to antibiotics tends to be slow, even with selection of an appropriate agent such as penicillin or ampicillin. Clindamycin, a ribosomal agent, may be added as an adjunct in toxin-mediated disease. Penicillin is the treatment of choice, although ampicillin is an alternative. Complications are common and include pneumothorax, pneumatoceles, bronchiectasis, and bronchopleural fistula.

Staphylococcal Pneumonia

S aureus is an uncommon cause of pneumonia in children who are immunocompetent, but it does occur in infancy. It also occurs more commonly after influenza infection and other viral URIs. Staphylococci are gram-positive organisms that occur in clusters. Pneumonia results from inhalation of organisms or from bacteremic spread. The clinical picture varies from a mild respiratory infection with fever, cough, and tachypnea to a rapidly progressive illness with dyspnea, cyanosis, and septic shock. The initial radiographic appearance is multiple nodular infiltrates, usually unilateral, which in a few days become cavitary, and pneumatoceles subsequently form. Pneumothorax is common, especially in infants receiving ventilation, and empyema is present in most cases.

The scenario described in the previous paragraph would be likely diagnosed as *S aureus* in an infant, but if the same findings were present in an older child, other organisms would be more likely, such as *Escherichia coli*, *Pseudomonas*, or *Klebsiella*. It is likely that the relative prevalence from pneumococcus to *S aureus* is increasing in older children and that there are increasing numbers of children with pneumonia caused by methicillin-resistant *S aureus*.[8]

If staphylococcal pneumonia is suspected, the increased prevalence of methicillin-resistant *S aureus* may require vancomycin or clindamycin for initial treatment until the sensitivities are known. Alternative agents include trimethoprim/sulfamethoxazole and ceftaroline fosamil, which has been shown to be an effective agent for treatment of pediatric CAP, and linezolid. Daptomycin is inactivated by surfactant and should therefore not be used to treat pneumonia.

Gram-Negative Bacteria

Pseudomonas aeruginosa

Pseudomonas is a gram-negative bacterium that has a predilection to moist environments. It is common to acquire *Pseudomonas*, with colonization in more than 50% of humans, and *Pseudomonas* often causes nosocomial infection. It is an unusual cause of pneumonia in children who are healthy.

Pneumonia caused by *Pseudomonas* is a common complication in patients with endotracheal tubes or tracheostomy. It is the dominant organism in cystic fibrosis (CF). It occurs more frequently in children with HIV infection, neutropenia, and complement deficiency[10] and those who are immunosuppressed. It is the most common cause of pneumonia in the intensive care environment. It also has been reported after exposure in hot tub spas.

Although the typical color of sputum produced in pseudomonal pneumonia is green, this color may be seen with pneumococcal and *Haemophilus* infections. The progression of *Pseudomonas* pneumonia to necrotizing bronchopneumonia may be rapid if untreated. Pleural effusion is common, and the pneumonia may have a lobar or diffuse bilateral bronchopneumonia radiographic pattern.

For children with chronic *Pseudomonas* infection, especially those with CF, there is a major problem of resistance when therapy with a single antibiotic is used. Therefore, the use of 2 antibiotics (a semisynthetic penicillin along with an aminoglycoside) is often indicated.

Burkholderia cepacia

Pseudomonas cepacia was described initially by Walter Burkholder in 1949 and is now named *B cepacia*. It is an important pathogen in causing pneumonia in patients with CF and has been reported to cause pneumonia in patients who are immunocompromised. *B cepacia* does not typically cause pneumonia in children who are healthy.

Klebsiella pneumoniae

K pneumoniae is a gram-negative rod-shaped bacillus and is clinically the most important member of the *Klebsiella* genus of Enterobacteriaceae. Pneumonia as a result of *K pneumoniae* is typically a nosocomial infection. It may also be community acquired, although this is rare in children who are otherwise healthy. Pneumonia tends to occur in children who are immunocompromised or debilitated. Pneumonia as a result of *K pneumoniae* is associated with an acute onset with fever and chills. The cough is productive and yields abundant thick sputum that is typically tinged with blood and is known as *red currant jelly sputum*. Pneumonia is usually complicated, and abscess formation, cavitation, and empyema are common. Infection is more commonly unilateral, occurring typically in the upper lobes. Hospitalization is indicated, including for CAP, because even with treatment, there is clinically significant mortality. Many *Klebsiella* organisms are resistant to various antimicrobials, and empirical therapy should take this into account. The potential choice is wide, including third-generation cephalosporins (eg, cefotaxime or ceftriaxone), cefepime, carbapenems (eg, meropenem), aminoglycosides, and quinolones. Infectious disease consultation is advisable.

Legionella pneumophila

Legionnaires' disease was first recognized in 1976 at an American Legion convention in Philadelphia. The organism that caused an outbreak of pneumonia was identified as a gram-negative bacillus, *L pneumophila*. Although an unusual cause of pneumonia in children, it is important to recognize. It is more common in children who are immunosuppressed, and more than one-third of pediatric cases have been in children younger than 1 year. Transmission occurs via aerosolization and inhalation or aspiration of water containing the organism. It has been linked to contaminated water in hospitals and respiratory therapy equipment, as well as cooling towers; central air conditioning systems; evaporative coolers; hot water systems, including showers and hot tub spas; and ice-making machines. The disease is particularly prevalent in hotels, cruise ships, and hospitals that have outdated cooling systems. The incubation period is 2 to 10 days; for milder disease, known as *Pontiac fever*, the incubation period is 1 to 2 days.

Clinical Features

Legionnaires' disease manifests with fever, chills, and cough, which is initially nonproductive. Constitutional symptoms include headache, muscle ache, and sometimes ataxia (loss of coordination) and diarrhea or vomiting. The lung examination typically reveals crackles.

Blood testing may reveal abnormal hepatic or renal function, and hyponatremia is common. A CXR typically shows unilateral or bilateral bronchopneumonia.

Management

Clues to the diagnosis are the constitutional symptoms and the laboratory test abnormalities, including hyponatremia. Detection of *L pneumophila* serogroup 1 is aided by detecting *Legionella* antigen in the urine.

Azithromycin is the drug of choice for children suspected of or confirmed as having *Legionella* pneumonia. Azithromycin should initially be administered intravenously, converting to orally when the child responds.

Anaerobic Organisms

The most common anaerobic gram-negative bacilli (AGNB) to cause pneumonia are the pigmented *Prevotella* species. The *Prevotella* species are important components of the bacterial flora of the mouth, nose, and nasopharynx. They are not often cultured because of the difficulty in specimen collection and growing in the microbiology laboratory. Anaerobic organisms are common causes of chronic sinusitis, chronic mastoiditis, chronic otitis media, and retropharyngeal abscess.

Pneumonia caused by anerobic organisms results from aspiration of upper airway or gastric secretions. Severe gingival disease is a risk factor for aspiration. After aspiration, there may be progression from pneumonia to necrotizing

pneumonia, and AGNB is an important cause of lung abscess.[11] Frequently, AGNB may be recovered in culture along with Enterobacteriaceae, *Pseudomonas*, and *S aureus*.

The *Prevotella* species are resistant to penicillin and typically susceptible to amoxicillin/clavulanate, clindamycin, metronidazole, and carbapenems.

Atypical Pneumonia

The term *atypical pneumonia* is applied because the causative organism is an atypical bacteria or virus. The agents that cause atypical pneumonia include *Mycoplasma pneumoniae*, *C trachomatis*, *Chlamydia pneumoniae*, and *Chlamydia psittaci*.

M pneumoniae

M pneumoniae is the most common cause of CAP in children older than 5 years and is often called *walking pneumonia*. It is common in children younger than 5 years.[12] The true incidence is unknown because many cases are treated empirically without confirmation of the diagnosis. There are no geographic limitations, and infection occurs year-round. There may be epidemics every 3 to 7 years, and outbreaks occur in schools and universities.

M pneumoniae is called *Mycoplasma* because of the plasticity of the bacterial forms, which resemble fungal elements. Instead of a cell wall there is a cell membrane containing sterols, which are not present in other bacteria or viruses. Unlike viruses, they do not require a cell to replicate and can grow in cell-free media, and they contain both RNA and DNA.

Clinical Features

M pneumoniae infections usually start with a URI with pharyngitis, cough, headache, and myalgias. There may be fever, which is usually less than 39°C (102°F). The cough is initially nonproductive and can be severe and debilitating. Blood streaking of the sputum is not uncommon, and the coughing may cause chest pain that is nonpleuritic. In 5% to 10% of children, the URI progresses to bronchitis or pneumonia. Small pleural effusions can occur in 5% to 20% of patients. Cutaneous manifestations are common and include maculopapular rash and erythema nodosum. Extrapulmonary symptoms are not uncommon and include bullous myringitis, which supports the diagnosis of *Mycoplasma*.

In sickle cell disease, a *Mycoplasma* infection may be severe and is considered an important cause of acute chest syndrome. It also can be severe in Down syndrome, especially in those with congenital cardiac disease. Both *Mycoplasma* and *Chlamydia* cause exacerbations of asthma in children and adolescents.

The physical examination usually reveals oropharyngeal inflammation. The chest examination results may be relatively benign, with few crackles and rhonchi, at the same time that a CXR shows clinically significant findings of pneumonia. Wheezing may occur, particularly if the child has asthma.

Laboratory

Cold agglutinins should not be used to confirm the diagnosis because they are nonspecific (only about 75% are positive). *Mycoplasma* immunoglobulins M and G may be useful to confirm the diagnosis, with a sensitivity of approximately 98% if both are measured. Immunoglobulin M results may be negative in the first week of illness and may be indicative of past infection. A PCR test is highly sensitive, but the results may reflect colonization when the sample is obtained from the nasopharynx.

Imaging

Infiltrates are more likely to be bilateral than unilateral. There may be lobar, multifocal, or diffuse disease with reticular infiltrates.[11] Pleural effusions are present in about 20% of cases (though they tend to be small), and hilar adenopathy is seen in 7% to 22%.

Management

First-line treatment for *M pneumoniae* is macrolide antibiotics, although there are now reports of macrolide resistance. Tetracycline is active, in particular doxycycline, and can be used for adolescents; if administered to children younger than 8 years, the duration should be 21 days or fewer. The newer fluoroquinolones are effective, but not as effective as macrolides. The lack of cell wall predicts that β-lactams are not effective, nor is trimethoprim. Most cases of CAP improve in a matter of days with no residual findings.

C trachomatis

C trachomatis is an important cause of sexually transmitted infection and trachoma. Although uncommon in the United States, trachoma is the most common cause of blindness in the world. *C trachomatis* causes pneumonia, especially in infants. Approximately 5% to 22% of pregnant women have *C trachomatis* of the cervix, and 30% to 50% of these will show culture evidence of infection. The infection in the newborn is conjunctivitis with or without nasopharyngitis, which in some cases results in neonatal pneumonia.

Clinical Features

Most infants with *C trachomatis* pneumonia have a history of conjunctivitis, nasal stuffiness, and cough with tachypnea. This pneumonia is characteristically afebrile. The chest examination reveals scattered crackles; wheezing is absent.

Imaging

The CXR shows either a lobar or interstitial pattern.

Management

The first-line therapy to treat infants with *C trachomatis* pneumonia is erythromycin 50 mg/kg/day divided every 6 hours for 14 days. Azithromycin is an alternative.

C psittaci

C psittaci causes psittacosis or ornithosis after exposure to infected birds. *Ornithosis* is the preferred name because it can be caused by any bird, including parrots, chickens, ducks, turkeys, pigeons, and sparrows. It is transmitted from birds to humans by either direct contact or aerosolization. It is much less common since the imposition of a quarantine for 30 days for imported birds and the introduction of bird feed laced with antibiotics.

It is quite difficult to diagnose, and it is possible that it is more common than appreciated. The most common disease is a mild pneumonia, but it can produce a more fulminant illness. There is fever without elevation of the pulse, which is usually associated with fever. Clues to the diagnosis include splenomegaly; a blanching erythematous maculopapular rash; and signs of hepatitis, disseminated intravascular coagulation, or meningoencephalitis, any of which may be present. *C psittaci* is sensitive to both macrolides and tetracyclines. Because the antibiotic only kills the organism when it is active, the bird should be treated for 45 days.

C pneumoniae

C pneumoniae causes a mild pneumonia or bronchitis in older children, adolescents, and adults. Approximately 50% of young adults have serological evidence of prior infection. *C pneumoniae* has been reported to cause 10% to 20% of CAP, but this is likely an overestimate. It is transmitted from person to person by respiratory secretion transfer. The incubation period is approximately 3 to 4 weeks.

Initially there is a URI, and many patients have no further symptoms. The symptoms can be prolonged, and helpful in the diagnosis is the presence of hoarseness and headache; fever is uncommon. The physical examination reveals crackles and rhonchi. Even with treatment, *C pneumoniae* tends to respond more slowly than does *Mycoplasma*, which may also be a clue to the diagnosis. Many cases are self-limiting and mild. Recommendations for treatment include macrolides as first-line treatment, with tetracyclines or fluoroquinolones as alternatives. Therapy duration depends on symptoms and typically is 10 to 14 days. Mortality of 9.8% has been reported in patients with sickle cell disease.[13]

Table 20-2 provides a template for management of CAP.

Table 20-2. Antibiotics for Community-Acquired Pneumonia

Age	Typical Bacterial Pneumonia	Atypical Bacterial Pneumonia
Outpatient: younger than 5 years	Amoxicillin (orally)	Azithromycin (orally)
	Alternative: amoxicillin + clavulanate (orally)	Alternatives: clarithromycin, erythromycin (orally)
Outpatient: 5 years or older	Amoxicillin (orally)	Azithromycin (orally)
	Alternative: amoxicillin + clavulanate (orally)	Alternatives: clarithromycin, erythromycin, doxycycline (<21 days) (orally), levofloxacin
Inpatient: all ages	Ampicillin or penicillin G	Azithromycin + β-lactam
	Alternative: ceftriaxone,	Alternatives: clarithromycin, erythromycin, doxycycline (<21 days), levofloxacin
	If MRSA suspected: add vancomycin or clindamycin	

Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.

Other Causes of Bacterial Pneumonia

Tularemia, anthrax, and plague are uncommon bacterial syndromes in which pneumonia may be a prominent feature. They should raise the suspicion of bioterrorism.

When selecting initial empirical antibiotics for a child with CAP, it is important to consider the child's age and immunization status as well as treatment locale (**Table 20-2**).[8] Because *S pneumoniae* is the most common bacterial organism, empirical therapy is initially targeted at that organism.

Previously, the recommended dosing interval for amoxicillin was twice daily, but administering the antibiotic 3 times per day significantly increases the active time kill.[15] Local microbiological and epidemiological information should be considered when selecting empirical antibiotic therapy in both the inpatient and outpatient settings. If a specific organism is identified, the antibiotic choice can be directed more specifically.[15] Additional antibiotic dosing and schedules can be found in Chapter 58, Antibiotics for Pulmonary Conditions.

Fungal Pneumonia

The most common endemic fungal pneumonias include histoplasmosis, coccidioidomycosis, blastomycosis, and cryptococcosis (caused by *Cryptococcus gatii,* not *Cryptococcus neoformans*). These infections are predominantly geographically restricted and can occur in those who are healthy as well as those who are immunocompromised (**Table 20-3**). With a more mobile population, the pneumonia might be discovered after return to home from travel to an endemic area, emphasizing the importance of a travel history.

The initial infection appears similar to CAP, and constitutional symptoms are frequent. The severity of infection ranges from barely noticeable to life-threatening acute respiratory distress syndrome. Other organ systems are commonly affected with dissemination of the infection (**Table 20-4**).

Table 20-3. Summary of Geographically Restricted Fungal Pneumonia

Organism	Geographic Area	High-Risk Exposures	Chest Radiographic Findings (Acute)	Notable Features
Histoplasmosis	Mississippi and Ohio River Valleys	Old buildings Chicken coops Bird roosts Caves Wood piles	Mediastinal or hilar adenopathy Diffuse or focal opacity	Popcorn calcifications
Coccidioidomycosis	Desert Southwest	Deserts Archeological digs Dust storms Prairie dog habitat	Diffuse or focal opacity	Eosinophilia Prolonged fatigue
Blastomycosis	Upper Midwest and Southeast	Rivers and wetlands Wooded areas Buildings with bat droppings	Diffuse or focal opacity	ARDS in 50%–70% (high mortality)

Abbreviation: ARDS, acute respiratory distress syndrome.

Adapted from Stillwell PC. Fungal pneumonia. In: Stokes DC, Dozor AJ, eds. *Pediatric Pulmonology, Asthma, and Sleep Medicine: A Quick Reference Guide.* American Academy of Pediatrics; 2018:421–426.

Table 20-4. Organs Commonly Infected With Geographically Restricted Fungal Diseases

Organ	Disease/Organism			
	Coccidioidomycosis	Histoplasmosis	Blastomycosis	Cryptococcal Infection
Lung	+++	+++	++	++
Brain and meninges	++	–	–	+++
Bone marrow and lymph nodes	–	+++	+++	–
Skin, bone, and joints	++	–	+++	–

Abbreviations: –, uncommon; ++, common; +++, very common.

Adapted from Stillwell PC. Fungal pneumonia. In: Stokes DC, Dozor AJ, eds. *Pediatric Pulmonology, Asthma, and Sleep Medicine: A Quick Reference Guide.* American Academy of Pediatrics; 2018:421–426.

The diagnosis of endemic fungal pneumonia can be challenging without a high index of suspicion because initially it appears similar to any other CAP and the organisms are often not identified with standard microbiological testing.[21] The patient's area of residence, travel history, and recreational or occupational activities can be suggestive of a fungal source. Radiographically, nodular opacities and hilar adenopathy can also offer clues to the nature of the infection. Acute histoplasmosis can have a radiographic appearance similar to those of tuberculosis or nontuberculous mycobacteria. Cavitary lesions are common with coccidioidomycosis. During the healing phase of these granulomatous infections, calcifications are common. Confirmation of the specific fungal organism can be established by means of culture, characteristic appearance with staining, serological testing, and antigen testing (**Table 20-5**).[21] More recently, *Aspergillus* PCR testing has been used for patients who are critically ill and suspected of having invasive *Aspergillus* pneumonia, and serum antibody testing for blastomycosis has become available to aid with the diagnosis of *Blastomyces* (anti-*Blastomyces* adhesin 1).[21]

Table 20-5. Aids in Establishing the Diagnosis of Fungal Pneumonia

Disease/Organism	Culture	Stains	Serological Testing	Antigen Testing
Histoplasmosis	+++	+ (blood and bone marrow)	++	+++ (especially urine)
Coccidioidomycosis	++	+++	+++	++ (blood test not used often)
Blastomycosis	+++	+++	++	+++ (especially urine)
Candida albicans	+++	++	Not yet	Not yet
Cryptococcus neoformans	+++	++	++	++
Aspergillus fumigatus (invasive)	+++	++	+	+++ (galactomannan)

Abbreviations: +, uncommon; ++, common; +++, very common.

Adapted from Stillwell PC. Histoplasmosis and other endemic fungal pneumonias. In: Stokes DC, Dozor AJ, eds. *Pediatric Pulmonology, Asthma, and Sleep Medicine: A Quick Reference Guide.* American Academy of Pediatrics; 2018:427–432.

Because spontaneous resolution is likely, treatment for endemic fungal pneumonia may be limited to observation if the patient experiences few symptoms and is at low risk for dissemination. Traditionally, itraconazole has been used for histoplasmosis and blastomycosis, and fluconazole has been used for coccidioidomycosis, but posaconazole and voriconazole have also been

effective against *Coccidioides*. For central nervous system infections or severe dissemination, amphotericin B may be required. Consultation with infectious disease experts is helpful in selecting the appropriate agent and duration of therapy and determining the success of therapy.

Children who are immunocompromised are at risk of developing pneumonia with opportunistic fungal organisms that typically do not infect those who are healthy (see Chapter 53, Pulmonary Complications of Immunologic Disorders, and Chapter 52, Pulmonary Manifestations of Oncologic Disease and Treatment), as well as pneumonia from organisms that do occur in those who are healthy. These opportunistic organisms include (but are not limited to) *Aspergillus fumigatus* (most common) and *Aspergillus* species, *Pneumocystis jirovecii*, *Candida albicans* and other *Candida* species, *C neoformans*, *Mucormycetes*, *Rhizopus*, *Scedosporium*, *Bipolaris*, and *Curvularia*. Prophylaxis against *P jirovecii* with trimethoprim/sulfamethoxazole can substantially reduce the incidence of this pneumonia. Children who are immunocompromised and have these fungal infections are usually very sick and may require intensive care. The correct diagnosis can be elusive and may require multiple methods of detection, including tissue biopsy.[21]

Prevention of Pneumonia in Children

The risk of pneumonia from many organisms can be reduced or eliminated by using the childhood immunization schedule recommended by the Centers for Disease Control and Prevention (CDC). Invasive pulmonary infections with *H influenzae* type B, *S pneumoniae*, *B pertussis*, varicella, and measles have been reduced substantially or prevented by immunizations.[22] Influenza immunization, recommended for all children 6 months or older, can reduce the number of children infected and reduce the severity of the infection for those who get influenza despite vaccination. COVID-19 vaccination is recommended by the CDC for all children 6 months and older, including getting boosters if eligible. Having the children in a community robustly immunized can help reduce the incidence of pneumonia by herd immunity.

Attempts at reducing RSV infections by means of vaccination have been somewhat more difficult than for other organisms. The prophylaxis currently available consists of only palivizumab, and revised guidelines to optimize patient outcomes balanced with cost-effectiveness limit its widespread use.

Reducing adverse environmental exposures such as tobacco smoke and infectious contacts can help reduce the risk of developing pneumonia. Relieving unsanitary or crowded living conditions should also reduce the risk of pneumonia. Although a cleaner air policy has improved children's overall respiratory health, there are challenges to establish that cleaner breathing conditions can specifically reduce the occurrence of childhood pneumonia.

In 2000, the CDC recommended PCV7 for children in the United States to reduce the incidence of pneumococcal pneumonia. The original vaccine, which contained 7 serotypes, was highly effective, but two-thirds of the invasive pneumococcal disease was caused by 6 serotypes not included in this vaccine. Subsequently, PCV13 was approved in February 2010 and is recommended for all children from 2 months through 5 years of age. Pneumovax-23 is approved for use in persons 50 years of age or older and persons younger than 2 years who are at increased risk of pneumococcal disease.

The CDC recommends that all individuals 6 months or older get a seasonal flu vaccine. The seasonal flu vaccine protects against 4 influenza viruses that research indicates will be most common during the upcoming season. The CDC also recommends that people in contact with certain groups of children get a seasonal flu vaccine the better to protect the child (or children) in their lives from the flu.

The CDC recommends that the following contacts of children receive seasonal influenza vaccination:

- Close contacts of children younger than 5 years (people who live with them), especially those younger than 6 months
- Out-of-home caregivers (nannies, child care providers, etc) of children younger than 5 years
- People who live with or have other close contact with a child or children of any age with a chronic health problem (asthma, diabetes, etc)
- All health care workers, to keep from spreading the flu to their patients

Additional considerations are *H influenzae* type B vaccine and varicella vaccine.

When to Refer

Most children with CAP will not require a consultation. If there are complications, such as pleural effusion or prolonged hypoxia, consultation with a pulmonologist may be indicated. If the child has a chronic illness, consultation with the specialist who is involved in the child's long-term care may be helpful. Consultation with infectious diseases or allergy specialists is indicated for children with allergies, comorbid conditions, or unresponsiveness to antibiotics.

When to Admit

Children with pneumonia and a chronic illness—for example, if they are immunocompromised—may require hospitalization. If the degree of respiratory distress is clinically significant, if there is hypoxia, and if they appear septic, they may require hospitalization. Currently, validated screening

systems do not exist to help predict which children with pneumonia should be hospitalized. Hospitalization is indicated with the following:

- Oxygen saturation consistently less than 90% (definite)
- Suspected sepsis (definite)
- Severe dehydration (definite)
- Inability to drink fluids (possible)
- Moderate or severe respiratory distress (possible)
- Failure of outpatient antibiotic treatment (clinical judgment)
- Home circumstance or social situation raising concerns (likely)
- Infants younger than 6 months (unless ideal caretaker)

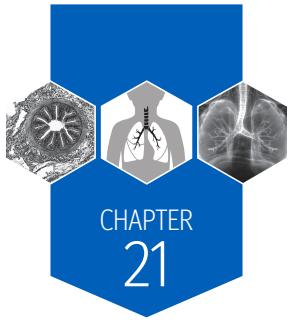
key points

- The cause of pneumonia is closely related to the age of the child.
- Imaging studies do not help differentiate viral from bacterial lower respiratory tract infections.
- Chest radiography is not necessary to diagnose pneumonia.
- Computed tomography is indicated for evaluation of complications of pneumonia.
- Ultrasonography is useful to characterize pleural effusion or empyema.
- Management depends on the age of the child and the likely diagnosis.
- Preventive immunization should follow CDC guidelines.

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Complications of Pneumonia

Paul C. Stillwell, MD, FAAP

Introduction

Community-acquired pneumonia (CAP) is a serious global health issue and a common cause of mortality in underserved areas of the world.[1] The prevalence of CAP in the United States is approximately 35 to 40 per 1,000 children younger than 4 years and about 10 per 1,000 in teenagers; fewer than 1% die of CAP.[2] A full recovery is the expected outcome for most children, with or without antibiotic therapy. Complications are not frequent but are a major source of morbidity when they occur. Complications of CAP include parapneumonic effusion, empyema, abscess, necrotizing pneumonia, bronchopleural fistula, and pneumatocele formation.[3–5]

Parapneumonic Effusion

Pleural effusions are an abnormal collection of fluid in the pleural space.[6] The most common etiology in children is a parapneumonic effusion, which occurs in approximately 13% of CAP cases.[2,7] While a wide variety of organisms are associated with parapneumonic effusions, *Streptococcus pneumoniae* and *Staphylococcus aureus* are the most common (**Box 21-1**).[4,7,8]

The evolution of a parapneumonic effusion occurs in 3 stages. The initial effusion, which is the exudative phase, is thin fluid with a yellow color. It is an inflammatory response of the pleura to the underlying parenchymal infection. The fluid is free flowing in the pleural space and is usually exudative in nature according to Light's criteria, which, while not validated in pediatrics, are often helpful in assessing effusions.[6] This phase lasts 2 to 5 days and is followed by the fibrinopurulent phase, which occurs 5 to 10 days after the onset of the pneumonia. Fibrin strands limit the flow of fluid in the pleural space, causing loculations. This phase often involves an empyema with a high white blood cell count and perhaps even pus in the pleural space. The third phase is the organizing phase, usually occurring during the second week of illness, when a thick fibrous peel forms in the pleural space; this is the last step in healing. If the fibrous peel does not resolve with progressive healing, a trapped lung may occur.

Box 21-1

Infections Associated With Parapneumonic Effusions in Children

Bacterial Causes

- Aerobic
  - *Streptococcus pneumoniae*
  - *Staphylococcus aureus*
  - *Streptococcus pyogenes*
- Anaerobic
  - *Bacteroides* species
  - *Peptostreptococcus* species
  - *Peptococcus* species
  - *Fusobacterium* species
- Atypical
  - *Mycoplasma pneumoniae*
  - *Actinomyces* species
  - *Nocardia* species
- *Mycobacteria tuberculosis*

Nonbacterial Infectious Causes

- Viral
  - Adenovirus
  - Influenza
  - Parainfluenza viruses
- Parasitic
  - *Paragonimus* species
  - *Cysticercus* species
  - *Entamoeba histolytica*
- Fungal
  - *Coccidioides immitis*

From Kupfer O, Stillwell PC. Complications of pneumonia: pleural effusions. In: Stokes DC, Dozor AJ, eds. *Pediatric Pulmonology, Asthma, and Sleep Medicine: A Quick Reference Guide.* American Academy of Pediatrics; 2018:433–438.

Clinical Presentation

The usual clinical presentation of a parapneumonic effusion or an empyema is a child with CAP (see Chapter 19, Viral Pneumonia, and Chapter 20, Nonviral Pneumonia) who has progressive respiratory deterioration with ongoing fevers, increased work of breathing, and chest pain.[3,7] This may progress despite the initiation of antibiotic treatment. Examination reveals decreased-intensity breath sounds over the affected side and dullness to percussion. Inspiratory crackles may be present above the area of the effusion but may not be appreciated directly over the effusion.

Diagnostic Considerations

If a parapneumonic effusion is suspected, the usual initial evaluation is a chest radiograph, both frontal and lateral views (**Figure 21-1**). Typically, there is an opacity representing the pneumonia and a fluid margin tracking up the chest wall (meniscus sign). A lateral decubitus film (affected side down; **Figure 21-2**) will clearly show the effusion if the fluid is free flowing; if there are loculations, this may not be evident.[9]

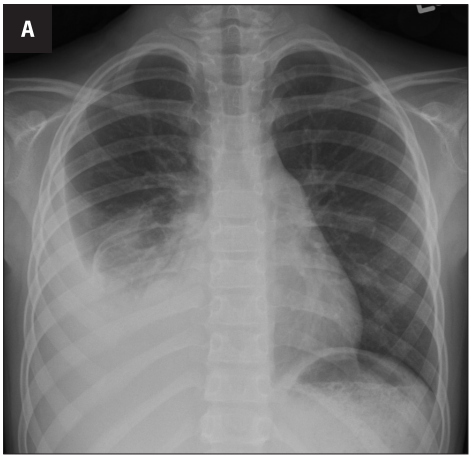




Figure 21-1. Frontal and lateral chest radiographic images of an 8-year-old with a right lower lobe pneumonia and a right-sided parapneumonic effusion.

Reproduced with permission from PREP Pulmonology.

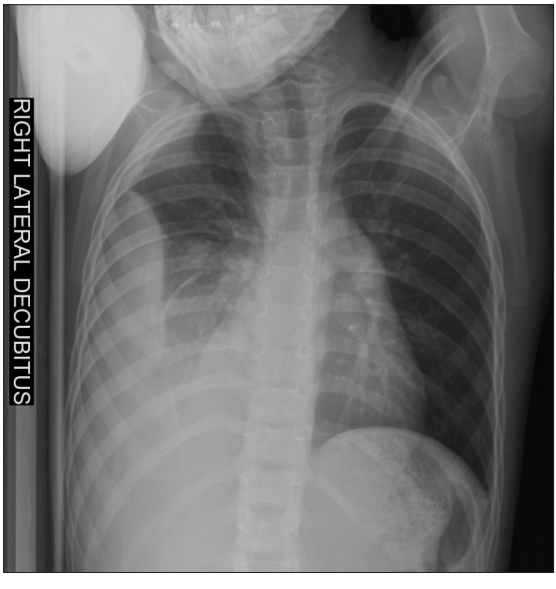


Figure 21-2. Right-side-down lateral decubitus radiograph shows the pleural fluid extending cephalad in the pleural space.

Reproduced with permission from PREP Pulmonology.

Ultrasonography (US) is an excellent, nontraumatic, radiation-free method of evaluating children for a parapneumonic effusion. It can approximate the size of the effusion, document whether the fluid is freely flowing or loculated, and determine the fluid's echogenicity. In addition, US can help guide the best location for a successful thoracentesis.[10] (**Figure 21-3**)

A chest computed tomographic (CT) scan will provide more exquisite detail of the lung and pleural space than either chest radiography or US (**Figure 21-4**). However, a CT scan is not often needed if the US is fully informative and satisfactory for managing the effusion.[9]

Sampling the effusion may help delineate a specific infectious etiology.[6] This can be done by thoracentesis or at the time a chest tube is inserted. The likelihood of a positive bacterial culture is reduced if the child has already received antibiotic therapy. Studies commonly obtained include white blood cell count with differential (see Chapter 29, Pleural Effusion [Noninfectious]), Gram stain, bacterial culture, pH, lactate dehydrogenase, and total protein. The use of Light's criteria to assess exudate versus transudate has not been validated in children and may not be helpful if the fluid is clearly pus; however, Light's



Figure 21-3. Pleural effusion. Longitudinal ultrasonographic image of the right chest demonstrates a septated, mixed echogenicity collection in the right pleural space, indicating complex effusion. Some of the echogenicity is due to opacified lung with pneumonia.

Image courtesy of Jason Weinman, MD, Department of Radiology, University of Colorado School of Medicine Anschutz Medical Campus and Children's Hospital Colorado.

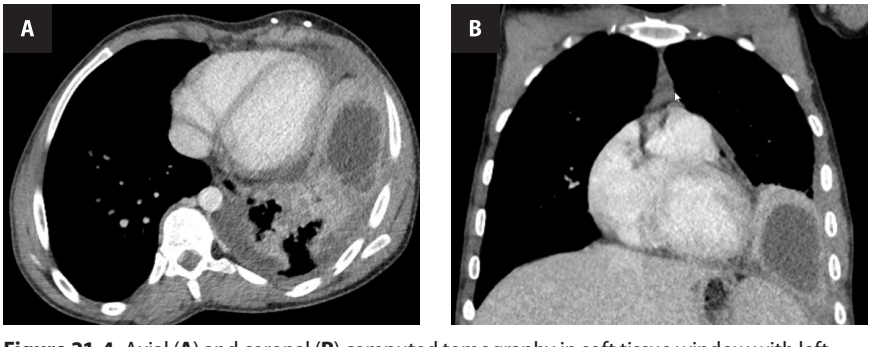


Figure 21-4. Axial (**A**) and coronal (**B**) computed tomography in soft tissue window with left lower lobe pneumonia and loculated left pleural effusion with peripheral contrast enhancement, consistent with empyema.

Courtesy of Mariangeles Medina Perez, MD.

criteria may be helpful with effusions of unknown etiology.[6,11] Patients with CAP and effusions are more likely to have positive blood culture findings, but the yield from a blood culture remains only about 20% to 30%.[3,4,7] The use of polymerase chain reaction to detect streptococcal infection in the pleural space may increase the ability to specify the offending organism.[7]

The parapneumonic effusion is considered an empyema if there is pus visible in the pleural fluid, if the Gram stain is positive, or if the white blood cell count is greater than 15,000/μL. The incidence of empyema-complicating CAP in hospitalized children is between 0.6% and 2%.[3,4,7] The incidence of complex pneumonia seems to be increasing despite the widespread introduction of pneumococcal conjugate vaccine.[12,13] The presence of an empyema usually mandates more aggressive drainage than that needed for a simple parapneumonic effusion.

Management

There are several potential approaches to managing the parapneumonic effusion, including simply treating with antibiotics,[14] antibiotics with chest tube drainage, antibiotics with repeated thoracenteses, antibiotics with chest tube drainage and fibrinolytics, or video-assisted thoracoscopic surgery (VATS).[15–17] Simple observation with antibiotic treatment and antibiotics with repeated thoracenteses are rarely used in tertiary care children's hospitals in current practice. The decision regarding chest tube insertion is based on the acuity of illness and the size of the effusion. Drainage is mandated if the effusion is large enough to compromise ventilation or cardiac output by compressing vital structures. With increased use of antibiotics along with chest tube insertion and fibrinolytics, the need for VATS has decreased.[15–18]

Prognosis for Complex or Complicated Community-Acquired Pneumonia

Most patients return to their usual state of health in 4 to 8 weeks. Findings on follow-up chest radiographs in 3 to 6 months are usually normal.[19] Typically, otherwise healthy children with no previous bacterial infections will not require a full immune workup. Children who do not recover quickly or who have atypical medical histories may require further evaluation.

Lung Abscess

The incidence of lung abscess has decreased with the use of more potent and broad-spectrum antibiotics.[20,21] Children at risk for pulmonary abscess often have had a period of altered consciousness, either transiently from anesthesia, seizure, or intoxication or as part of a more global neurologic deficit such as that which may be present with spastic quadriplegia and intellectual disability or traumatic brain injury.[20,21] The most common organisms are presented in **Box 21-2**.[22]

Box 21-2

Organisms Associated With Aspiration Pneumonia and Pulmonary Abscess

Aerobes	Anaerobes
– *Pseudomonas aeruginosa*	– *Peptostreptococcus* spp
– *Streptococcus pneumoniae*	– *Prevotella*
– *Escherichia coli*	– *Porphyromonas* spp
– *Klebsiella pneumoniae*	– *Fusobacterium nucleatum*
– *Staphylococcus aureus*	– *Bacteroides fragilis*
– Alpha hemolytic *Streptococcus*	– *Bacteroides* spp
– *Haemophilus influenzae*	– *Bifidobacterium* spp

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Many of these organisms are anaerobic mouth flora, which should be taken into account when selecting the antibiotic strategy. Occasionally, a patient with underlying lung disease or immunodeficiency will have a lung abscess as a result of impaired healing from CAP.[17,22]

Clinical Presentation

Fever and cough are the most common symptoms, followed by dyspnea, chest pain, anorexia, purulent sputum, rhinorrhea, and malaise/lethargy. If the infection is anaerobic, the breath may smell fetid and the fevers may be only low grade.[22] There may be few findings on examination since a single abscess is usually isolated away from the chest wall surface and is not communicating well with the airways.

Diagnostic Considerations

Chest radiography usually identifies a round-shaped opacity, often in an upper lobe distribution, that may or may not have an air-fluid level (**Figure 21-5A**). The CT scan provides additional detail to support the diagnosis of pulmonary abscess (**Figure 21-5B**).[17] Ultrasonography can be a useful complement to chest radiography.[10]

Infections with *Mycobacterium tuberculosis* or atypical mycobacteria and vasculitic disease such as granulomatosis with polyangiitis may have a similar radiographic appearance and should be considered in the differential diagnosis of pulmonary abscesses (see Chapter 23, Tuberculosis; Chapter 24, Nontuberculous Mycobacteria; and Chapter 26, Respiratory Disorders Associated With Systemic Inflammatory Diseases).[17]

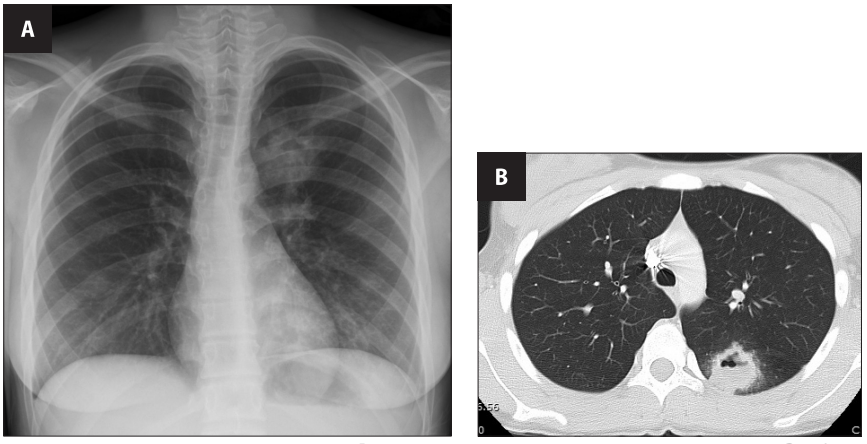


Figure 21-5. Frontal chest radiograph (**A**) and chest computed tomographic (CT) scan (**B**) of a 17-year-old experiencing chest pain after sedation for an orthodontic procedure. The chest radiograph shows a round opacity with central lucency in the left upper lobe. The CT scan confirms the presence of a thick-walled abscess in the left upper lobe, most likely from aspiration of bacteria during the procedure.

Reproduced with permission from PREP Pulmonology.

Management

Treatment of a pulmonary abscess is usually successful with antibiotic therapy alone.[17,20–22] The decision regarding hospitalization should be based on the severity of illness; many children with pulmonary abscesses are well enough to be treated on an outpatient basis. Surgical intervention or interventional radiology is seldom required unless the course of antibiotic therapy is not successful. The empiric antibiotics selected usually include anaerobic coverage (eg, clindamycin or amoxicillin) and a cephalosporin. The choice of oral or intravenous antibiotic depends on the severity of the illness and the likelihood of successful oral administration.[20] The duration of treatment is not well known, but it is often 2 weeks or longer.[22]

Prognosis

Limited data are available regarding the outcome of lung abscesses in children. The prognosis is generally very good for full and complete recovery unless there is underlying lung disease or immunodeficiency. Resolution of the radiographic abnormality may take weeks to months.[20]

Necrotizing Pneumonia and Bronchopleural Fistulas

Necrotizing pneumonia occurs when the CAP is not successfully contained and significant parenchymal damage occurs.[23–25] The most commonly identified organism is *S pneumoniae* and occasionally *S aureus* (usually methicillin resistant).[23,24] When air leaks are present, they often heal very slowly and a bronchopleural fistula persists, which can result in a prolonged need for chest tube drainage.[25]

Clinical Presentation and Diagnosis

Children with necrotizing pneumonia have presenting signs and symptoms that are similar to those in uncomplicated pneumonia, except their illness progresses without improvement and they usually become severely ill.[23–25] The chest radiograph shows a large opacity involving many lung segments, and chest CT is usually required to demonstrate the multiple cavitary lesions within the consolidation characteristic of necrotizing pneumonia[23–25] (**Figure 21-6**, **Figure 21-7**). If a bronchopleural fistula is present, there will be evidence of a pneumothorax and an ongoing air leak in the water seal component of the chest tube apparatus (**Figure 21-8**).

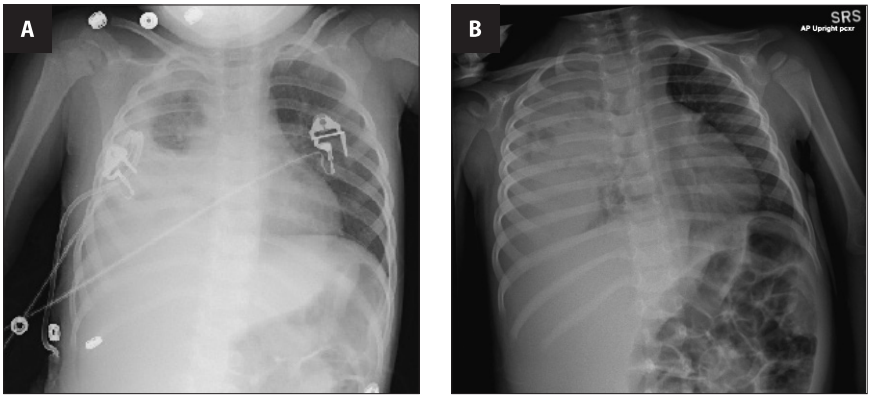


Figure 21-6. A, Frontal radiograph of a previously healthy 2-year-old with progressive respiratory symptoms 10 days after respiratory syncytial virus and entero/rhinovirus upper respiratory tract infection. **B** is from the same patient 3 days later, showing near complete opacification of the right hemithorax and suggestions of lucencies, consistent with necrotizing pneumonia.

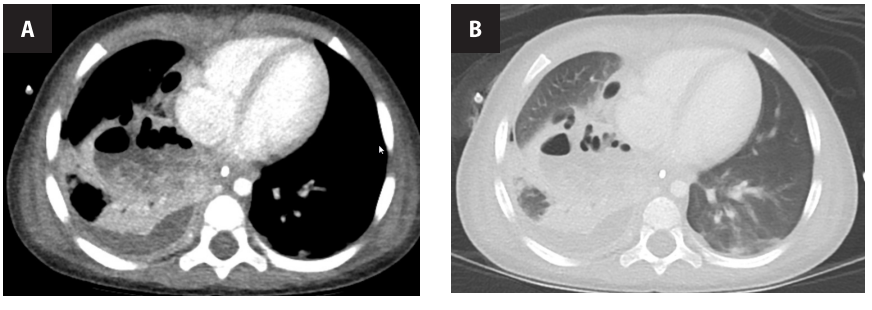


Figure 21-7. Axial computed tomography images in soft tissue and lung window show necrotizing pneumonia of the right lower lobe and a right posterior empyema.

Courtesy of Mariangeles Medina Perez, MD.

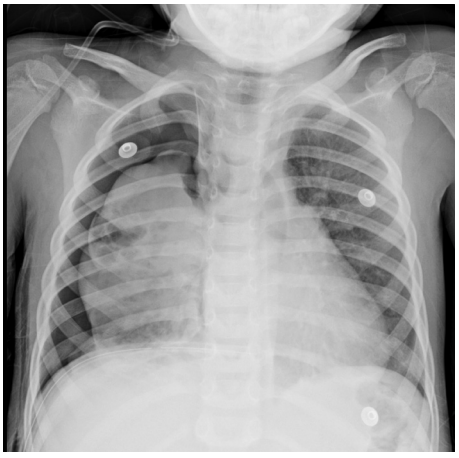


Figure 21-8. Chest radiograph of a 5-year-old with complications from necrotizing pneumonia shows a persistent pneumothorax due to a bronchopleural fistula.

Management

Because most children with necrotizing pneumonia are very sick, treatment is typically initiated in the intensive care unit setting with intravenous antibiotics.[23] If an infecting organism has been identified, antibiotics targeting that organism should be selected. Often, no specific organism can be identified so the antibiotic therapy is targeted toward resistant *S pneumoniae* as well as *S aureus*.[23,24] It is common to insert a chest tube for drainage of associated empyemas, drainage of the pneumothorax, or both. The optimal duration of treatment is not known, but often several weeks of antibiotics are needed.[23,24]

Prognosis

The mortality rate for necrotizing pneumonia is higher than that for other complicated pneumonia and may reach as high as 5.5% to 7%.[23] Children who survive necrotizing pneumonia often return to baseline with normal pulmonary function test results and normal chest radiographic findings.

Pneumatocele

A pneumatocele is a thin-walled cyst located in the lung parenchyma. It can be a single cyst or can encompass several cysts. Pneumatoceles most commonly occur as a pneumonia heals, but they can also occur after hydrocarbon inhalation, trauma, or lung injury from mechanical ventilation.[26,27] It is possible that pneumatoceles, which are rare in adults and occur more frequently in younger children, are more common in developing lungs. One theory is that the pores of Kohn, which allow collateral ventilation, are not fully developed, and therefore air cannot escape from an obstructed region.

Pneumatoceles are more common in children younger than 3 years. Although bacteria are not always recovered, *S aureus* is frequently determined to be the responsible organism.

Clinical Presentation

Patients with pneumatoceles secondary to pneumonia may not have any additional findings. The pneumatoceles are usually identified as the primary pneumonia is healing and do not cause any additional symptoms.[26]

Pneumatoceles typically can be diagnosed with plain radiographs (**Figure 21-9**).

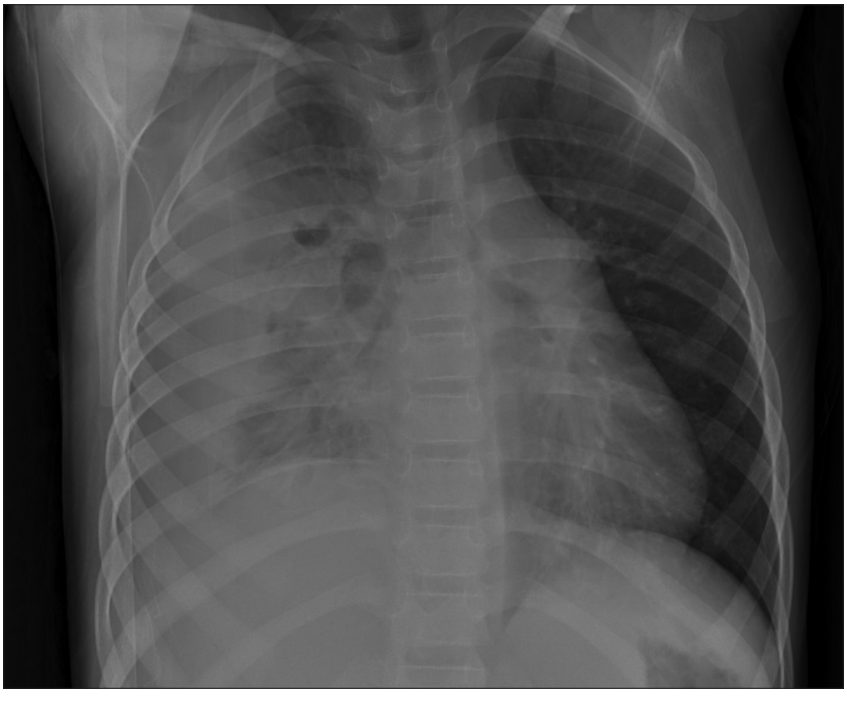


Figure 21–9. Pneumatoceles in the right middle lung zone following successful therapy for a right upper lobe pneumonia and right parapneumonic effusion in a 7-year-old.

Image courtesy of Jason Weinman, MD, Department of Radiology, University of Colorado School of Medicine Anschutz Medical Campus and Children's Hospital Colorado.

Management

Most pneumatoceles caused by infection will resolve within 2 to 6 months with successful treatment of the underlying pneumonia.[26] Children with uncomplicated cases who have few clinical complaints, minimal atelectasis, and involvement of less than 50% of the hemithorax can be observed with the expectation of spontaneous clinical improvement.[26] If the pneumatocele is complicated by a large size, an increasing size, or an infection, surgical intervention may be required.[26,27] A growing pneumatocele is a risk for pneumothorax.

Prognosis

Simple pneumatoceles have an excellent prognosis and typically resolve without treatment. Typically, there are no visible sequelae on radiographs in 2 months, though some patients may require as long as 6 months to fully recover.

When to Refer

Children with complex or complicated pneumonias are often quite ill and may require input from several specialists, including pulmonologists, infectious disease consultants, pediatric surgeons, and intensive care specialists. Therefore, early referral to a tertiary care children's facility should be considered as soon as it is recognized that the pneumonia is not a simple CAP.

When to Admit

Many of the complications of pneumonia are diagnosed in patients who have experienced failed outpatient therapy or in those who are already hospitalized. All of these patients should be treated with intravenous antibiotics, and many will require further medical and/or surgical treatment. Experienced pediatric interventional radiologists or surgeons should be involved in the care of any patient who may need chest tube placement or surgical intervention, such as VATS. Pediatric surgeons, interventional radiologists, pediatric pulmonologists, and pediatric infectious disease specialists should, as a team, help determine the best approach for the patient.

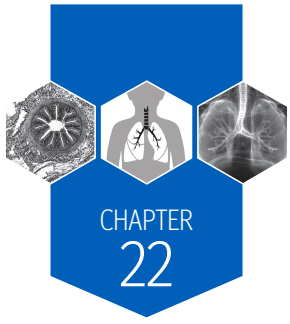
key points

- Complications of pneumonia typically require hospitalization.
- Complications are usually associated with the most common causes of CAP.
- Complications frequently require multidisciplinary care at a tertiary children's hospital.
- Even in very ill children, the long-term prognosis is generally very good.

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CHAPTER
22

Recurrent Pneumonia

Paul Houin, MD
Paul C. Stillwell, MD, FAAP

Introduction

Recurrent pneumonia is defined as 3 or more episodes of pneumonia in a lifetime or 2 episodes within a 12-month period.[1–3] In pediatric practice, the diagnosis of pneumonia is commonly established based on clinical history and physical examination findings alone without chest radiographs, despite recommendations for radiographic confirmation in community-acquired pneumonia in adults.[4] Diagnosing a pneumonia based on clinical findings alone is challenging in the pediatric population because the signs and symptoms of pneumonia, asthma, and bronchiolitis often overlap in infants.[4] Clinicians often neglect to obtain a follow-up radiograph to document resolution of the pneumonia if the patient returns to their usual state of health, making it difficult to determine if there actually has been recurrent pneumonia or whether the problem is persistent rather than recurrent.[3] Documenting resolution of pneumonia is important because the differential diagnosis of a persistent radiographic abnormality can be different than recurrent pneumonia. The lack of consistent radiographic confirmation for each episode can make it difficult to ascertain whether the abnormality recurs in the same lung segments or in a variety of different segments.[3] In under-resourced countries, where pneumonia is a major cause of childhood mortality and radiographs may be more difficult to obtain, the clinical findings of lower chest wall indrawing and rapid respiratory rate are sufficient to diagnose pneumonia and institute appropriate intervention.[5] The British Thoracic Society guidelines support the diagnosis and management of a mild, uncomplicated acute lower respiratory tract infection without using a radiograph to confirm whether a pneumonia is present.[6] Despite the British Thoracic Society guidelines, a clinician should consider radiographic confirmation for patients who seem to have frequent lower respiratory tract symptoms. Recurrent pneumonia can lead to persistent lung injury, such as bronchiectasis, if not prevented. Early identification of a potential underlying cause of recurring pneumonia may be beneficial for long-term lung health by allowing for initiation of a more targeted therapy earlier in the course of the disease.[1–3] (See **Figure 22-1**.)

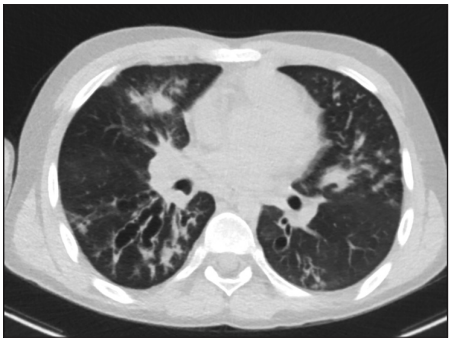


Figure 22-1. Chest computed tomography scan of an adolescent showing bronchiectasis and severe lung damage as a result of long-standing aspiration and immunodeficiency (PI3Kδ syndrome type 1 [APDS1] due to a deleterious mutation in *PIK3CD*).

Pathophysiology

Box 22-1 categorizes conditions causing recurrent pneumonia in children. A careful history, physical examination, and review of the radiographs will help tailor the investigation to identify the underlying cause.[1–3] Several risk factors for recurrent pneumonia have been established, including a history of bronchopulmonary dysplasia, atopy with either allergic rhinitis or eczema, tobacco exposure, overcrowding, and air pollution (both indoor and outdoor).[1]

Because of the high frequency of asthma in developed countries, a clinician should evaluate for signs of asthma as the cause of recurrent acute lower respiratory tract infections.[3] The mechanism of recurrent pneumonia in the child with asthma is likely mucus plugging during acute asthma exacerbations. The usual trigger is a viral upper respiratory tract infection, which may cause a fever as well. The constellation of fever, respiratory difficulty, abnormal auscultation, and an abnormal chest radiograph leads the clinician to the diagnosis of pneumonia. If asthma is the cause of recurrent pneumonia, patients will often have recurrent cough and acute wheeze with upper respiratory infections. The symptoms are usually worse at night; they may also have cough, wheeze, or respiratory difficulty apart from viral infections (eg, allergen, irritant, or exercise triggers). Improved asthma control often eliminates or reduces the episodes of pneumonia if asthma is the cause.[3]

Immunodeficiency syndromes, although overall uncommon, are a common cause of recurrent pneumonia in children and can be familial.[3,7] Associated signs and symptoms of infections in other systems usually provide a clue to the underlying diagnosis. Poor B-cell function often leads to predominantly respiratory tract infections such as otitis media, sinusitis, and pneumonia caused by common respiratory tract pathogens. Immunoglobulin (Ig) G deficiency, IgG subclass deficiency, and IgA deficiency are B-cell–related deficiencies associated with recurrent sinopulmonary infections. If the child has poor growth and serious infections in other organ systems, the immunodeficiency is more likely to be in the T-cell–mediated system or in the phagocytic portion (eg, neutropenia or chronic granulomatous disease) of the immune system.

Box 22-1

Conditions Leading to Recurrent Pneumonia in Children

Impaired Mucociliary Clearance

- Asthma
- Cystic fibrosis
- Primary ciliary dyskinesia
- Tracheomalacia/bronchomalacia
- Restricted chest wall (weakness, immobility, uncoordinated cough)

Mechanical Abnormalities

- Aspiration
- Intrinsic obstruction (tumor, retained foreign body)
- Extrinsic compression (tumor, adenopathy, enlarged cardiac structure)

Immune Deficiency (congenital or acquired)

- Abnormal cell-mediated immunity (T cell)
- Hypogammaglobulinemia (or B-cell deficiency)
- Neutrophil/macrophage dysfunction
- Mucosal surface immunodeficiency (immunoglobulin [Ig] A deficiency, IgG subclass deficiency)
- Syndromes associated with immunodeficiency

Systemic and Immune-Mediated Diseases

- Hypersensitivity pneumonitis
- Collagen vascular disease
- Idiopathic hemosiderosis
- Renal-pulmonary syndromes
- Granulomatous diseases (tuberculosis, congenital, sarcoidosis)
- Allergic bronchopulmonary aspergillosis
- Pulmonary alveolar proteinosis
- Acute chest syndrome (in sickle cell disease)

Congenital Anomaly

- Bronchogenic cyst
- Sequestration
- Esophageal duplication cyst
- Congenital pulmonary airway malformation
- Congenital lobar overdistention
- Tracheal bronchus (or other abnormal tracheobronchial branching)

Non-Pulmonary Causes

- Pulmonary edema
- Lymphangiectasis
- Diaphragmatic hernia
- Mediastinal mass
- Anomalous pulmonary venous return

These infections can be due to common respiratory pathogens or opportunistic pathogens. Complement pathway deficiencies are the rarest type of immunodeficiency and can lead to pyogenic pneumonia.[3,7] (See Chapter 53, Pulmonary Complications of Immunologic Disorders.)

Persistent pneumonia or recurrent pneumonia in one particular lung lobe should prompt the clinician to consider congenital anomalies such as a congenital pulmonary airway malformation or an airway obstruction from a foreign body, adjacent lymphadenopathy, or tumor.[8] (See **Figure 22-2.**)

Children with cystic fibrosis (CF) may present with a history of recurrent pneumonia.[9] Cystic fibrosis should be considered as the cause of recurrent pneumonia if there is associated steatorrhea, recurrent productive cough, or failure to thrive. It is important to know that approximately 10% to 15% of patients with CF are pancreatic sufficient; therefore, a patient with CF may not have growth failure.[10] Although CF occurs most commonly in white individuals, it should be considered in other races and ethnicities as well. Since 2010, all states in the United States have newborn screening for CF, which should identify 95% or more of the patients with CF shortly after birth.[11] Because the newborn screen can have false-negative results, if the clinician suspects CF as a possibility with recurrent pneumonia, the patient should have the gold-standard diagnostic sweat chloride measurement at a Cystic Fibrosis Foundation–accredited site.[10,11] (See Chapter 45, Cystic Fibrosis.)

Patients with primary ciliary dyskinesia (PCD) may have recurrent pneumonia. A patient with PCD usually has unexplained respiratory distress starting in the neonatal period; this should prompt consideration of this diagnosis as a cause

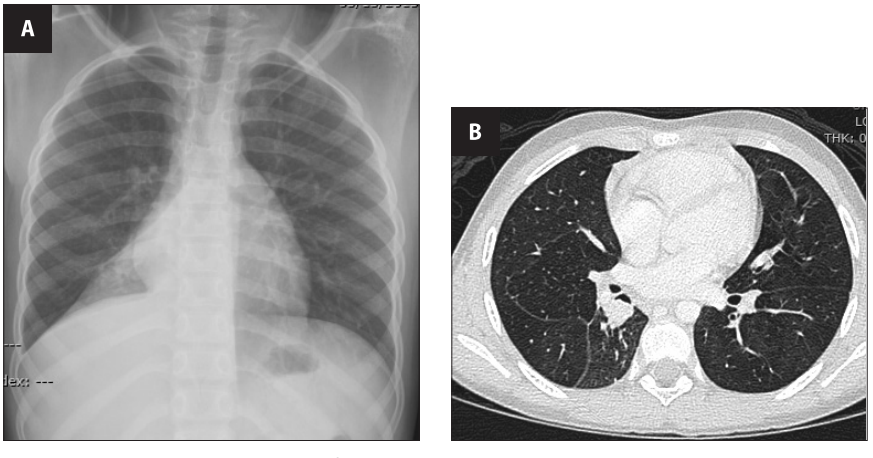


Figure 22–2. (**A**) Chest radiograph of an adolescent with post-obstructive pneumonia and atelectasis of the right lower lobe. (**B**) Chest computed tomography scan of the same patient showing near complete obstruction of the proximal right lower lobe bronchi by an endobronchial tumor (arrow).

of recurrent pneumonia.[12] Approximately 50% of patients will have associated dextrocardia and abdominal *situs inversus*. Chronic cough, neonatal respiratory distress, nasal congestion, and recurrent otitis media occur in more than 80% of patients with PCD. The diagnosis is often difficult to confirm and is usually established by a combination of respiratory cilia abnormalities on electron micrographs, reduced exhaled nasal nitric oxide, and recently improving techniques and sensitivities of DNA analysis.[12] (See Chapter 47, Primary Ciliary Dyskinesia and Other Genetic Lung Diseases.)

Children with reduced cough efficiency may have recurrent pneumonia because they have poor control or clearance of normal secretions. This occurs commonly in children with neurologic disorders (eg, cerebral palsy) and weakness (eg, muscular dystrophy), but it also can occur in children with other types of chest wall restriction, such as kyphoscoliosis.[3] Excessive dynamic collapse of the trachea or main stem bronchi (tracheomalacia/bronchomalacia) may also impair mucus clearance. In addition to recurrent pneumonia, these children may have stridor or wheezing. The etiology of tracheomalacia and bronchomalacia is usually unknown, and the collapse usually improves with age, although patients with prior surgery for a tracheoesophageal fistula commonly have dynamic airway collapse that persists into adulthood.[13,14]

Dysphagia and aspiration are common causes of recurrent pneumonia in children.[3] Aspiration can occur while swallowing directly or after esophageal reflux. Children with neurologic disorders are at increased risk because of hypotonia of the swallowing muscles as well as poor mucus clearance, although neurologically normal children can aspirate as well. Any child with gastroesophageal reflux (GER) is at risk for aspiration during periods of decreased consciousness (such as sleep) and while recumbent.[15] It is controversial whether aspiration of normal oral secretions causes recurrent pneumonia, but signs of airway inflammation can be seen on bronchoscopy of patients that aspirate.[16] Laryngeal clefts and H-type tracheoesophageal fistulas are rare causes of aspiration.[15]

Evaluation of the Child With Recurrent Pneumonia

A careful history and physical examination should lead to a concise differential diagnosis, and the subsequent laboratory evaluation can then be tailored for the most likely underlying condition. **Box 22-2** lists common diagnostic tools that often help in evaluating the child with recurrent pneumonia.[1–3]

The first step is to gather all the chest radiographs for review. It is helpful to have the radiographs interpreted by a pediatric radiologist who has access to all the images at the same time and has a clinical summary. Certain patterns may suggest other tests or simply a different therapeutic approach. For example, a child whose chest radiographs repeatedly show overinflation, diffuse

Box 22-2

Diagnostic Evaluation of the Child With Recurrent Pneumonia

- Pulmonary function testing
  - Flow-volume loops before and after bronchodilator
  - Lung volume studies
  - Diffusion capacity
  - Challenge tests (exercise, methacholine, cold air)
- Videofluoroscopic swallow study (with speech therapist present)
- Fiberoptic endoscopic evaluation of swallowing
- Flexible bronchoscopy with bronchoalveolar lavage
- Screening for immunodeficiency
- Testing for cystic fibrosis (sweat chloride test, DNA analysis)
- Testing for primary ciliary dyskinesia (electron microscopy studies, DNA analysis, fractional nasal exhaled nitric oxide)
- Chest computed tomography with expiratory images
- Esophagram and upper gastrointestinal series
- Other tests for reflux and aspiration
  - Gastric emptying study
  - Radioactive lung scintiscan
  - Esophagogastroduodenoscopy with gastroenterologist
  - pH/impedance probe

increased peribronchial markings, and subsegmental atelectasis with normal findings in between may not need additional studies but may need more aggressive asthma management.

If a defect in the immune system is suspected, initial screening studies should be considered, such as a complete blood cell count; white cell differential including lymphocyte differentiation; quantitative immunoglobulins (IgG, IgM, and IgA); antibody response to *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, and tetanus immunizations; total complement; human immunodeficiency virus serology; and measurement of neutrophil function with oxidative burst assay.[1–3]

The gold-standard test for CF is the sweat chloride measurement. Even if the newborn screen was negative for CF, a sweat test should be performed for any child with recurrent pneumonia unless there is a clear alternative explanation. DNA analysis is another available diagnostic test for CF and should be performed to confirm the diagnosis and potentially direct specific gene-targeted treatments. Specialized tests, such as the mucosal electrical potential difference, are not commonly available.[10]

The traditional test for PCD is electron microscopic evaluation of the ciliary ultrastructure. Cilia from respiratory mucosa can be obtained with mucosal

biopsy by brushing the mucosa with a cytology brush or curette scraping of the nasal mucosa. Patients with PCD have a decreased exhaled nasal nitric oxide level, and this can be diagnostic when CF testing is negative.[17] DNA analysis for PCD mutations has recently become more extensive and useful in diagnosis with new panels reporting over 75% to 80% sensitivity for diagnosis. Assessment of the ciliary waveform and beat frequency by microscopic examination on live cilia can also document ciliary dyskinesia, but this test is not commonly available.[12]

Aspiration can be identified with certainty only if contrast material is identified in the airway during a videofluoroscopic swallow study, fiberoptic endoscopic evaluation of swallowing, or upper gastrointestinal contrast study. If GER is identified without evidence of aspiration, additional testing may be pursued to determine if there is a link between GER and recurrent pneumonia. Milk scintiscan is one test that can document aspiration after reflux, but it is insensitive.[18] The use of the lipid index (semi-quantification of lipid-laden macrophages obtained during bronchoalveolar lavage) to document aspiration is controversial.[19]

Computed tomography of the chest is helpful in identifying congenital lung anomalies; chronic airway damage, such as bronchiectasis; bronchial obstruction; and tracheobronchial branching pattern abnormality.[20] Because of the high radiation exposure with computed tomography scanning, this test should be ordered after prudent consideration and performed with pediatric-specific algorithms to reduce the total radiation dose.[20]

Flexible bronchoscopy is useful for identifying airway abnormalities, obtaining lower airway and alveolar samples to stain and culture for infection, and mucosal biopsy for ciliary electron microscopy to assess PCD. Bronchoalveolar lavage is useful to assess acute and chronic infection, including opportunistic infection in the immunocompromised patient, and assess for hemosiderin or lipid-laden macrophages.

Treatment

If a specific underlying etiology for the recurrent pneumonia can be identified, therapy should be directed at that etiology. If the underlying etiology is asthma, comprehensive and aggressive management of the asthma should stop the recurrence of the pneumonia. Similarly, preventing aspiration from occurring usually prevents the recurrence of the pneumonia. Some children will be at risk for recurring pneumonia despite appropriate therapy, such as a child with a neurological disability with impaired secretion control. Assisting these patients with airway clearance techniques may minimize the frequency of their pneumonia. There are several options for assisting airway clearance, such as inhaled bronchodilators and corticosteroids, chest physical therapy with postural drainage, high-frequency chest wall oscillation, and cough assist

devices. There are some pharmacologic treatments targeted for patients with CF that have not been extensively studied in other lung diseases, such as nebulized antibiotics, dornase alfa, and hypertonic saline. New cystic fibrosis transmembrane regulator (CFTR) conductance gene correctors and highly effective modulators continue to be developed to improve CF care as well. Other preventive lung-protective strategies should be recommended, including complete childhood immunization, annual influenza immunization, and avoidance of toxicities, such as environmental tobacco poisoning.

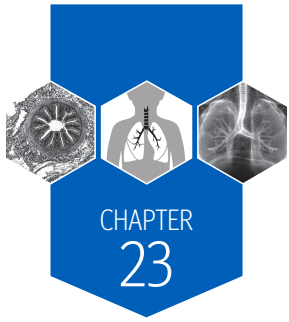
key points

- A careful history and physical examination, coupled with radiographic documentation of suspected lower respiratory tract infections, allow a directed evaluation to discover an underlying cause for the recurrent pneumonia.
- Treatment is tailored to a specific cause once identified. Every effort should be made to protect and preserve lung function.

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CHAPTER 23

Tuberculosis

Carol Conrad, MD

Introduction

Tuberculosis (TB) is an infectious disease that has coevolved with humans and has been described in human records at least since Neolithic times, 10,000 BCE, when the development of farming began. Tuberculosis is typically caused by *Mycobacterium tuberculosis* and occasionally by *Mycobacterium bovis* and *Mycobacterium africanum*. The most frequently infected organs are the lungs, although other modes of infection with *M tuberculosis* can occur by contamination of an open wound, such as an insect bite or an abrasion of the skin. Congenital infection occurs either transplacentally or by inhalation of infected amniotic fluid at the time of delivery. Infection by *M bovis* results primarily from ingestion of unpasteurized milk or dairy products that contain it. *M bovis* infections most commonly localize in extrapulmonary sites, causing cervical lymphadenitis, gastrointestinal disease, and meningitis, although latent infection can progress to pulmonary disease. Infection by *M bovis*, representing about 1% to 2% of TB cases, is more likely to occur in developing countries where control of TB in cattle and pasteurization of milk are not available and may occur in children of families entering the United States from countries where TB is endemic or those who may have traveled for extended stays to countries where TB is endemic.

Tuberculosis is one of the leading causes of death from infectious disease globally. It is estimated that 2 billion persons are infected with *M tuberculosis*. In a report released by the Centers for Disease Control and Prevention (CDC) National Tuberculosis Surveillance System in 2019, the number of TB cases reported in the United States increased 20% during the period from 1985 to 1992 after having shown a decrease for nearly 30 years previously. In 2009, the TB rate (3.8 cases per 100,000 population) was the lowest that had been recorded in the United States since 1953. Annually, the percentage change in rate slowed from an average decrease of 6.7% during the period from 2007 to 2012 to an average decrease of 2.2% between 2012 and 2017 but has remained frustratingly stable during those years. In 2019, 8,920 new cases were reported, and 70.9% of these new cases were detected in patients not born in the United States, but the rate of new cases had decreased by 1.5%. Overall, the TB rate

among patients not born in the United States (14.6%) was nearly 15 times the rate of people infected with TB who were born in the United States (Figure 23-1).[1]

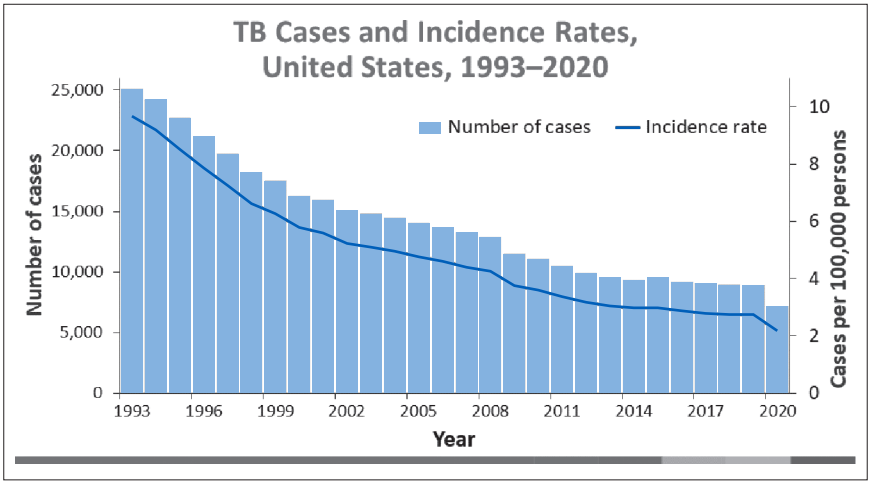


Figure 23-1. Number and rate of tuberculosis (TB) cases in the United States from 1993 to 2020 among persons born in the United States and those born elsewhere according to the year reported.

From Deutsch-Feldman M, Pratt RH, Price SF, Tsang CA, Self JL. Tuberculosis—United States, 2020. *MMWR Morb Mortal Wkly Rep*. 2021;70(12):409–414.

Approximately 10 million people globally developed TB disease in 2019, with about one-tenth of those being children. Tuberculosis infection (TBI) caused nearly 1.2 million deaths among people who were HIV negative in 2019 and an additional 208,000 deaths among people who were HIV positive, which indicates a slight decrease compared with 2018 statistics.[2]

The global number of new and relapse TB cases per 100,000 population have both been decreasing between 2014 and 2019 but not quickly enough to reach the #EndTB goals put forth by the World Health Organization (WHO). The cumulative reduction from 2014 to 2019 was 9%, rather than the expected decrease of 20% by 2020.[2]

Drug-resistant TB species pose the greatest obstacle to achieving control of TB disease and are most concerning in southern Africa, China, India, and countries of the former Soviet Union. Multidrug-resistant TB (MDR-TB) is defined as TB having resistance to at least isoniazid (or isonicotinic acid hydrazide [INH]) and rifampin (RIF). Extensively drug-resistant TB (XDR-TB) is a type of MDR-TB that demonstrates resistance to both a fluoroquinolone and a second-line injectable agent (amikacin, kanamycin, and/or capreomycin). The term *pre-XDR-TB* is used to identify MDR-TB with additional resistance to either, but not both, of those classes of drugs.[3]

In 2020, the WHO published an updated global surveillance report that included the incidence of MDR-TB and XDR-TB. At least 30% of people with new and previously treated TB in 2017 had RIF-resistant TB. Globally, that accounted for 718,684 cases of MDR-TB, which was at least double the incidence reported in 2016. Of those, more than 8% were estimated to be infected with XDR-TB. Nearly one-half of the XDR-TB cases were detected in China and India. As of early 2018, 127 countries confirmed having at least 1 case of XDR-TB.[2]

According to the CDC, the incidence of TB among children and adolescents in the United States is low and continues to decrease, but continued challenges are presented to the health care system. From 2010 to 2017, 6,072 TB cases in children and adolescents were documented. In the United States, 3,520 (68%) of 5,175 cases occurred among children who were born in the United States, including 2,977 (76%) of 3,896 children and 543 (42%) of 1,279 adolescents. However, the incidence rate among children and adolescents decreased by 47.8% between 2007 and 2017. Children and adolescents of color are disproportionately infected with TB, as are those living in islands affiliated with the United States and children born in, or to parents from, TB-endemic countries.[4,5] Factors such as poverty and crowded housing likely contribute to these disparites.

Almost all cases of TB are acquired through person-to-person contact via droplet nuclei formed by sneezing, coughing, or phonating. The tubercle bacilli establish infection in the lung after droplets containing 2 or 3 bacilli (small enough [5–10 μm] to reach the alveolar space) are inhaled. If the bacterial clusters contain more bacilli, the droplets are larger and will not cause infection because the droplet will be cleared quickly by the mucociliary transport defense mechanisms of the larger airways. Whether a particle that reaches the alveoli will cause infection or disease depends on the virulence of the bacilli and the killing capacity of the host macrophages.

Primary Infection

The initial host defense in the alveoli involves phagocytosis by the macrophages. However, a tubercle bacillus can multiply slowly within the macrophage without being killed. Once bacterial numbers are large enough (10^3–10^4 organisms), a cellular response is elicited by macrophage activation. At the slow rate of replication by *M tuberculosis*, this process takes about 4 to 8 weeks. A *tubercle*, or *granuloma*, is a formation of an epithelioid cluster of macrophages with phagocytosed bacilli and is the primary focus of infection. The infection spreads through the lymphatic vessels to the hilar lymph nodes. A *Ghon complex* consists of the primary focus, lymphangitis, and the regional hilar lymph node inflammation associated with it. Ghon complexes are generally located in the middle or lower lobes of the lungs. The spread of

infection is contained by stimulation of cell-mediated immunity processes. The granuloma will proceed to fibrosis and calcification and produce an isolated, calcified spot seen on a chest radiograph.

Dissemination

Bacilli can escape before the innate defense system of the host is able to respond or if it cannot mount an effective cell-mediated response to eliminate the infection. The bacilli multiply inside alveolar macrophages and kill the infected cells. Dying cells release TB bacilli into the surrounding lung parenchyma and cause progressive destruction of the lung. Bacilli can spread locally by erosion of the caseating lesions into the lung airways or instead can form cavities in the injured tissue. Once bacilli are present within the airspaces, the host becomes infectious to others, and infection is spread via droplet nuclei created when coughing. In a person who is infected, bacilli may also spread hematogenously and seed other portions of the lungs or other organs, which can result in the formation of numerous small granulomas. These have the appearance of small nodules on chest radiographs and indicate the presence of miliary TB. Symptomatic hematogenous spread is rare, except in patients who are immunocompromised.

As cell-mediated immunity develops, TBI is more reliably detected. For example, the reaction to the skin test occurs as a result of delayed-type hypersensitivity, in which sensitized T-helper ($CD4^+$) cells move to the site of antigen deposition and release lymphokines, which results in the characteristic indurated area created in the purified protein derivative (PPD) skin test. The skin test reaction and other tests for TBI are discussed in detail later in this chapter (see "Diagnosis").

The nature of pathological findings in persons who are infected is relative to the antigen load and the degree of hypersensitivity elicited. If few antigens are present and hypersensitivity is active, the classic tubercle develops, characterized by the presence of organized lymphocytes, macrophages, Langerhans giant cells, and fibroblasts that result in the formation of the classic tuberculous granuloma. A large bacterial load can overwhelm the immune system. The resulting hypersensitivity reaction can be destructive to cells and surrounding tissues. In some of the granulomas, incomplete necrosis occurs. *Caseation* is a process that occurs through the release of hydrolytic, destructive enzymes; reactive oxygen species; and cytotoxic lymphokines, producing the classic caseating granuloma seen at pathological examination. The TB bacillus can replicate at a very high rate in a liquefaction process such as this, which further increases antigen load and the destructive response by the host immune system. Healing can occur only when growth of the tubercle bacilli is inhibited. With caseous, liquefied cavities, the body isolates lesions with a primarily fibrotic process.

Clinical Presentation

Primary Pulmonary Disease

Tuberculous *infection* is different from tuberculous *disease*. Most initial infections are asymptomatic and controlled by cell-mediated immunity. When infection is present, the child has a positive test for TBI (skin test or blood-based test), but there is no clinical, radiographic, or laboratory evidence that indicates organ involvement. Approximately 10% of children who become infected with *M tuberculosis* develop manifestations of disease, but nearly one-half of infants younger than 12 months infected with TB will develop disease after infection, and postpubertal adolescents are also at high risk of developing disease.

Pulmonary disease is the most common manifestation of TB in children. Fever is the most frequent symptom of disease; cough is less commonly present. Symptoms are highly variable in children and also include weight loss or poor weight gain, night sweats, and chills. Pulmonary disease due to TB should be considered if a fever of 100.4°F (38°C) has persisted for at least 2 weeks, and other causes have been treated or excluded, or if a child develops a chronic unremitting cough that does not improve with treatment and has lasted more than 3 weeks. In addition, if weight loss or failure to thrive is notable at examination, TB should be considered because growth delay may be a manifestation of disease.[3] These signs and symptoms are nonspecific, so a history of an exposure to a person who is infected and a positive skin test will direct the differential diagnosis toward TB. However, a negative test for TBI (skin test or blood-based test) does not rule out TB. If other features are suggestive of TB, the diagnosis should be considered, even if the test for TBI is negative. These findings, along with the characteristic abnormalities of a pulmonary infiltrate associated with hilar lymph node enlargement seen on chest radiographs, nearly confirms the diagnosis. However, children have infiltrates at radiographic evaluation less frequently than do adults, but children more frequently have regional lymphadenopathy, lymphohematogenous spread, and calcified lesions than do adults. Approximately one-third of all patients develop a pleural effusion that is visible on a chest radiograph in addition to the Ghon complex previously described. Lymphadenopathy may be robust and can cause bronchial compression with resultant atelectasis of the associated bronchial segment. In short, any child who is treated for pneumonia, pleural effusion, cavitary lesion, or mass lesion in the lung that does not improve with standard antibacterial therapy should be assessed for TBI.

Once infected, infants younger than 1 year are at highest risk of developing disseminated TB (10%–20%) as well as pulmonary TB (30%–40%). The risk for dissemination decreases as the age increases, with the 5- to 10-year-old

age group having the least risk of developing disease (**Table 23-1**).[6–8] Infants and children who develop disseminated disease will develop symptoms related to the organ affected. The most common sites of extrapulmonary disease in children are the superficial lymph nodes and the central nervous system. Neonates are at the highest risk for progression of TB disease with meningeal involvement and are likely to present with seizures or stroke associated with high fevers.[6]

Approximately 5% of individuals who are infected develop disease within the first 5 years of infection if it is not treated. The likelihood of developing disease decreases as time passes, but another 5% of individuals who are infected will develop disease after the first 5 years, particularly if immunocompetence is lost.[5,8] Thorough evaluation of infants and young children is important because of their higher rate of progression to TB disease. Disease in other organs appears to follow a specific timetable of manifestation characteristic to the organ: meningitis usually occurs within 3 to 6 months after the initial infection, pleuritis develops within 3 to 9 months, bone and joint disease develops within 1 to 3 years, and renal disease develops within 5 to 25 years.

After TBI, several factors can influence whether it remains latent or progresses to active disease. These include age,[8] nutritional status,[9] previous vaccination,[10] and, importantly, baseline immune function.[11] Studies in animal and human hosts have shown reduced microbial killing and diminished monocyte recruitment to the site of infection in infants compared with those in adults.[6] The relative immaturity of the innate immune defenses of the neonate and infant allow *M tuberculosis* to establish infection before initiation of an antigen-specific immune response. Data from areas where infection rates are high but there is little available antibiotic treatment suggest that most children younger than 2 years (60%–80%) have detectable radiological abnormalities after infection.[12]

Table 23-1. Risk of Pulmonary and Extrapulmonary Disease in Children After Infection With *Mycobacterium tuberculosis*

Age	Risk of Disease After Primary Infection		
	Disseminated TB or TB Meningitis	Pulmonary TB	No Disease
< 1 y	10%–20%	30%–40%	50%
1–2 y	2%–5%	10%–20%	75%–80%
2–5 y	0.5%	5%	95%
5–10 y	< 0.5%	2%	98%
> 10 y	< 0.5%	10%–20%	80%–90%

Abbreviation: TB, tuberculosis.

Derived from Marais BJ, Gie RP, Schaaf HS, et al. The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. *Int J Tuberc Lung Dis*. 2004;8(4):392–402.

Latent TB

A minority of individuals infected with TB will ever develop TB disease. Although the biological mechanisms that permit persistence of the bacillus have been studied extensively, it is unpredictable who will develop signs of clinical disease. The latent or dormant state of the *M tuberculosis* bacillus is maintained by activated macrophages and interferon (IFN) γ–producing T cells.

Reactivation Disease

Reactivation of latent disease is primarily a phenomenon that occurs in adolescents and adults. Reactivation TB results when the persistent bacteria in a host begin to proliferate. Patients who are immunosuppressed are at high risk for reactivation TB, but the immunologic factors that actively suppress the reactivation are not known. The infection can remain latent for several years, and the trigger for release of the latent state has not been defined (**Box 23-1**). Primary TB usually resolves spontaneously, but reactivation disease can recur in 50% to 60% of patients who have not received a course of antibiotic therapy to prevent development of TB disease. Reactivation TB begins insidiously over a period of weeks to months. Cough is common, with a slow increase in sputum production, and is often accompanied with constitutional symptoms including fever, weight loss, anorexia, and night sweats. Episodes of streaky hemoptysis are not unusual in this stage. Reactivation appears to be related to bacillus replication, rupture of dormant lesions, and the release of caseating material into the bronchi and parenchyma, which causes cavity formation. This form of TB is the classic upper lobe, cavitating disease.

In contrast to the manifestation of primary disease, reactivation TB is more often localized and often not associated with regional lymph node involvement, and the caseating process is generally less prominent. The lesion typically occurs at the lung apexes. Unless the host is severely immunosuppressed, dissemination does not often occur.

Box 23-1

Immunosuppressive Conditions Associated With Reactivation Tuberculosis

- **HIV infection and AIDS**
- **Solid organ transplant**
- **Diabetes mellitus**
- **Lymphoma**
- **Corticosteroid use**
- **Diminution in cell-mediated immunity**

Chronic Disease

Ten percent of children with acute *M tuberculosis* infection who develop TB disease will recover spontaneously, but a fraction of those will develop chronic disease. However, in more recent decades, with aggressive detection programs and treatment being more available, the proportion of children who will develop chronic disease is unknown. Chronic disease caused by TBI is characterized by repeated episodes of reactivation, eventually controlled by the host with a fibrotic healing response surrounding the lesions. In the process, tissue is destroyed bit by bit. Successful healing through spontaneous eradication of the bacilli rarely, if ever, occurs. Unchecked bacterial growth and the resultant tissue damage can lead to disseminated TB by means of hematogenous spread.

Extrapulmonary Disease

Approximately 15% of patients with active TB also present with TB disease in an extrapulmonary site; the risk is increased in patients who are immunocompromised as well as in children younger than 2 years.[11,13] The most commonly involved sites include, in order of frequency, the lymph nodes, pleural space, heart, skin, genitourinary tract, bone and joint sites, meninges, and peritoneal-gastrointestinal tract.[12]

Diagnosis

Screening Tests

A diagnosis of TB (pulmonary or extrapulmonary) in a child is suspected with the classic triad of (1) recent close contact with a known infectious index case, (2) a positive tuberculin skin test (TST) or IFN-γ release assay (IGRA) result, and (3) findings at imaging or physical examination that are suggestive of TB.

The American Thoracic Society, Infectious Diseases Society of America, and CDC suggest using the following approach for evaluation of a child suspected of having TB[14]:

- Careful history (including history of TB contact and symptoms consistent with TB)
- Clinical examination (including growth assessment)
- Tuberculin skin test and/or IGRA (if both tests are available, the sensitivity and specificity of the IGRA supersede those of the TST, so IGRA is the preferred method)[15–17]
- Bacteriologic confirmation whenever possible

- Evaluation for all organ involvement with relevant imaging and functional studies
- HIV testing (in areas with a high HIV prevalence or populations at risk)

All data, including thorough history, physical examination, and diagnostic testing, must be considered carefully. A history of recent close contact with an infectious (positive sputum smear) case of TB is a critical factor in establishing the diagnosis of TB in children, especially for those younger than 5 years.

Skin Testing

In a situation in which an IGRA cannot reliably be performed, the American Academy of Pediatrics (AAP) suggests that a TST be used to assess for TBI if any of the following are true[3]:

- Contact with confirmed or suspected contagious TB (contact investigation)
- Radiographic or clinical findings that suggest TB disease
- Consumption of unpasteurized milk or unpasteurized cheese
- Recent immigration from areas with TB-endemic infection (eg, Asia, Middle East, Africa, Latin America, countries of the former Soviet Union), including international adoptees
- Recent history of travel to countries with TB-endemic infection and/or substantial contact with people from those countries
- HIV-infected children and incarcerated adolescents
- Before initiation of immunosuppressive therapy, which includes prolonged steroid administration or use of tumor necrosis factor α antagonists in children treated for collagen vascular disorders or candidates for organ transplant who will receive immunosuppressive therapy

Before the IGRA was developed, the TST was the only practical tool for diagnosing TBI in children without symptoms. For children of all ages, IGRAs are available (see "Improving Immunologic Diagnosis") and are the preferred method for testing. The preferred skin test is the Mantoux test, which contains 5 tuberculin units of PPD injected intradermally.[16] The sensitivity of TSTs ranges from 80% to 96% if read within 48 to 72 hours after placement, but they are falsely positive in children who have received the bacille Calmette-Guérin (BCG) vaccine. The TST is correctly read by measuring the largest diameter of induration surrounding the injection site (not redness) and is best performed by experienced health care professionals. However, fewer people are properly trained to read TSTs, and there are many causes of both false-positive and false-negative results (**Box 23-2**), so IGRA should be performed whenever possible.[15,17,18]

Box 23-2

Causes of False-Negative TST Reactions

- **Infections (eg, early TB infection [< 12 weeks], active TB, HIV, measles, varicella, typhoid fever, brucellosis, typhus, leprosy, blastomycosis)**
- **Live virus vaccines can suppress tuberculin reactivity for 4 to 6 weeks. Live virus vaccines can be administered concomitantly with the TST, but if not administered on the same day, they should be separated by at least 6 weeks.**
- **Medical conditions (eg, chronic renal failure, malignancies, sarcoidosis, poor nutrition) and glucocorticoid therapy (if initiated before the TST was placed)**
- **Technical factors (eg, inadequate dose, improper storage, failure to administer intradermally, improperly timed reading)**

Abbreviations: TB, tuberculosis; TST, tuberculin skin test.

False-positive TST reactions can result if the patient has prior exposure to nontuberculous mycobacteria or has received whole-blood transfusions from donors with positive TSTs or if the individual reading the test is inexperienced or biased. Furthermore, vaccines against TB are in early phases of development, and the vaccines are designed to create a T-cell response. Some infants and children may have false-positive reactions, but this result does not last long, and repeat testing in 6 to 8 weeks is merited in a patient who does not have symptoms or is at low risk. False-positive reactions also may occur in children who have received BCG vaccine.[15,16] Although the TST can be affected by receipt of the BCG vaccine,[19] interpretation of the TST depends on the child's risk factors.[20]

Interpreting Skin Test Results

A wide spectrum of PPD skin testing results occurs in the general population. Reactions depend in part on the type of exposure to TB among tested populations. People with a history of contact and subsequent TBI frequently have a prominent reaction to the skin test. In this population, the median diameter of induration is 16 to 17 mm, and there are few reactions smaller than 10 mm. In comparison, the general population without a significant history of TB contact has a different distribution of reactivity, with reactions varying from none (no

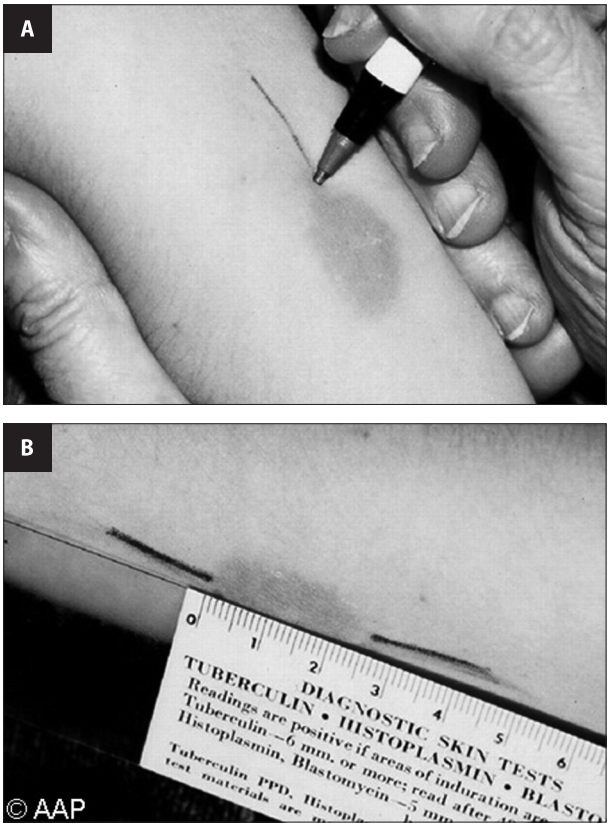


Figure 23-2. Positive skin test for tuberculosis.

infection) to reactions with induration less than 10 mm. Cross-reaction to other *Mycobacteria* is commonly associated with this type of reaction (**Figure 23-2**).

Because of these potential confounding elements, the CDC recommends using different criteria to determine whether a positive reaction is present. These are based on the prior likelihood of true TBI (**Box 23-3**). **Figure 23-3** is a flowchart that assists in the evaluation of a child exposed to a known positive contact.

Box 23-3

Definition of Positive TST Results in Infants, Children, and Adolescents[a,b]

Induration 5 mm or Greater

Children in close contact with people who are known to be or are suspected of being contagious with TB disease

Children suspected of having TB disease

- **Findings on chest radiograph consistent with active or previous TB disease**
- **Clinical evidence of TB disease[c]**

Children receiving immunosuppressive therapy[d] or with immunosuppressive conditions, including HIV infection

Induration 10 mm or Greater

Children at increased risk of disseminated TB disease

- **Children younger than 4 years**
- **Children with other medical conditions, including Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, or malnutrition**
- **Children with likelihood of increased exposure to TB disease**
- **Children born in high-prevalence regions of the world**
- **Children with significant travel[e] to high-prevalence regions of the world**
- **Children frequently exposed to adults who are HIV infected, homeless, users of illicit drugs, residents of nursing homes, incarcerated or institutionalized, or migrant farm workers**

Induration 15 mm or Greater

Children without any risk factors

Abbreviations: TB, tuberculosis; TST, tuberculin skin test .

[a] See www.cdc.gov/tb/publications/guidelines/pdf/ciw778.pdf.

[b] These definitions apply regardless of previous bacille Calmette-Guérin immunization; erythema alone at a TST site does not indicate a positive test result. Tests should be read 48 to 72 hours after placement.

[c] Evidence by physical examination or laboratory assessment that would include TB in the working differential diagnosis (eg, meningitis).

[d] These include immunosuppressive doses of corticosteroids or tumor necrosis factor α antagonists or blockers or immunosuppressive drugs used in recipients of transplants.

[e] Some experts define *significant travel* as travel or residence in a country with an elevated TB rate for at least 1 month.

From American Academy of Pediatrics. Tuberculosis. In: Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021–2024 Report of the Committee on Infectious Diseases*. 32nd ed. American Academy of Pediatrics; 2021:786–814.

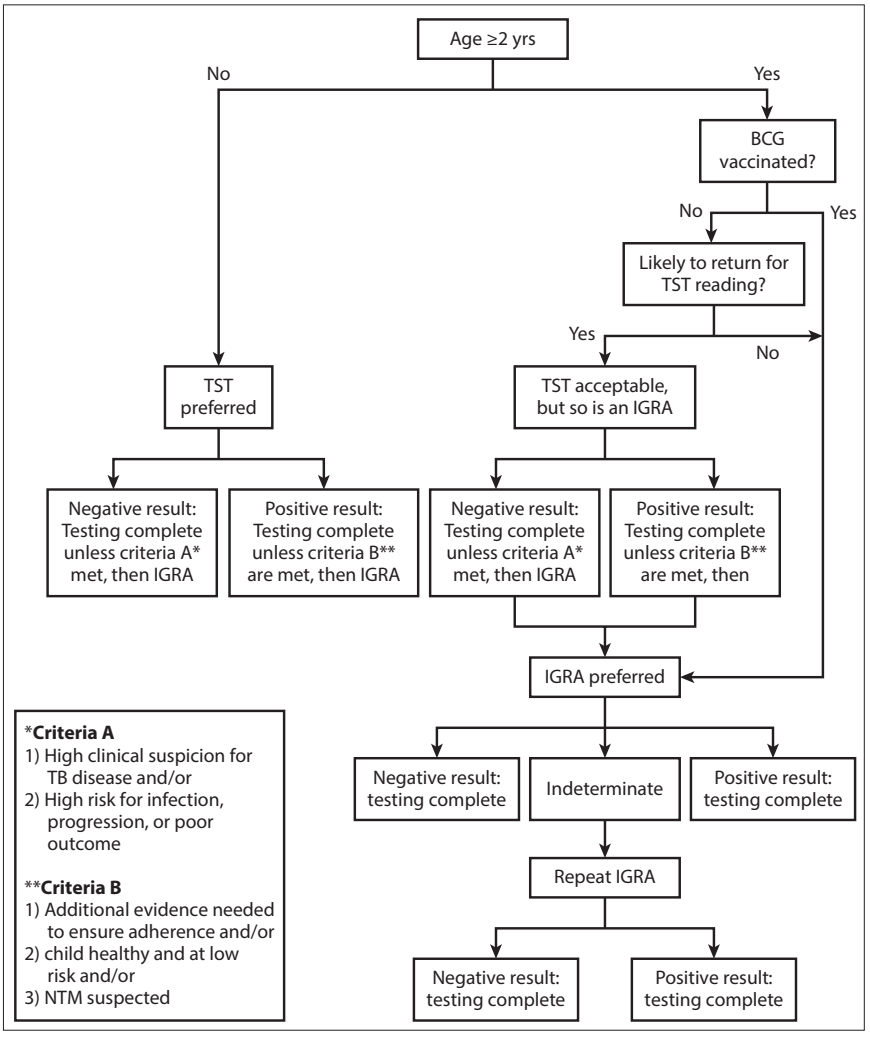


Figure 23-3. Evaluation of a child exposed to a person with contagious TB. Guidelines for the use of either the TST or IGRA in children older than 2 years with 1 or more risk factor.

Abbreviations: BCG, bacille Calmette-Guérin; IGRA, interferon γ release assay; NTM, nontuberculous mycobacteria; TB, tuberculosis; TST, tuberculin skin test.

From American Academy of Pediatrics. Tuberculosis. In: Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021–2024 Report of the Committee on Infectious Diseases*. 32nd ed. American Academy of Pediatrics; 2021:786–814.

Effect of BCG Vaccine

Bacille Calmette-Guérin vaccination often results in tuberculin conversion; most recipients of the vaccine develop tuberculin reactions 10 mm or greater within 8 to 12 weeks after vaccination. However, for infants who receive BCG vaccination during the neonatal period, the TST reactions diminish fairly rapidly; among more than 1,000 individuals who received vaccination in the first year after birth, no effect on tuberculin reactions 10 mm or greater could be detected after 10 to 25 years.[19]

For individuals who receive the BCG vaccine after the first year after birth or those who receive a second dose of BCG vaccine, however, tuberculin reactions wane more slowly. In a study that included more than 1,000 individuals with history of BCG vaccination, those vaccinated between the ages of 6 and 10 years had a higher rate of persistent tuberculin reaction than did those vaccinated at the ages of 2 and 5 years (20%–25% vs 10%–15%, respectively).[19] Nevertheless, a history of previous BCG vaccination is not a valid reason to dismiss a positive TST reaction. Positive results should prompt evaluation for infection, preferably with an IGRA according to the interpretation guidelines outlined previously.[18] Repeated PPD testing or 2-step testing can boost BCG vaccine–induced sensitivity. If the TST reaction is positive, an IGRA is the preferred test to distinguish reactivity caused by BCG vaccine sensitization versus that from TBI (see "Improving Immunologic Diagnosis" later in this chapter). The usefulness of the IGRA has not been verified in children younger than 2 years, but studies have been published that demonstrate its high sensitivity and specificity.[3] In addition, a search for the organism in sputum, gastric aspirates, or bronchoalveolar lavage fluid may be necessary if the source of infection cannot be verified.

Positive Response to the TST

A person infected with *M tuberculosis* will react to the TST with a delayed-type hypersensitivity T-lymphocyte response. Activated T cells and other recruited immune cells infiltrate the site and create maximal induration 48 to 72 hours after inoculation with the TST. Skin test conversion occurs within 2 to 12 weeks after primary infection. The ability to respond to a TST is often maintained for many years after the primary infection, although the intensity of the reaction can wane over time.

Sputum Analysis

It is somewhat difficult to establish a diagnosis of TB in children, given that they tend to be unable to expectorate and the bacterial load within the sputum is low, because there is a generally low incidence of cavitary disease in the pediatric population. However, if endobronchial caseating lesions are present and caseating lymph nodes have eroded into a bronchus, the bacterial load and likelihood of smear positivity increases. Nonetheless, children tend to swallow

sputum rather than expectorate it, so, in general, the bacteriologic specimens must be collected by obtaining early morning gastric aspirate washings. This method requires overnight fasting with collection on 3 consecutive days and is often best performed during a hospitalization. Even so, the rate of positive confirmation with acid-fast bacilli staining using this method is only 10% to 15%, and cultures are negative approximately 70% of the time.[21] All specimens obtained should be sent for bacteriologic evaluation, and nontuberculous mycobacteria should also be considered with a positive smear. If gastric specimens do not yield positive acid-fast bacilli test results, bronchoscopy for lavage of airways where there might be endobronchial granulomas can often increase the detection of *M tuberculosis*. Polymerase chain reaction (PCR) detection of TB should always be performed because this method is much more sensitive. Tissue biopsy can be performed on endobronchial lesions, and the specimens can be stained for acid-fast bacilli testing and quantitative PCR testing. Nevertheless, for 25% of infants and 50% of children with pulmonary TB diagnosed, no organism is isolated, even with the most optimal culture techniques. Without definitive diagnosis, treatment is based on exposure history, results of the cultures obtained from the infection source, clinical features, the TST and/or IGRA results, and radiographic results.

Improving Analysis of Specimens Obtained

Sputum can be obtained successfully by means of induction procedures with nebulization of hypertonic saline in children who are old enough to cooperate with huff coughs and expectoration maneuvers. However, this is a procedure that can also generate aerosol of bacterial particles, so it is impractical if tried outside of hospital settings. Avoiding infection of the person performing the procedure requires strict adherence to infection control procedures.[22]

Detection of *M tuberculosis* With Sequencing-Based Techniques

Molecular methods for detecting *M tuberculosis* have been developed that concomitantly identify both the presence of the bacterium and RIF resistance. These methods include PCR techniques that can be performed on samples of sputum, gastric aspirate, bronchoalveolar lavage and/or pleural fluid, nasopharyngeal swabs, stool, and tissue biopsy specimens[20] and are highly sensitive and specific. The most frequent PCR test in use is the GeneXpert MTB/RIF assay (Cepheid, Inc, Sunnyvale, CA). It is an automated test that is substantially more sensitive than smear microscopy.[23] Real-time PCR testing amplifies specific DNA targets in *M tuberculosis* and is combined with the use of specific fluorogenic hybridization probes that bind directly with both *M tuberculosis* DNA and resistance mutations in the *rpoB* and *katG* genes associated with MDR-TB. Study results demonstrated a sensitivity of 91% for BD MAX (Beckton, Dickinson and Company, Franklin Lakes, NJ) and 90%

for Xpert on processed sputum samples.[23,24] Sensitivity and specificity for RIF resistance compared with those for phenotypic drug sensitivity testing were 90% and 95%, respectively.[24] The Xpert Ultra cartridge is a more recent iteration of the BD MAX technology and is a more sensitive method of detection in specimens with low numbers of bacilli.[25,26] Sputum, nasopharyngeal aspirate, gastric aspirate, and stool specimens can be tested with the Xpert Ultra cartridges.[27]

The Xpert Ultra cartridges are easily modified to include detection of resistance genes to several antibiotics used in XDR-TB treatment regimens. These antibiotics include INH, fluoroquinolones, ethionamide, amikacin, kanamycin, and capreomycin, with sensitivities of 94%, 94%, 54%, 73%, 86%, and 61%, respectively, and 98% specificity for those same antibiotics, and performance was equivalent to that of line probe assays in a head-to-head comparison study by Penn-Nicholson et al[26] in 2021.

New sequencing technologies, compared with the rapid molecular tests, are better able to provide detailed information about resistance mutations for multiple gene regions. Line probe assays are designed to detect closely spaced resistance genes of the *M tuberculosis* chromosome. Line probe assays require the use of complex DNA-based assays and are limited to use in experienced reference laboratories.[28]

Urine-based testing that detects the mycobacterial lipoarabinomannan antigen is available to detect TB in people infected with HIV. Because these tests have low sensitivity, they are unsuitable to use as a general screening test for TB, but they have demonstrated improved sensitivity for diagnosing TB among individuals coinfected with HIV with low T-lymphocyte counts, on which the quantitative IGRAs depend (see the next section, "Improving Immunologic Diagnosis"). Lipoarabinomannan testing is associated with a decrease in mortality in people living with HIV by providing an earlier diagnosis, thus allowing treatment to start sooner.[29]

Improving Immunologic Diagnosis

Blood-based IGRAs are the preferred method and, since 2019, have replaced the TST, which is neither sensitive nor specific. The IGRAs rely on stimulation of host T lymphocytes with *M tuberculosis*–specific antigens and measure the consequent production of IFN-γ in response. These are termed *T-cell–based IGRAs*. Two principal IGRAs are used to detect TBI: the QuantiFERON-TB Gold (Qiagen, Hilden, Germany) and the T-SPOT.*TB* (Oxford Diagnostic Laboratories, Oxfordshire, United Kingdom) assays. The

former has been validated for use in children older than 2 years and can be used to increase the sensitivity for detecting TBI, particularly in younger children.[30] T-cell assays are more specific (not affected by BCG vaccine) than are TSTs but, like the TSTs, do not distinguish between active disease and TBI. In addition, the IGRA cannot distinguish among infection by *M tuberculosis*, *Mycobacterium kansasii*, *Mycobacterium szulgai*, or *Mycobacterium marinum*. Interpretation therefore depends on the clinical context and culture results from sputum or other infected samples or the source of infection.[20,31–33] At this time, the TST is no longer considered the gold standard for diagnosing TBI. The AAP recommendations for using IGRAs in children are as follows[3]:

- For children 2 years or older who are immunocompetent, IGRAs can be used in place of TSTs to confirm cases of TBI and likely will yield fewer false-positive test results.
- Children with a positive IGRA result should be considered infected with *M tuberculosis* complex. A negative IGRA result cannot universally be interpreted as absence of infection.
- Because of their higher specificity and lack of cross-reaction with BCG vaccine, IGRAs are the preferred diagnostic method for TBI in children who have received the BCG vaccine. A child with a false-positive TST reaction caused by the BCG vaccine will have a positive TST but a negative IGRA result.
- Interferon-γ release assays can be used in children older than 2 years and have a sensitivity similar to that of TSTs.[33,34]
- Indeterminate IGRA results do not exclude TBI. Further diagnostic procedures should be performed to guide clinical decisions.

IGRAs can improve the ability to detect TBI, especially in settings where resources are scarce, which is where better and more sensitive tests are needed the most.

Treatment of TBI (Positive IGRA/TST Results and Negative Chest Radiographs)

With no evidence of active disease, TBI in a patient at low risk can be treated with single-drug therapy. Isoniazid is the drug of choice and is prescribed for a minimum of 6 months. For patients unable to take INH or who are known to have been exposed to INH-resistant *M tuberculosis*, RIF daily for 4 months is an alternative therapy (**Table 23-2**).

Table 23-2. Treatment of Tuberculosis Infection Without Evidence of Disease

Agents	Dosage and Age Group	Administration	Duration, mo	Age Restriction	Comments
INH + Rifapentine (3HP)	**Age ≥ 12 y** INH: 15 mg/kg, rounded up to nearest 50 or 100 mg (max 900 mg) Rifapentine (by weight): 10–14 kg: 300 mg 14.1–25 kg: 450 mg 25.1–32 kg: 600 mg 32.1–49.9 kg: 750 mg ≥ 50.0 kg: 900 mg **Age 2–11 y** INH: 25 mg/kg, rounded up to nearest 50 or 100 mg (max 900 mg) Rifapentine: see above	Weekly (SAT or DOT)	3	Not for children < 2 y	Take with food, containing fat if possible; pyridoxine for selected patients[a]
Rifampin (4R)	**Adult:** 10 mg/kg (max 600 mg) **Child:** 15–20 mg/kg (max 600 mg)	Daily (SAT)	4	None	Drug–drug interactions
INH + Rifampin	Same doses as when drugs are used individually	Daily (SAT)	3	None	Not considered unless 3HP or 4R are not feasible
INH	**Adult:** 5 mg/kg (max dose 300 mg) **Child:** 10–15 mg/kg (max 300 mg)	Daily (SAT)	6 or 9	None	Seizures with overdose; pyridoxine for selected patients[a]
	Adult: 15 mg/kg (max dose 900 mg) **Child:** 20–30 mg/kg (max 900 mg)	Twice weekly (DOT)			

Abbreviations: DOT, directly observed therapy; INH, isoniazid; max, maximum; SAT, self-administered therapy.

[a] Infants who were exclusively breastfed and children and adolescents with meat- and milk-deficient diets; children with nutritional deficiencies, including all children with symptoms living with HIV infection; and pregnant adolescents and women.

Adapted from Nolt D, Starke JR. Tuberculosis infection in children and adolescents: testing and treatment. *Pediatrics*. 2021;148(6):e2021054663.

Treatment of TB Disease

Tuberculosis infection in infants and children younger than 4 years has a high likelihood of dissemination, so treatment should begin as soon as test results support the diagnosis. Children who do not have symptoms who have a positive IGRA or PPD skin test result and an abnormal chest radiograph should receive combination chemotherapy with the quadruple drug regimen of INH, RIF, pyrazinamide, and ethambutol daily or 3 times per week as initial therapy for 2 months. The subsequent 4 months of therapy with INH and RIF is prescribed in drug-susceptible isolates or if the risk of MDR-TB is low. Directly observed therapy (DOT) (as described later) should be established to avoid emergence of drug-resistant TB in the setting of incomplete adherence to the drug regimen.[3]

Careful consideration must be given to the risk group to which the individual belongs before deciding on a treatment regimen. Tuberculosis that originates in the United States is unlikely to be caused by MDR-TB or XDR-TB strains. The risk of infection due to MDR-TB is much higher in most other countries, particularly for immigrants from southern Africa, China, India, and countries of the former Soviet Union. The decision-making process for effective treatment is complex but can be aided by the use of molecular and well-tested diagnostic assessments that can quickly help determine susceptibility to the first-line drug regimen. The use of second-line drugs may create certain morbidities and toxicities. The decision to use them for prolonged treatment durations must balance these factors with the drugs' potential benefits. In these situations, consultation should be sought with a TB expert when suspicion is high for MDR-TB. Experts can be found through CDC-supported TB Centers of Excellence at (https://www.cdc.gov/tb/education/tb_coe/default.htm) and through local health department TB control programs (https://www.cdc.gov/tb/links/tboffices.htm) in the United States. Online sources of expert advice and information can also be obtained through the British Thoracic Society MDR-TB Clinical Advice Service (http://mdrtb.brit-thoracic.org.uk).

All children from another country who have no known contact with an index case with known drug susceptibility should begin treatment with the recommended 5-drug MDR-TB regimen as is recommended for adults (**Table 23-3**). To avoid toxicities and morbidities, physicians should try to obtain culture of the organism and its antibiotic sensitivities.

The American Thoracic Society, in a joint publication with the CDC, European Respiratory Society, and Infectious Diseases Society of America, has recommendations in the approach to treating MDR-TB.[35] These MDR-TB guidelines are noted in **Box 23-4**.

Table 23-3. Recommended Treatment Regimens for Drug-Susceptible TB Disease in Infants, Children, and Adolescents

Infection or Disease Category	Regimen	Remarks
M tuberculosis infection (positive TST or IGRA result, no disease)[a]		
Isoniazid susceptible	12 weeks of isoniazid plus rifapentine, once a week	Most experts consider isoniazid-rifapentine to be the preferred regimen for treatment of TBI for children 2 years or older, and some experts prefer isoniazid-rifapentine therapy for TBI in children 2 years or older.
	OR	
	4 mo of rifampin, once a day	Continuous daily therapy is required. Intermittent therapy even with DOT is not recommended.
	OR	
	3 mo of isoniazid plus rifampin, once a day	To be considered if more than 2 regimens are not feasible
	OR	
	6 or 9 mo of isoniazid, once a day	If daily therapy is not possible, DOT twice a week can be used; medication doses differ with daily and twice-weekly regimens.
Isoniazid resistant	4 mo of rifampin, once a day	Continuous daily therapy is required. Intermittent therapy even with DOT is not recommended.
Isoniazid-rifampin resistant	Consult a TB specialist.	Moxifloxacin or levofloxacin with or without ethambutol or pyrazinamide are most commonly used.

Table 23-3. Recommended Treatment Regimens for Drug-Susceptible TB Disease in Infants, Children, and Adolescents *(continued)*

Infection or Disease Category	Regimen	Remarks
Pulmonary and extrapulmonary disease (except meningitis)[b]	2 mo of rifampin, isoniazid, pyrazinamide, and ethambutol (RIPE) daily or 3 times per week, followed by 4 mo of isoniazid and rifampin[c] with DOT[d] for drug-susceptible *M tuberculosis*	Some experts recommend a 3-drug initial regimen (isoniazid, rifampin, and pyrazinamide) if the risk of drug resistance is low; DOT is highly desirable. If there is only hilar adenopathy and the risk of drug resistance is low, a 6-mo course of isoniazid and rifampin is sufficient. Directly observed therapy is required for intermittent regimens. Drugs can be administered daily or 3 times per week; 2 times per week is acceptable if DOT resources are scarce.
	At least 9 mo of isoniazid and rifampin for *Mycobacterium bovis* susceptible to these drugs	
Meningitis	2 mo of isoniazid, rifampin, pyrazinamide, and ethionamide, if possible, or an aminoglycoside[e] or capreomycin, once a day[f,g]; followed by 4–10 mo of isoniazid and rifampin, once a day or 3 times per week (9–12 mo total) for drug-susceptible *M tuberculosis* At least 12 mo of therapy without pyrazinamide for *M bovis* susceptible to isoniazid and rifampin	

Abbreviations: DOT, directly observed therapy; IGRA, interferon γ release assay; TB, tuberculosis; TBI, TB infection; TST, tuberculin skin test.

[a] See the current edition of the American Academy of Pediatrics *Red Book* for comments and additional acceptable and alternative regimens.

[b] Duration of therapy may be longer for people living with HIV infection, and additional drugs and dose administration intervals may be indicated.

[c] Medications should be administered daily for the first 2 weeks to 2 months of treatment and then can be administered daily or 3 times per week with DOT; twice weekly is acceptable if resources for DOT are limited. Intermittent therapy is not recommended for people living with HIV infection.

[d] If the initial chest radiograph shows pulmonary cavities and/or sputum culture results after 2 months of therapy remain positive, the continuation phase is extended to 7 months, for a total treatment duration of 9 months.

[e] Parenteral streptomycin, kanamycin, or amikacin.

[f] Many experts add a fluoroquinolone to this initial regimen.

[g] When susceptibility to first-line drugs is established, the ethionamide, aminoglycoside (or capreomycin), and/or fluoroquinolone can be discontinued.

From American Academy of Pediatrics. Tuberculosis. In: Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021–2024 Report of the Committee on Infectious Diseases*. 32nd ed. American Academy of Pediatrics; 2021:797–798.

Box 23-4

Selection of Effective MDR-TB Treatment Regimen and Duration

- **Use at least 5 drugs in the intensive first phase of treatment and 4 drugs in the continuation phase of treatment.**
- **Intensive phase duration of treatment should be 5 to 7 months after culture conversion.**
- **Total treatment duration should be for 15 to 21 months after culture conversion.**
- **In patients with pre-XDR-TB and XDR-TB, total treatment duration should be 15 to 24 months after culture conversion.**

Abbreviations: MDR-TB, multidrug-resistant TB; XDR-TB, extensively drug–resistant.

Derived from Nahid P, Mase SR, Migliori GB, et al. Treatment of Drug-Resistant Tuberculosis. An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2019;200(10):e93–e142. Erratum in: *Am J Respir Crit Care Med*. 2020;201(4):500–501.

For patients with drug intolerance or who are infected with minimally resistant organisms, alternative regimens can be substituted. *Mycobacteria* can develop drug resistance rapidly, particularly when single-drug regimens are used. Thus, a 2-drug combination is the minimum recommended by the WHO and the CDC for treatment of disease and is recommended only for patients who absolutely cannot tolerate a more rigorous regimen.[2,3] See **Table 23-4**, **Table 23-5**, and **Box 23-5** for dose administration regimens, alternate regimens, and medication toxicities.

Therapies for TB tend to be associated with multiple toxicities. Isoniazid and RIF are often associated with hepatic toxicity, so laboratory evaluation for evidence of hepatitis should be performed at least once in the first month of treatment, and more frequently for patients who have a history of hepatitis or renal insufficiency (those who are treated with streptomycin or other aminoglycosides). However, routine monitoring of transaminase levels in children

Table 23-4. Treatment of TB Disease in Patients at Low Risk (Suspects/Cases) for Susceptible and Isoniazid-Resistant *Mycobacterium tuberculosis*

Consult CDC guidelines for the treatment of active TB disease with alternative anti-TB regimens.					
Drug	**Dose**	**Interval**	**Adverse Effects**	**Monitoring**	**Comments**
INH	**Adults:** 300 mg **Children:** 10–15 mg/kg up to 300 mg	Every day	Hepatitis, peripheral neuropathy, mild CNS effects, skin rash, increased phenytoin levels, increased tacrolimus levels	LFTs (transaminases) once; more if history of chronic liver disease or other hepatotoxic drugs; not normally needed for children unless signs of hepatitis occur during therapy	Administer pyridoxine 25–50 mg/day to prevent neuropathy in elderly, IDDM, nutritional deficiency, pregnancy, HIV, and renal disease; in infants exclusively breastfed; and in children with meat and milk-deficient diets.
Disease caused by an INH-resistant but rifampin- and pyrazinamide-susceptible strain can be treated with a 6-month regimen of rifampin, pyrazinamide, and ethambutol.					
Rifampin	**Adults:** 10 mg/kg up to 600 mg **Children:** 10–20 mg/kg up to 600 mg; for < 45 kg, use 450 mg	Every day	Orange discoloration of secretions, cholestatic hepatitis, febrile (flu-like reaction), thrombocytopenia, drug interactions, skin rash	Baseline CBC count; LFTs once; more if history of chronic liver disease or other hepatotoxic drugs	Warn patient about orange discoloration of urine and other body secretions, such as tears. Can discolor contact lenses. Induces hepatic microsomal enzymes.
Ethambutol	**Adults:** 15–25 mg/kg **Children:** 20–25 mg/kg (2.5-g max for all ages)	Every day	Optic neuritis very rare at 15 mg/kg if renal function is normal Reversible if discontinued Skin rash	Red-green color discrimination and visual acuity should be checked at baseline and monthly.	Dose adjustment needed for renal disease.
Pyrazinamide	**Adults**: 20–25 mg/kg **Children:** 30–40 mg/kg (2-g max for all ages)	Every day	Hepatitis, GI upset, hyperuricemia, arthralgia, photosensitive dermatitis	LFTs at start and monthly, uric acid if renal disease	Dose adjustment needed for renal disease. Safety is not established in pregnancy.

Abbreviations: CBC, complete blood cell; CDC, Centers for Disease Control and Prevention; CNS, central nervous system; GI, gastrointestinal; IDDM, insulin-dependent diabetes mellitus; INH, isoniazid; LFT, liver function test; max, maximum; TB, tuberculosis;.

Table 23-5. Treatment of Multidrug-Resistant Tuberculosis Disease in Children of All Ages

Drug	Dose	Interval	Adverse Effects	Monitoring
Amikacin	**Children:** 15–30 mg/kg (IV or IM) up to 1 g Max dose 1 g all ages	Every day	Auditory and vestibular toxic effects, nephrotoxic effects	Creatinine check initially, then weekly Audiological testing at initiation and in 6 months, then annually
Capreomycin	**Children:** 15–30 mg/kg IM Max dose 1 g all ages	Every day	Auditory and vestibular toxic effects, nephrotoxic effects	Creatinine check initially, then weekly Audiological testing at initiation and in 6 months, then annually
Cycloserine	10–20 mg/kg/day orally, administered in 2 divided doses Max dose 1 g all ages	Twice a day	Psychosis, personality changes, seizures, rash	Clinical follow-up
Ethionamide	15–30 mg/kg/day Max dose 1 g all ages	3 times a day	GI disturbances, hepatotoxic effects, hypersensitivity reactions, hypothyroidism	LFTs at start and monthly
Kanamycin	15–30 mg/kg/day Max dose 1 g all ages	Every day	Auditory and vestibular toxic effects, nephrotoxic effects	Creatinine check initially, then weekly Audiological testing at initiation and in 6 months, then annually
Levofloxacin	15–20 mg/kg Max dose 1 g all ages	Every day	Possible effect on growing cartilage, tendinitis, GI disturbances, cardiac disturbances, peripheral neuropathy, rash, headache, restlessness, confusion	Preinitiation radiological evaluation of growth plates, ECG, clinical follow-up
Linezolid	< 10 y: 10 mg/kg/day > 10 y: 10 mg/kg/day Max dose 600 mg all ages	Twice a day Every day	Bone marrow suppression	CBC count at initiation, and weekly or monthly
Streptomycin	20–40 mg/kg/day Max dose 1 g all ages	Every day	Auditory and vestibular toxic effects, nephrotoxic effects	Creatinine check initially, then weekly Audiological testing at initiation and in 6 months, then annually

Abbreviations: CBC, complete blood cell; ECG, electrocardiogram; GI, gastrointestinal; IM, intramuscular; IV, intravenous; LFT, liver function test; max, maximum.

Box 23-5

Priority-Ordered Groups of Medicines Recommended by the World Health Organization for Use in Longer Multidrug-Resistant Tuberculosis Regimens

Group A = levofloxacin or moxifloxacin, with bedaquiline and linezolid

Group B = clofazimine and either cycloserine or terizidone

Group C = ethambutol, delamanid, pyrazinamide, imipenem-cilastatin or meropenem, amikacin or streptomycin, ethionamide or prothionamide, and *p*-aminosalicylic acid

From World Health Organization. WHO consolidated guidelines on tuberculosis, Module 4: treatment—drug-resistant tuberculosis treatment. 2020. Accessed May 4, 2022. https://www.who.int/publications/i/item/9789240007048.

taking INH alone is not recommended by the AAP,[3] except in the case of severe and disseminated disease. In addition, RIF may accelerate elimination of drugs metabolized by the cytochrome P450 complex in the liver, resulting in the need to alter dose administration regimens of those medications. Rifampin will discolor urine and tears orange; patients should be cautioned that soft contact lenses will be permanently stained. Ethambutol is associated with optic neuritis in addition to the aforementioned other typical toxicities, so follow-up to assess changes in visual acuity may be necessary. Finally, these medications are not generally available in liquid or suspension form, leading to a potential for decreased adherence to the regimen in younger children.

Development of New Antibiotics and Recycling Older Antibiotics

New drugs active against TB are urgently required. Novel drugs that can both reduce the number of drugs and the duration of treatment are needed to treat drug-susceptible TB and MDR-TB effectively. As of 2018, the WHO reported

clinical trials in phase 1, 2, or 3 with 20 drugs for the treatment of drug-susceptible TB, MDR-TB, and latent TBI. There are several new compounds under development, including bedaquiline, delamanid, GSK3036656, pretomanid, and SQ109. Bedaquiline, delamanid, and pretomanid are the most advanced in development for the treatment of MDR-TB (**Table 23-6)**. Each is highly effective and well tolerated; the WHO indications for treatment include RIF-resistant MDR-TB in children but are limited to children 3 years or older for delamanid and 6 years or older for bedaquiline.[45,46] Which regimen provides the best outcomes with fewest adverse drug reactions remains under investigation. These agents can be associated with QT prolongation, which must be further addressed. Other known antibiotics are being repurposed including clofazimine, linezolid, levofloxacin, moxifloxacin, rifampicin (high dose), and rifapentine (**Table 23-6**). Few of these drugs have been tested in randomized, placebo-controlled studies in children, so dose administration regimens are not included in this chapter, but the WHO has determined that bedaquiline may be used in children 6 years or older who have infection with INH-resistant *M tuberculosis*.

Investigators in several phase 2 or 3 trials in progress are testing various combination regimens with new or repurposed drugs (**Table 23-6**). Pretomanid is a novel drug that potentially shortens the duration of treatment in both drug-susceptible and drug-resistant TB.[37,44] The TB Alliance in South Africa has implemented the NiX-TB trial to test the safety and efficacy of a 6-month all-oral regimen combining bedaquiline, pretomanid, and linezolid in patients with XDR-TB, patients intolerant of standard MDR-TB treatment, and patients for whom the MDR-TB regimen was not effective. The primary end point was bacteriologic failure, relapse, or clinical failure during the 6 months after completion of treatment. This trial had a cure rate of 87% for the first 15 patients enrolled.[41] A follow-on trial, ZeNix, is an ongoing clinical trial to evaluate the efficacy, safety, and tolerability of various doses and durations of linezolid plus bedaquiline and pretomanid after 26 weeks of treatment in participants with pulmonary XDR-TB, pre-XDR-TB, or treatment-intolerant or nonresponsive MDR-TB, and lower doses and shorter durations of linezolid are used to minimize toxicity. The study remains active.[47]

In a phase 2c/3 clinical trial with delamanid completed in patients who had either drug-susceptible TB or MDR-TB, investigators targeted the primary end point as culture conversion at 2 months after having concluded a phase 2b safety study of the bedaquiline, pretomanid, moxifloxacin, and pyrazinamide regimen with delamanid (a bactericidal drug) added. In it, the investigators found almost 100% culture conversion at 2 months in patients with MDR-TB.[43]

The open-label single-center NixTB study included 109 patients with XDR-TB and MDR-TB[41] and was designed to evaluate the safety and efficacy of the combination of bedaquiline, pretomanid, and linezolid for 26 weeks in patients with XDR-TB and MDR-TB previously not responsive to treatment or for whom the medication regimen was not well tolerated and discontinued. The results at 6 months after finishing the regimen demonstrated good bacteriologic outcome (remained culture negative) in 90% of the 109 patients enrolled. In 10% of the subjects, severe adverse events occurred related to neurological and optic nerve toxicity, but the WHO has determined that all patients with MDR-TB would likely benefit from this all-oral regimen, and similar patients should be treated under observed and monitored conditions. **Table 23-6** lists these and other trials that have been completed to a phase 1 or 2 level.[36–44]

These worldwide, multicenter antibiotic trials have resulted in a dramatic shift in treatment for MDR-TB and XDR-TB. The WHO has published recommendations for treatment of drug-resistant TB (**Box 23-5**).

Table 23-6. Medications Under Clinic Trial for Use in MDR-TB

Agent	NCT ID, Phase, Type, Date Initiated	Class of Drug	End Date Results
OPC-167832[36]	NCT03678688[a] 9/2018 A phase 1/2, active-controlled, randomized, open-label trial to evaluate the safety, tolerability, pharmacokinetics, and efficacy of multiple oral doses of OPC-167832 tablets in subjects with uncomplicated, smear-positive, drug-susceptible pulmonary tuberculosis	Carbostyril derivative, affects cell-wall synthesis	Result pending 4/2021
Bedaquiline[37,38]	NCT02365623[b] 2/2015 An open-label study of safety, efficacy, and PK in Japanese patients with pulmonary MDR-TB for 24 weeks in combination with 5 of the following: PZA, ETH, streptomycin, kanamycin, ethionamide, cycloserine, *p*-aminosalicylic acid, amikacin, or levofloxacin or other fluoroquinolone	Diarylquinoline Inhibits the proton pump of mycobacterial ATP synthase, an enzyme that is essential for the generation of energy in *Mycobacterium tuberculosis*.	9/2019 Tolerated, but increased incidence of SAEs, risk for prolonged QTc interval. Effective in sputum culture conversion of MDR-TB (58%) and XDR-TB (72%) by 24 weeks of treatment.
SQ109 added to Rifafour + moxifloxacin	NCT01785186[c] 4/2013 Multiple-arm, multiple-stage, open-label, randomized, controlled clinical trial to compare the efficacy and safety of SQ109 added to standard control regimen in patients with smear-positive, pulmonary TB	SQ109, Ethylenediamine Inhibitor of MmpL3, a mycolic acid transporter required for incorporation of mycolic acid into the *M tuberculosis* cell wall	Phase 2 Study was terminated early for lack of additive or synergistic efficacy compared with the standard of care. 9/2017

GSK3036656[39]	NCT03557281[d] Phase 2a open-label study of the early bactericidal activity, safety, and tolerability of GSK3036656 in patients infected with drug-sensitive *M tuberculosis*	GSK3036656 selectively inhibits the enzyme leucyl-transfer RNA synthetase in *M tuberculosis* and suppresses protein synthesis.	Expected 2/2022
Telacebec[40]	NCT03563599[e] Phase 2a, open-label, randomized study in patients who were treatment naive and had smear-positive, drug-sensitive pulmonary TB to assess the early bactericidal activity of telacebec. Begun 6/2018	Imidazopyridine amide targets the cytochrome bcc complex, a variant of the cytochrome bc1 complex (complex III) of the respiratory chain of mycobacteria. Targets *M tuberculosis* cellular energy production through inhibition of cytochrome bc1 complex. In vitro, depletion of ATP synthesis resulted in cell death regardless of the replication status of the bacteria. Comparative study with Rifafour.	9/2019 Increasing doses of telacebec were associated with greater reductions in viable mycobacterial sputum load.
Sutezolid[41]	NCT03959566[f] 5/2019 Different doses of sutezolid in combination with bedaquiline, delamanid, and moxifloxacin in adults with newly diagnosed, uncomplicated, smear-positive, drug-sensitive pulmonary TB	Oxazolidinone antibiotic	Last update 9/2021 No results posted
Pretomanid[37]	NCT01498419[g,h] 3/2012 Phase 2, open-label partially randomized trial 207 patients with newly diagnosed drug-sensitive or MDR-TB, smear-positive TBI taking a combination of moxifloxacin, pretomanid, and PZA orally daily for 8 weeks versus standard 4-drug regimen of Rifafour	Nitroimidazooxazine drug that inhibits synthesis of mycolic acid	7/2013 Completed. It is active against both replicating and nonreplicating *M tuberculosis*.

(continued)

Table 23-6. Medications Under Clinic Trial for Use in MDR-TB *(continued)*

Agent	NCT ID, Phase, Type, Date Initiated	Class of Drug	End Date Results
Pretomanid[42]	NCT02333799[i,j] 1/2015 109 patients with XDR-TB taking pretomanid in combination with bedaquiline and linezolid had a favorable outcome at 6 months after the end of treatment.	Nitroimidazooxazine drug that inhibits synthesis of mycolic acid	11/2020 Complete and attained the approval of the US Food and Drug Administration in August 2019 for adults with pulmonary XDR-TB or treatment-intolerant or nonresponsive MDR-TB. Activity of pretomanid, moxifloxacin, and PZA was superior to standard treatment on daily change in colony-forming units and time to culture conversion in rifampicin-susceptible TB.
Nix-TB[41] Pretomanid, bedaquiline, and linezolid	NCT02333799[k] 3/2015 109 patients 26-week safety and efficacy of bedaquiline plus pretomanid plus linezolid in adult subjects with pulmonary MDR-TB	Pretomanid is a nitroimidazooxazine drug that inhibits synthesis of mycolic acid and thus cell-wall synthesis Bedaquiline is a diarylquinoline that inhibits the proton pump of mycobacterial ATP synthase, an enzyme that is essential for the generation of energy in M tuberculosis. Linezolid is an oxazolidinone that inhibits bacterial protein synthesis.	8/2020 98 patients (90%; 95% CI, 82.7%–94.9%) had a favorable outcome at 6 months after the end of treatment. Linezolid toxicities of peripheral neuropathy (81% of patients) and myelosuppression (48% of patients) were managed by reductions of dose and/or interruptions in linezolid.

Pretomanid[43]	NCT03338621[l] Evaluate the efficacy, safety, and tolerability at 8 weeks (2 months), 52 weeks (12 months), and 104 weeks (24 months) after the start of the following treatment regimens in participants with drug-sensitive TB(BPaMZ for 17 weeks vs standard HRZE/HR for 26 weeks) and patients with drug-resistant TB: (BPaMZ for 26 weeks or 6 months)	Nitroimidazole inhibits mycolic acid synthases and is bactericidal.	Study concluded 2/2022
Delamanid[38,43,44]	NCT01859923[m] (extension of NCT01856634)[n] Phase 2, open-label, dose-finding study in 37 pediatric patients with MDR-TB infection treated with levofloxacin, bedaquiline, linezolid, clofazimine (optimized baseline regimen, WHO)	Nitroimidazole inhibits mycolic acid synthases and is bactericidal.	11/2020 Well-tolerated, QTc prolongation potential

Abbreviations: ATP, adenosine triphosphate; BPaMZ, bedaquiline, pretomanid, moxifloxacin, and pyrazinamide; ETH, ethionamide; HRZE/HR, isoniazid (H), rifampin (R), pyrazinamide (Z), and ethambutol (E)/isoniazid (H) and rifampin (R); MDR-TB, multidrug-resistant TB; MmpL3, mycobacterial membrane protein Large 3; NCT, National Clinical Trial; PK, pharmacokinetics; PZA, pyrazinamide; SAE, serious adverse event; TB, tuberculosis; TBI, TB infection; XDR-TB, extensively drug–resistant; WHO, World Health Organization.

a https://clinicaltrials.gov/ct2/show/NCT03678688.
b https://clinicaltrials.gov/ct2/show/NCT02365623.
c https://clinicaltrials.gov/ct2/show/NCT01785186.
d https://clinicaltrials.gov/ct2/show/NCT03557281.
e https://clinicaltrials.gov/ct2/show/NCT03563599.
f https://clinicaltrials.gov/ct2/show/NCT03959566.
g https://clinicaltrials.gov/ct2/show/NCT01498419?term=NCT01498419&draw=2&rank=1.
h Deb U, Biswas S. Pretomanid: the latest USFDA-approved anti-tuberculosis drug. *Indian J Tuberc*. 2021;68(2):287–291.
i https://clinicaltrials.gov/ct2/show/NCT02333799?term=pretomanid&draw=2&rank=12.
[j] Conradie F, Diacon AH, Ngubane N, et al; Nix-TB Trial Team. Treatment of highly drug-resistant pulmonary tuberculosis. *N Engl J Med*. 2020;382(10):893–902.
k https://clinicaltrials.gov/ct2/show/NCT02333799.
l https://clinicaltrials.gov/ct2/show/NCT03338621.
m https://clinicaltrials.gov/ct2/show/NCT01859923.
n https://clinicaltrials.gov/ct2/show/NCT01856634.

Directly Observed Therapy

Because TB is highly contagious, the mortality rate due to TB is high, and poor adherence to the multidrug regimen can lead to multidrug resistance, DOT medication administration systems have been developed. With DOT, a health care worker is assigned to watch the patient swallow every dose. It is generally accepted that DOT is the most optimal means of ensuring that children receive TB therapy. Directly observed therapy can be accomplished by trained personnel in many settings, including medical clinics, public health facilities, the home, and school. Frequently, proper administration of anti-TB medications necessitates using crushed pills and suspensions to attain correct doses. Tolerance of the medications must be monitored closely, and children may resist taking their prescribed medications. Parents should not be relied on to supervise DOT. If a patient experiences toxicity from the medications, this can be detected early with routine blood tests. Directly observed therapy is also helpful to allow and encourage ongoing patient education. In some patients, the multidrug regimen for TB can be administered 3 times weekly rather than daily. Directly observed therapy services increase the likelihood of successful treatment of TB, decreasing mortality due to TB, and preventing the spread of MDR-TB in the United States. This system has proved successful in other countries where access to medical care is limited.

Prognosis

In general, the prognosis for patients infected with TB is good, but mortality rates increase when patients have comorbidities such as malnutrition, disseminated disease, or immunodeficiency (especially HIV), and mortality rates increase dramatically in patients infected with MDR-TB. Globally, the mortality rate for positive cases of MDR-TB in the HIV-negative population in 2008 was estimated at about 26%, though the range varied between 16% and 58%.[2] The high mortality rate due to MDR-TB can eventually be addressed if resources to provide adequate prevention, diagnosis, treatment, and care are present. In the United States, although a substantial portion of the population is medically and economically indigent, most cases are likely detected at some point in the disease course. Conversely, most cases of people who are infected in China and Africa go undetected, and these patients do not receive adequate treatment and have high mortality. A global decrease in MDR-TB mortality can be effected with appropriate antibiotic coverage and as DOT programs expand. Infection control measures that have been considered and systematically instituted can potentially reduce transmission throughout the populations most at risk, and mortality due to MDR-TB will eventually be reduced, if not eliminated.

Control of TB

Control of TB requires a concerted and consistent public health effort involving state and local health departments, individual health care providers, and

other institutions, including hospitals and incarceration units. The local health department often plays an important role in the following areas once a TB case is identified:

- Thoroughly investigating contacts of an index case and ensuring that contacts receive appropriate testing for evidence of infection
- Ensuring that the index case receives appropriate standard therapy or therapy for MDR-TB on the basis of laboratory evaluation and that all infected contacts receive appropriate evaluation, monitoring, and therapy
- Providing a mechanism so that all patients receive DOT for TB
- Ensuring that all patients receive regular monitoring for secondary effects of anti-TB therapy
- Ensuring that high-risk groups such as individuals who are incarcerated, individuals who are HIV positive, and health care workers receive regular screening for TB
- Ensuring that children and adults return to school and the workplace as soon as able after treatment for TB is initiated

Most children younger than 10 years are not contagious, primarily because of the rare occurrence of cavitary disease in children. However, children with (1) cavitary pulmonary TB; (2) positive sputum acid-fast bacilli smears; (3) laryngeal involvement; (4) extensive pulmonary infection; or (5) congenital TB who are undergoing oropharyngeal procedures, such as endotracheal intubation, can infect others. Precautions should always be taken when treating these types of pediatric patients.

Vaccine Development

Most countries outside the United States provide the BCG vaccination as an element of the routine childhood vaccinations according to the epidemiological characteristics of TB for each country; 158 countries vaccinated their pediatric population in 2017, and most reported that their effort covered approximately 90% of children.[2] The WHO's #EndTB strategy to eliminate TB by 2035 challenges these countries to reach this goal, but further research and development must proceed at an aggressive pace as well.[2] Although many breakthroughs have been announced, the programs must be accelerated so that many more breakthroughs are achieved. By 2025, TB cases must decrease by at least 17% per year, not the current rates of less than 5%. Vaccine development is a priority to reduce the risk of infection, but the effect of the BCG vaccine wanes within a few years. New vaccine and new drug development must be supported.

As of 2020, 12 vaccine trials were begun and some have been completed and are in various stages of development (**Table 23-7**).[48–59] Some are safety and dose-ranging trials (phases 1 and 2); others have progressed to phase 3 placebo-controlled trials designed to either prevent disease from developing in people with TBI or improve the outcomes of those with TB disease.[60,61]

Table 23-7. Results of Vaccine Trials to Prevent TB Dissemination

Vaccine/Phase/ Composition	Mechanism of Efficacy	Results
DAR-901/2b[48,49] Inactivated whole-cell TB booster vaccine in adolescents who are BCG vaccine primed (NCT02712424) Phase 2a completed 5/2021	Induces $CD4^+$ T-cell cytokine profiles that correlate with protection	A 3-dose series of 1 mg DAR-901 was safe and well tolerated but did not prevent initial or persistent IGRA conversion. Recipients of DAR-901 with IGRA conversion had enhanced immune responses to ESAT-6.
M72/$AS01_E$/3 RDBPC[50,51] Vaccine contains a recombinant fusion protein derived from 2 *Mycobacterium tuberculosis* antigens (Mtb32A and Mtb39A) combined with the $AS01_E$ adjuvant system. (NCT01755598) A phase 2b study completed in men aged 18 to 50 years with TBI defined by positive IGRA results without evidence of active TB disease at centers in Kenya, South Africa, and Zambia, with 1:1 ratio to receive 2 doses of either M72/$AS01_E$ or placebo, administered 1 month apart, in participants who were HIV negative	Induces M72-specific antibodies and increases the frequencies of M72-specific $CD4^+$ T cells. Efficacy of M72/$AS01_E$ to prevent active pulmonary TB disease according to the first case definition (bacteriologically confirmed pulmonary TB) followed for 3 years after the second dose.	The vaccine efficacy at month 36 was 54% to prevent active pulmonary TB disease according to the case definition. Future steps: GlaxoSmithKline outsourced M72/$AS01_E$ to the Gates Medical Research Institute for continued development and potentially for use of the vaccine candidate in countries with high TB burdens.
NCT04556981[a] M72/$AS01_E$ randomized, placebo-controlled, observer-blind, phase 2 study to evaluate safety and immunogenicity of the investigational M72/$AS01_E$ *M tuberculosis* vaccine	Start date 11/2020 402 participants with HIV who were virally suppressed and treated with HAART	Results pending

NCT01378312[b] AERAS-402 is a replication-deficient Ad35 vaccine that encodes a fusion protein of the *M tuberculosis* antigens 85A, 85B, and TB10.[52] Phase 1 Healthy male participants aged 18–45 years with a negative QFT. 12 participants enrolled	Randomized 2:1 to receive 2 intramuscular injections of either AERAS-402 or placebo on study days 0 and 28. Safety and immunogenicity parameters were evaluated for up to 182 days after the second injection. Immunogenicity was assessed with a flow cytometry–based intracellular cytokine staining assay and transcriptional profiling.	$CD8^+$ T-cell responses were induced and dominated by cells that coexpressed IFN-γ, tumor necrosis factor α, and IL-2 (polyfunctional cells) and were more robust than $CD4^+$ T-cell responses.
NCT02414828[53] Phase 1 RDBPC dose-escalation study in adults recently treated for pulmonary TB 72 participants Single or booster doses	Phase 2 randomized, placebo-controlled, double-blind dose-escalation study in an adult South African cohort (n = 72) that was HIV negative with active pulmonary TB (receiving treatment for 1–4 mo) or pulmonary TB treated at least 12 months before study entry and considered cured	Study ended 4/2016 AERAS-402 candidate TB vaccine administered in participants with current or previous pulmonary TB induced a robust immune response, but analysis of the vaccine-induced $CD8^+$ T cells revealed that the induced cells did not recognize the *M tuberculosis*–infected cell.
NCT01198366[54] Phase 2 RDBPC, multicenter study to evaluate the safety and immunogenicity of AERAS-402 in infants who were BCG vaccinated, HIV uninfected, and without evidence of TB	487 infants aged 16–26 weeks Received 2–3 doses IM vaccine or placebo Follow-up for 24 months	Antibodies directed against Ag85A and Ag85B were detected. Low magnitude $CD4^+$ and $CD8^+$ polyfunctional T-cell responses were observed at all dose levels. The addition of a third dose of AERAS-402 at the highest dose level did not increase frequency or magnitude of antibody or $CD8^+$ T-cell responses.
South Africa National Clinical Trial Register (DOH-27-0209-2655)[55] Phase 2 RDBPC, dose-escalation trial, in 57 infants aged 6–9 months who were BCG vaccinated and sequentially randomly assigned to receive an increasing dose strength of AERAS-402 or placebo	AERAS-402 in infants, administered as a boost after a prime with BCG vaccine	AERAS-402 is safe in healthy infants previously vaccinated with BCG vaccine and induces dose-dependent $CD4^+$ and $CD8^+$ T-cell responses.

(continued)

Table 23-7. Results of Vaccine Trials to Prevent TB Dissemination *(continued)*

Vaccine/Phase/ Composition	Mechanism of Efficacy	Results
NCT01113281[c,56] Phase 1 study VPM1002, a recombinant BCG vaccine in which the urease C gene is replaced by the listeriolysin O gene from *Listeria monocytogenes*	Promotes phagolysosomal maturation and impedes the survival of mycobacteria inside the macrophage	The immunogenicity of VPM1002 as measured with IFN-γ release by T cells was dose dependent. VPM1002 induced multifunctional $CD4^+$ and $CD8^+$ T-cell subsets that play a role in protection against TBI.
NCT01479972[d,57] Phase 2 open-label, randomized, controlled study to evaluate safety and immunogenicity of VPM1002 in comparison with BCG in newborns who were HIV unexposed and BCG vaccine naive in South Africa	This is the first investigation of VPM1002 in newborns.	Safe, well-tolerated, and efficacious vaccine
NCT03152903[e,58] A multicenter, RDBPC phase 2/3 trial in adults with a single dose of VPM1002 or placebo to determine efficacy of the vaccine against recurrent TB	A 2,000-participant 3-arm multicenter RPC phase 2/3 trial to assess the ability of VPM1002 or Immunovac/MIP to prevent disease in contacts of patients with sputum-positive pulmonary TB diagnosed in India	Expected end date 5/2022
Immunovac/MIP[59] RDBPC in 890 participants with smear-positive pulmonary TB	Evaluated the immunotherapeutic potential of MIP as an adjunct to treatment in patients with smear-positive pulmonary TB	Immunovac/MIP was safe with no adverse effects. Although sputum smear conversion did not show any statistically significant difference, a significantly higher number of patients in the MIP group achieved sputum culture conversion at fourth week compared with results in the placebo group (67% vs 57%), suggesting a role of MIP in clearance of bacilli.

Abbreviations: Ad35, adenovirus serotype 35; BCG, bacille Calmette-Guérin; CD, cluster of differentiation; ESAT, early secretory antigenic target; HAART, highly active antiretroviral therapy; IFN-γ, interferon γ; IGRA, IFN-γ release assay; IL-2,interleukin 2; IM, intramuscular; MIP, *Mycobacterium indicus pranii*; NCT, National Clinical Trial; QFT, QuantiFERON-TB Gold (Qiagen, Hilden, Germany); RDBPC, randomized, double-blind, placebo-controlled; TB, tuberculosis.

a https://clinicaltrials.gov/ct2/show/NCT04556981.
b https://clinicaltrials.gov/ct2/show/NCT01378312.
c https://clinicaltrials.gov/ct2/show/NCT01113281.
d https://clinicaltrials.gov/ct2/show/NCT01479972.
e https://clinicaltrials.gov/ct2/show/NCT03152903.

When to Refer

- All patients suspected of having active TBI should be reported to the local health department according to state statute (usually within 1 working day).
- In many areas, young children with latent TBI should be reported to the local health department, according to local regulations.
- Ideally, a pediatrician experienced in TB should manage TB disease in children. If a specialist is not available, close and ongoing consultation with a pediatric TB expert should be established.

When to Admit

- Children suspected of having a TBI should be admitted to the hospital for culture collection. Early-morning gastric aspirates have the highest yield when obtained from gastric secretions after a nasogastric tube is placed the night before and the child has not yet arisen or eaten.
- Patients with increased work of breathing, meningitis, or complicating simultaneous conditions should be admitted to the hospital for supportive and aggressive care.

key points

- Only children who have a new risk for TB exposure since the last TST or who have features suggestive of TB disease should undergo testing with a TST or IGRA.
- Interferon-γ release assay testing is the first line of testing in most patients aged 2 years or older.
- All children with latent TBI diagnosed should be treated and monitored for adherence and toxicity.
- Tuberculosis disease is diagnosed clinically and radiographically in children, often without the benefit of culture confirmation.
- Vaccines are in development, but none have yet been developed that prevent TBI (**Table 23-6**).

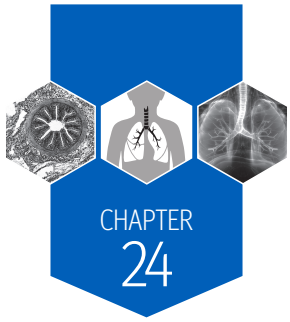
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Nontuberculous Mycobacteria

Stacey L. Martiniano, MD
Patricia Lenhart-Pendergrass, MD, PhD
Kenneth N. Olivier, MD, MPH

CASE REPORT 24-1

A 14-year-old girl who has been followed in the cystic fibrosis center for several years underwent computed tomography scanning because the usual therapy for a pulmonary exacerbation failed. She reported recent weight loss and night sweats. The computed tomography scan showed 2 cavities in the right upper lobe. She produced minimal sputum, so bronchoscopy with bronchoalveolar lavage was performed, and a smear revealed acid-fast bacilli. *Mycobacterium abscessus* subspecies *abscessus* was cultured, and she was treated with intravenous amikacin, intravenous imipenem, oral azithromycin, and oral linezolid. Subsequent therapy will be decided based on response to treatment and sensitivity patterns.

Introduction

All species of mycobacteria, with the exception of *Mycobacterium tuberculosis*, *Mycobacterium leprae*, and *Mycobacterium ulcerans*, can be categorized as nontuberculous mycobacteria (NTM). More than 200 different species of NTM have been reported in the literature to date,[1] but only a small subset are associated with human disease. Nontuberculous mycobacteria are found ubiquitously in the environment, including soil, dust, and water sources such as tap water and even hospital water sources.[2] Unlike *M tuberculosis* infections, NTM infections are almost exclusively caused by direct acquisition from the environment, although results from whole-genome sequencing studies suggest that direct or indirect transmission between patients has occurred.[3] Nontuberculous mycobacteria infections can occur in both the immunocompetent and the immunocompromised host. Pulmonary disease from NTM most commonly occurs in hosts with underlying pulmonary conditions, such as cystic fibrosis (CF), primary ciliary dyskinesia, or other non-CF bronchiectasis, and is rare in

healthy children. Other pulmonary manifestations include thoracic or endobronchial nodal disease and hypersensitivity pneumonitis. Extrapulmonary manifestations include lymphadenitis, skin and soft-tissue infections, and catheter-associated infections. Disseminated disease can be seen in hosts with primary immunodeficiency or secondary immune suppression. Diagnosing NTM infection can be challenging, and treatment strategies remain complex.

Pathophysiology

Acquisition of NTM most commonly occurs through exposure to environmental sources. Inhalation into the respiratory tract is thought to be the source for pulmonary parenchymal disease, as well as endobronchial and mediastinal disease. Although person-to-person spread is thought to present a low risk, incidences of person-to-person spread of NTM in patients with CF have been reported.[3,4] The oropharyngeal mucosa is the likely portal of entry in patients with cervical lymphadenitis. Direct inoculation can occur through abrasions or via surgical incisions and central catheters. Entry through the gastrointestinal tract can be associated with disseminated disease. Infection tends to remain localized to the site or organ of infection, but dissemination can occur in patients with HIV infection and in patients with congenital immune defects of the interleukin 12 (IL-12)/interferon γ (IFN- γ) axis.[5]

Nontuberculous mycobacteria are acid-fast bacteria that require special media to grow in the laboratory and can be classified by their speed of growth. Appropriately identifying organisms in children with CF requires working with a knowledgeable microbiology laboratory that is adept at isolating these pathogens and at using proper isolation techniques (eg, *Pseudomonas aeruginosa* can overgrow NTM in culture).[6] Nontuberculous mycobacteria that grow rapidly (within 1 week) and are commonly associated with lung disease include the *Mycobacterium abscessus* species (which includes subspecies *abscessus*, *massiliense*, and *bolletii*), *Mycobacterium fortuitum*, and *Mycobacterium chelonae*.[7] Slow-growing NTM typically take weeks to grow and include *Mycobacterium avium* complex (MAC; which includes the species *M avium*, *Mycobacterium intracellulare*, and *Mycobacterium chimaera*, among others), *Mycobacterium kansasii*, *Mycobacterium xenopi*, and *Mycobacterium simiae*. Most human pulmonary disease is caused by a limited number of NTM, so identifying the species (and subspecies for *M abscessus* species) helps determine whether the isolated species is pathogenic and, therefore, guides therapy. Because NTM are ubiquitous, environmental contamination can occur in the laboratory. For example, *Mycobacterium gordonae* is thought to be the least pathogenic of all mycobacteria, and isolation is typically regarded as a contaminant. Thus, interpretation of single

isolates of NTM needs to include the context of the clinical presentation and ideally repeat isolation from additional samples. Nontuberculous mycobacteria species identification is ideally performed using specific DNA probes, polymerase chain reaction techniques, or DNA sequence analysis. Some study results have shown that matrix-assisted laser desorption ionization–time of flight mass spectrometry may be useful in providing rapid species identification of many NTM species, but not all species can be identified reliably with this method.[8–10]

Clinical Features

Pulmonary Disease

Pulmonary NTM isolation rates in the general population range from 6 to 22 per 100,000 in North America.[11] In children, NTM infection is most commonly associated with CF. The prevalence of pulmonary NTM infection in children with CF increases with age; NTM infection in the first decade of life is less common, with a prevalence of about 5% to 10%, increasing to a prevalence of 6% to 19% among adults with CF.[11–13] Pulmonary NTM is also associated with other syndromes affecting the mucociliary clearance that lead to bronchiectasis, such as primary ciliary dyskinesia and certain immunodeficiency conditions such as autosomal dominant hyperimmunoglobulin E (Job) syndrome.[14,15] In these other disorders of mucociliary clearance, incidence of NTM infection also increases with age and is less likely in young children. Isolation rates for NTM are increasing over time among those with CF[12,16,17] and in the general population[18] for reasons that are uncertain but that may relate to improving surveillance and culture techniques. *M avium* complex is the most frequently recovered NTM in the United States, but rapid growers, typically *M abscessus* species, are also common. The prevalence and species of NTM vary geographically across the United States, which may be related in part to atmospheric water vapor pressure and other environmental factors.[19,20] Symptoms can include an increase in respiratory symptoms such as cough, sputum production, and hemoptysis. A decrease in FEV_1 can occur. Systemic symptoms such as fever, night sweats, or weight loss may be present. Imaging findings can include the development of nodules; tree-in-bud opacities; segmental consolidation; and, at times, cavitary lesions.[21] Unlike MAC and *M abscessus* species, *M kansasii* is a rare pathogen in children and adolescents and is seen more frequently in older men; however, it can occur in individuals with underlying lung disease. *M kansasii* infection most closely mimics tuberculosis (TB). Hot tub lung, a rare, diffuse pulmonary disease that occurs after exposure to aerosolized MAC droplets, occurs typically with poorly drained indoor hot tubs and manifests as a hypersensitivity-like pneumonitis with fever, dyspnea, and cough.[22]

Extrapulmonary Disease

Localized lymphadenitis is the most common manifestation of NTM infection in children, particularly those in the preschool age range. The most commonly affected nodes are in the cervicofacial region, most often unilateral. The presentation is typically subacute, occurring over the course of weeks, and the child often appears well without systemic symptoms. A positive NTM culture, histopathological test result, or polymerase chain reaction result from a tissue specimen of the affected node can establish the diagnosis.[23] *M avium* complex is the most common group of NTM identified in lymphadenitis.

Isolated thoracic node or endobronchial disease likely has a pathogenesis similar to that of cervical node disease and most commonly results from MAC. Manifestation typically occurs within the first few years of life, often with persistent wheeze or stridor unresponsive to bronchodilator therapy. Similar to findings in patients with NTM lymphadenitis, systemic findings such as fever are reported but are not always present, and children with these findings often appear well. Given that cross-reactivity between MAC and TB may occur, findings may also be identified incidentally on chest images obtained as evaluation for a positive purified protein derivative test result. The diagnosis is typically determined after chest computed tomography or bronchoscopy is performed for the persistent pulmonary findings. Results from biopsy of the node or endobronchial lesion show granulomatous inflammation, and acid-fast bacteria may be seen on smears and grow in culture.[24]

Skin and soft-tissue infections can occur both in individuals who are healthy and in those who are immunocompromised. These infections can be caused by *M abscessus* species and other rapidly growing NTM species, as well as *Mycobacterium marinum* and *M ulcerans*. Infections can be superficial, but abscess formation can occur, especially with the rapidly growing species. Nontuberculous mycobacteria should be suspected in infections that fail to respond to typical antibiotic treatment regimens.[25]

Disseminated NTM may manifest with pulmonary disease (typically consolidation or miliary nodular involvement) and extrapulmonary disease and is associated with immunodeficiency. Individuals typically present with fever, night sweats, and weight loss. Lymphadenopathy and hepatosplenomegaly may be present at physical examination, and HIV should be excluded in individuals with disseminated NTM.[26] Inherited and acquired immunodeficiency or disorders of the IFN-γ/IL-12 pathway, such as defects of the IFN-γ receptor, defects of IL-12 or IL-12 receptor, *GATA*^{2} deficiency, and defects of nuclear factor-κB essential modulator operon, may also cause patients to be susceptible to NTM infections, including disseminated disease.[5,27]

Diagnosis

Pulmonary Disease

Pulmonary NTM in children and adolescents occurs most frequently in the setting of underlying bronchiectasis from CF, primary ciliary dyskinesia, or other underlying diseases. Nontuberculous mycobacteria should be considered in the setting of a pulmonary exacerbation unresponsive to treatment of typical pathogens or with unexpected clinical decline.[28,29] A high index of suspicion for mycobacteria is necessary because symptoms may not differ much from those of pulmonary exacerbation from other pathogens. Routine screening for NTM infection is also an important aspect of diagnosis. The Cystic Fibrosis Foundation and European Cystic Fibrosis Society have published guidelines on managing NTM in CF and recommend surveillance mycobacterial cultures be performed annually in patients who can expectorate spontaneously and have a stable clinical course.[30] In the absence of clinical features that suggest NTM pulmonary disease, patients who do not produce sputum do not require routine screening. Cultures should be obtained from sputum and not from oropharyngeal swabs.[30] Because of these practices, many NTM infections are initially detected as part of routine screening, in the absence of clinical features. In patients who have clinical symptoms suggestive of NTM, additional cultures from spontaneously expectorated or induced sputum should be obtained. The usefulness of gastric aspirates in children unable to produce sputum for diagnosing NTM pulmonary infection is not well delineated, and diagnosis by means of bronchoscopy with bronchial wash, bronchoalveolar lavage, or biopsy should be strongly considered in patients who have symptoms but cannot expectorate.

The diagnosis of NTM pulmonary disease requires a combination of clinical, radiographic, and microbiological evidence of disease. The American Thoracic Society, European Respiratory Society, European Society of Clinical Microbiology and Infectious Disease, and Infectious Diseases Society of America have compiled specific criteria for diagnosing NTM pulmonary disease (**Box 24-1**).[7] The Cystic Fibrosis Foundation and European Cystic Fibrosis Society guidelines also support the use of these criteria for diagnosis in patients with CF.[30] Although these guidelines have been developed for adults, they likely can be applied to children and adolescents who are capable of sputum production. Consultation with a pulmonologist or infectious diseases physician with experience in diagnosing NTM disease is advisable. Evaluating pulmonary disease should include clinical assessment; examination of the chest by means of radiography (**Figure 24-1)** or computed tomography (**Figure 24-2**); obtaining at least 3 sputum samples for culture of acid-fast

Box 24-1

Criteria for Diagnosis of Nontuberculous Mycobacteria Pulmonary Disease

Clinical and Radiographic Criteria

- **Pulmonary or systemic symptoms, AND**
- **Compatible chest imaging results, including nodular or cavitary opacities on chest radiographs or bronchiectasis with multiple small nodules on chest computed tomography scans, AND**
- **Exclusion of other diagnoses**

Microbiological Criteria

- **Positive culture from at least 2 sputum samples, OR**
- **Positive culture from at least 1 bronchial wash or bronchoalveolar lavage, OR**
- **Transbronchial or other lung biopsy results with mycobacterial histopathological features (granulomatous inflammation or acid-fast bacilli) and positive culture for nontuberculous mycobacteria from biopsy, sputum, or bronchial washing**

Adapted from Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med.* 2007;175:367–416. © American Thoracic Society

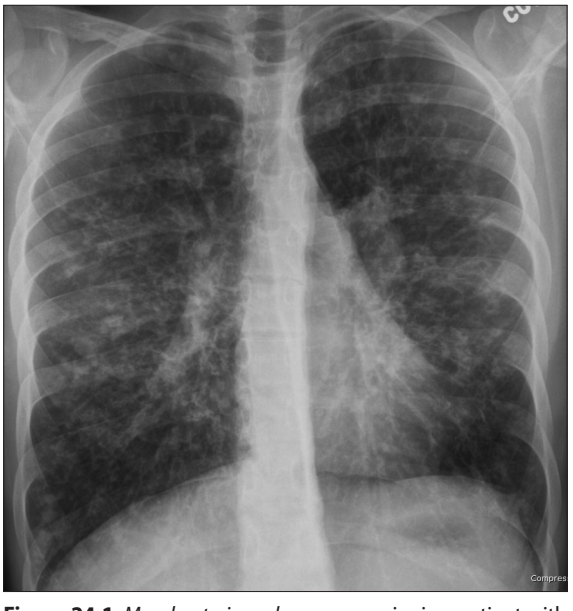


Figure 24-1. *Mycobacterium abscessus* species in a patient with cystic fibrosis. Frontal chest radiograph shows the lungs are hyperinflated, and there is extensive peribronchial thickening. Scattered lucencies due to bronchiectasis and nodular foci due to mucous plugging are seen throughout the lungs.

From Stillwell PC, Martiniano S. Nontuberculous mycobacterial pulmonary disease. In: Stokes DC, Dozor AJ, eds. *Pediatric Pulmonology, Asthma, and Sleep Medicine: A Quick Reference Guide.* American Academy of Pediatrics; 2018:415–419.

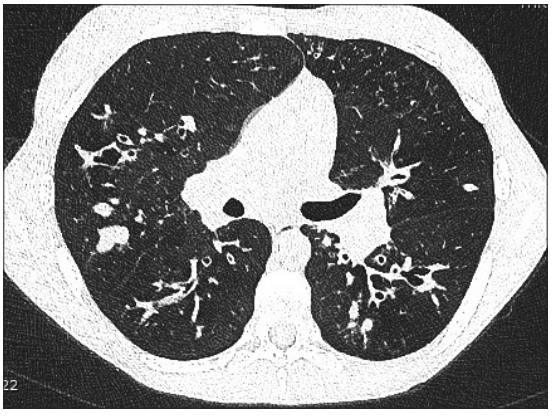


Figure 24-2. *Mycobacterium abscessus* species infection in a patient with cystic fibrosis. Computed tomography axial scan reveals scattered nodules due to mucous plugging (arrow), bronchiectasis, cavity formation, and tree-in-bud opacities (arrowhead).

From Stillwell PC, Martiniano S. Nontuberculous mycobacterial pulmonary disease. In: Stokes DC, Dozor AJ, eds. *Pediatric Pulmonology, Asthma, and Sleep Medicine: A Quick Reference Guide.* American Academy of Pediatrics; 2018:415–419.

bacilli; and exclusion of other entities, such as TB. Microbiological criteria require positive cultures from 2 or more sputum samples; a positive culture from bronchoalveolar lavage or bronchial wash; or a lung biopsy with mycobacterial histological features, which include granulomatous inflammation or acid-fast bacilli; and at least 1 positive NTM culture from a respiratory source.

In individuals with CF and other causes of underlying bronchiectasis, the diagnosis can be confounded by overlap of similar clinical symptoms and radiographic features related to coinfection with other bacterial isolates (eg, *P aeruginosa* or *Staphylococcus aureus*) or because of comorbidities (eg, CF-related diabetes or allergic bronchopulmonary aspergillosis).[31] Aggressive treatment of other coinfections isolated in CF may help determine the clinical significance of NTM. If the patient continues to have symptoms of a pulmonary exacerbation despite aggressive treatment, NTM pulmonary disease should be considered and appropriate cultures obtained. Because the presentation is largely subacute or chronic, there is typically time to collect this information before initiating therapy to ensure evidence of NTM pulmonary disease exists. On average, 40% of patients with CF who are infected with NTM ultimately have NTM pulmonary disease diagnosed.[31]

Extrapulmonary Disease

A diagnosis of nodal or endobronchial NTM disease is typically established through positive culture of a biopsy or needle aspirate specimen in the context of a compatible clinical presentation. Results from biopsy of the node or endobronchial lesion show granulomatous inflammation, and acid-fast bacteria may be seen on smears and grow in culture.[24] For extrapulmonary or disseminated disease, a single positive biopsy or blood culture result is sufficient to establish the diagnosis and initiate treatment.

Management

Proper identification of the NTM infection to the species level is critical for antibiotic selection. In addition, identification to the subspecies level for *M abscessus* species can provide additional clinical and epidemiological information to help guide treatment.[7] For example, culture conversion to negative is less likely to occur in patients infected with *M abscessus* subspecies *abscessus* than in those with *M abscessus* subspecies *massiliense*, likely related to the presence of a functional *erm*(41) gene in subspecies *abscessus*, which results in inducible macrolide resistance.[32] Thus, patients infected with subspecies *abscessus* (or subspecies *bolletii*) typically require additional antibiotics in their regimen. Consensus guidelines recommend susceptibility-based treatment for macrolides and amikacin over empiric therapy for MAC and *M abscessus* species pulmonary disease.[7] Beyond macrolides and amikacin, there is little correlation between results from in vitro susceptibility tests and clinical response for other antibiotics in the treatment of NTM.[33–35]

Treating pulmonary NTM disease requires combination antibiotic drug regimens to prevent resistance (**Table 24-1**). The choice of antibiotics requires knowledge of species-specific regimens, as well as the antibiotic history of the specific patient. In addition, drug–drug interactions and adverse events need to be considered on an individual basis. Given the complexity of these regimens, consultation with a pulmonologist or infectious disease specialist who is experienced in managing NTM infections is advisable. Lung resection surgery can be a beneficial adjunctive treatment in selected patients with localized or refractory disease.[7,36] The decision to proceed with lung resection should be weighed against risks and should be performed by a surgeon experienced in mycobacterial surgery.[7,37] Notably, lung resection is generally not performed in patients with CF or in pediatric populations.[30] The decision to treat and timing of treatment require a careful assessment of the morbidity of the illness and the patient's ability to commit to a prolonged, combination antimicrobial course. Because individuals with parenchymal NTM disease often have comorbidities (eg, bronchiectasis, concomitant pulmonary pathogens), objective data that can be tracked to assist in treatment response are necessary. Inflammatory markers, pulmonary function tests, semiquantitative sputum acid-fast bacilli smears and cultures, and imaging studies may help assess response to therapy. In addition, airway clearance measures, such as use of chest percussion or postural drainage, a percussion vest, handheld oscillatory or positive expiratory pressure devices, and inhaled hypertonic saline treatments, should be initiated or continued to augment medical treatment.

Consensus guidelines recommend that the treatment regimen for macrolide-susceptible pulmonary MAC infection is a 3-drug oral regimen that includes a macrolide (azithromycin preferred over clarithromycin).[7] Typical regimens

Table 24-1. Example Treatment Regimens of Typical Nontuberculous Mycobacteria Infection (With Consultation of an Expert)

Organism	Example Antimicrobial Regimens	
Mycobacterium avium complex	• Oral azithromycin or clarithromycin, rifampin, and ethambutol • For macrolide-resistant, cavitary, or severe disease, addition of an IV aminoglycoside course	
Mycobacterium abscessus group, macrolide susceptible	**Initial phase (3 or more drugs)** • IV amikacin • IV imipenem or cefoxitin • Oral azithromycin	**Continuation phase (2 or more)** • Inhaled amikacin • Oral azithromycin • Oral clofazimine or linezolid
Mycobacterium abscessus group, mutational or inducible macrolide resistant	**Initial phase (4 or more drugs)** • IV amikacin • IV imipenem or cefoxitin • Oral clofazimine • Oral linezolid	**Continuation phase (2 or more)** • Inhaled amikacin • Oral clofazimine • Oral linezolid
Mycobacterium kansasii	• Oral rifampin, isoniazid or macrolide, and ethambutol	

Abbreviation: IV, intravenous.

include a macrolide plus ethambutol and rifampin. In the setting of macrolide resistance or cavitary, advanced, or severe disease, addition of an intravenous (IV) aminoglycoside (amikacin or streptomycin) may be included in the initial regimen.[7] Drug–drug interactions need to be assessed in all patients. Interactions occur most commonly with rifamycins, in particular in patients with CF who are prescribed medications containing ivacaftor. Amikacin liposome inhalation suspension is a treatment of refractory MAC approved by the US Food and Drug Administration for use in adults. Clofazimine is also an option to be used in combination therapy for initial or refractory MAC.[38] Fluoroquinolones have previously been included as a treatment option; however, when combined with a macrolide, there may be an increased incidence of macrolide resistance than is seen with the combination of macrolides with ethambutol and a rifamycin.[33] The first treatment course has the best chance of response; therefore, multidrug therapy is very important. In adults with macrolide-susceptible, noncavitary, nodular or bronchiectatic MAC pulmonary disease, treatment may be condensed into thrice-weekly dosages.[7] However, little is known of the efficacy of these regimens for children, and daily treatment regimens are required for patients with CF.[30]

M kansasii responds well to rifamycin-containing regimens, with a typical regimen (similar to that used for TB) consisting of rifampin, ethambutol, and isoniazid or a macrolide. In patients with rifampicin-resistant *M kansasii* or intolerance to first-line antibiotics, a fluoroquinolone (eg, moxifloxacin) can be used.[7] Three-times weekly regimens can be used for rifampicin-sensitive,

noncavitary *M kansasii* treated with rifampin, ethambutol, and a macrolide. Isoniazid-containing regimens should be administered daily.[7] For all regimens, toxicities need to be reviewed, and a strict monitoring plan is required (**Table 24-2**). For MAC and *M kansasii*, optimal length of therapy is not well defined, but a typical regimen is 12 months of therapy beyond the date of conversion to a negative sputum culture.[7,39]

Treatment of *M abscessus* species requires an initial phase of treatment including IV antibiotics followed by a continuation phase with a combination of oral and/or inhaled agents.[7,39] Because of the usual severity of infection and potential for drug resistance, treatment of *M abscessus* species requires multidrug therapy, typically 3 or more active drugs, guided by in vitro susceptibility.[7] Specific drug selection and duration of treatment should follow published guidelines[7] and be managed by an expert in treating patients with *M abscessus* species pulmonary disease. *M abscessus* strains develop macrolide resistance through chromosomal mutations in the 23S ribosomal RNA (*rrl*) gene, as well as through the presence of a functional *erm*(41) gene that causes inducible macrolide resistance.[7] In *M abscessus* species strains without inducible or mutational resistance, the most reliably effective antimicrobial is a macrolide (azithromycin and clarithromycin), which should be included in the treatment regimen. In strains with resistance, macrolides may be included for immunomodulatory purposes but should not be counted as an active drug in the treatment regimen.[7] Other antibiotics that generally have activity against *M abscessus* species and can be used in a multidrug treatment regimen include parenteral agents such as amikacin, imipenem, tigecycline, and cefoxitin; oral clofazimine or linezolid; and inhaled amikacin.[7] Newer tetracyclines, including omadacycline (IV or oral),[40] may have a role in clinical management in the future. The role of bedaquiline, an agent developed for the treatment of multidrug-resistant TB, is still unknown for the treatment of NTM disease.[41]

Published dosage guidelines for NTM antibiotics are available.[7] An optimal NTM drug dosage in children is not well described, and consultation with an expert is advisable. Therapeutic drug monitoring is indicated when using IV amikacin to reduce toxicities and may be helpful for other antibiotics in patients with refractory disease or in patients with medical conditions (eg, reduced renal function or CF) that are suspected to lead to subtherapeutic or toxic drug concentrations.[7,42] The antibiotics used to treat *M abscessus* species are frequently associated with adverse reactions and toxicities; therefore, education of patients and a close monitoring plan should be established at the beginning of treatment (**Table 24-2**).[7]

Table 24–2. Antimicrobial Toxicities and Monitoring

Drug	Major Adverse Effects	Monitoring, in Addition to Clinical Symptoms
Amikacin	Vestibular toxicity or ototoxicity, nephrotoxicity	Audiograms, periodic renal function tests, drug levels
Amikacin liposome inhalation suspension	Dysphoria, vestibular toxicity or ototoxicity, nephrotoxicity, cough, dyspnea	Audiograms, periodic renal function tests, drug levels
Azithromycin, clarithromycin	Gastrointestinal disturbance, hepatotoxicity, decreased hearing, QT interval prolongation	Periodic liver function tests, audiograms, electrocardiograms
Cefoxitin	Drug hypersensitivity, cytopenias	Periodic complete blood cell counts
Clofazimine	Discoloration of skin and body secretions, hepatotoxicity, QT interval prolongation	Periodic liver function tests, electrocardiograms
Ethambutol	Optic neuritis (loss of red–green discrimination and acuity), peripheral neuropathy	Visual acuity and color discrimination
Imipenem	Hypersensitivity (rash), cytopenias, nephrotoxicity	Periodic complete blood cell counts, renal function tests
Isoniazid	Hepatitis, peripheral neuropathy	Periodic liver function tests
Linezolid	Cytopenias, peripheral neuropathy, optic neuritis	Periodic complete blood cell counts, visual acuity and color discrimination
Moxifloxacin	Tendinitis, hepatotoxicity, QT interval prolongation	Electrocardiograms, periodic liver function tests
Rifampin	Orange discoloration of body secretions, hypersensitivity, hepatotoxicity, cytopenias, drug–drug interactions	Periodic complete blood cell counts, liver function tests
Tigecycline	Tooth staining < 8 years old, gastrointestinal disturbance, hepatitis or pancreatitis	Periodic liver function tests, amylase and lipase levels

Other pulmonary manifestations of NTM infection, such as hot tub lung, can be treated by removal of the source of exposure and administration of steroids. Antibiotic treatment is rarely necessary. Lymphadenitis does not always require treatment; in mild cases, observation for spontaneous resolution may be appropriate. If treatment is required, complete surgical excision

of the affected node is considered the definitive therapy, with or without antibiotics directed at the primary pathogen. Appropriate antibiotic therapy, with or without surgical excision, is also used in the treatment of endobronchial NTM infections.[24] Skin and soft-tissue infections also typically require treatment with multidrug antibiotic regimens.[25] Treatment of NTM infections associated with defects in the IFN-γ/IL-12 axis, typically disseminated disease, may include immunomodulatory therapy. If response to INF-γ is predicted by the defect, or documented in vitro, this therapy may augment antimicrobial therapy. Consultation with an immunologist or infectious disease expert is advisable.

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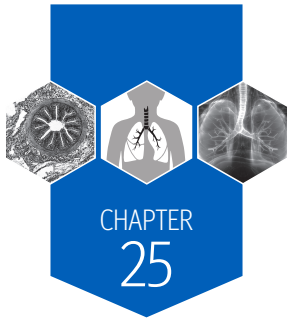
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CHAPTER 25

Atelectasis

Girish D. Sharma, MD, FAAP, FCCP

CASE REPORT 25-1

A 14-year-old boy with congenital muscular dystrophy and history of marked weakness, chronic respiratory insufficiency, tracheostomy, and assisted ventilation is brought to the emergency department with shortness of breath and low pulse oximeter readings. He has not used the cough assist device prescribed in the neuromuscular pulmonary clinic. Physical examination results are remarkable for diminished air entry in the left lower zone posteriorly. Venous blood gas has worsened since the last blood gas measurement, with evidence of hypercarbia and hypoxia, and the chest radiograph showed left lower lobe opacity with reduced intercostal spaces. Left lower lobe atelectasis is diagnosed.

Introduction

Atelectasis refers to a loss of lung volume owing to collapse of part or all of the lung. Usually the magnitude of the collapsed alveolar spaces is severe enough to appear on a plain chest radiograph. Patients with conditions associated with increased and more viscid secretions, such as cystic fibrosis (CF), are more likely to develop atelectasis, which may result in transient hypoxemia due to ventilation/perfusion mismatching. Secondary infection of the atelectatic lung and bronchiectasis in the atelectatic portion of a chronically infected lung may occur.

Epidemiology

Atelectasis is almost always a secondary phenomenon, occurring more frequently in young children because their airways are small and thus prone to blockage. In the newborn lung, the interalveolar holes (pores of Kohn) are either absent or few in number, thereby preventing collateral communication. Therefore, infants are more prone to developing atelectasis than are older children or adults.[1] The incidence of atelectasis varies according to the cause and background conditions. The most common cause is asthma, but there are no incidence data in children. Patients with CF tend to develop atelectasis (up to

5%).[2] A much higher incidence is reported in patients postoperatively (up to 23%)[3] and in patients with neuromuscular disorders (up to 85%).[4] In children with congenital heart disease, extrinsic compression of the airways owing to enlarged heart chambers or dilated blood vessels can lead to atelectasis, especially postoperatively. Patients in the intensive care unit after they have undergone intubation and are using a ventilator have a tendency to develop atelectasis because of secretions blocking the airways and inability to cough. Shallow breathing, associated with sedation, anesthesia, mode of ventilation such as oscillatory ventilation, and extracorporeal membrane oxygenation, may lead to the development of atelectasis. Medications such as anticholinergics may increase the viscosity of the airway secretions, impairing the mucociliary clearance. The current emphasis on airway clearance in children with conditions such as primary ciliary dyskinesia,[5] neuromuscular disorders,[6,7] and CF,[8] and in patients postoperatively after various surgeries,[9] should result in a lower incidence of atelectasis (see Chapter 55, Airway Clearance Techniques). Airway obstruction due to plastic bronchitis in patients who have undergone a Fontan procedure may cause clinically significant airway obstruction, atelectasis, and increased need for assisted ventilation.[10]

Etiology

Atelectasis can result from either obstructive or nonobstructive causes (**Box 25-1**).

Obstructive Atelectasis

Obstructive atelectasis involves a loss of communication between alveoli and the trachea, resulting in reabsorption of the gas from the alveoli. There is lack of ventilation in the area distal to the obstruction. The pores of Kohn, which normally provide collateral communication between the adjacent alveoli, are absent in young infants[11] and may not form for the first 3 to 4 years.[12] The air from the airways, distal to the obstruction, is absorbed by the circulating blood, leading to collapse of the corresponding alveoli. In the early stages, blood perfusion in this area continues, resulting in ventilation/perfusion mismatching and arterial hypoxemia.[13] Because oxygen from the airways is absorbed more rapidly than is the nitrogen in room air (within minutes versus hours), atelectasis develops more rapidly during ventilation with a high inspired oxygen fraction.[12] The alveolar spaces may be filled with secretions, thereby preventing complete collapse of the atelectatic lung. There may be compensatory distention of the uninvolved surrounding lung tissue. When there is a large area of atelectasis, there can be a shift of the heart and the mediastinum toward the atelectasis, the diaphragm may be elevated, and the chest wall may flatten. These findings can appear within a period of a few hours if there is an extensive area of atelectasis, and removal of the obstruction

Box 25-1

Causes of Atelectasis

Intrinsic Obstruction of the Airways
- Asthma
- Bronchiolitis
- Aspiration
- Endobronchial lesions (tuberculosis)
- Foreign body
- Cystic fibrosis (viscid secretions)

Extrinsic Compression of the Airways
- Enlarged lymph nodes
- Tumors
- Enlarged heart or vasculature

Compression of Lung Tissue
- Decoupling of the inward recoil of the lung and outward recoil of the chest wall because of the presence of air, blood, pus, or chyle in the pleural space
- Pneumothorax
- Hemothorax
- Pyothorax
- Chylothorax
- Compression due to causes other than pleural space disease
- Intrathoracic abdominal mass
- Chest wall mass
- Enlarged heart
- Overdistended adjacent lung tissue
- Space-occupying lesions of the lung
- Skeletal deformities of the chest wall

Incomplete Expansion of the Alveoli and Collapse
- Hypoventilation due to muscle weakness in neuromuscular disorders
- Postoperative period
- Splinting of the chest wall because of painful lesions resulting in hypoventilation
- Drug-induced hypoventilation
- Cicatrization atelectasis due to severe parenchymal scarring

Lack of Surfactant
- Lack of production (prematurity, acute respiratory distress syndrome)
- Inactivation (radiation pneumonitis, blunt trauma to the lung)
- Surfactant washout (drowning, pulmonary edema)

leads to return to a normal state. In a protracted case of atelectasis, such as that caused by the viscid secretions in patients with CF, chronic aspiration, or undiagnosed foreign body, infection may occur. Persistent, untreated infection can lead to bronchiectasis.

The site of obstruction dictates the extent and distribution of atelectasis; for example, the obstruction of a lobar bronchus will cause lobar atelectasis. Intrinsic obstruction of the airways is the most common cause of atelectasis in children, and asthma is the most common predisposing disorder. Children with airway inflammation caused by asthma may have thicker secretions, which, in conjunction with airway narrowing, result in subsegmental or lobar atelectasis.

This situation poses a diagnostic dilemma when children with asthma present with an exacerbation, an abnormal radiograph, and a possible diagnosis of pneumonia. Some other common causes of obstruction are bronchiolitis aspiration from any cause, including gastroesophageal reflux and oropharyngeal incompetence; foreign body aspiration; and airway obstruction due to viscid secretions (eg, in CF).

Extrinsic compression of the airway from enlarged lymph nodes or an enlarged heart compressing the left main or left lower lobe bronchus, as well as airway wall thickening caused by edema and inflammation, may be causative factors. The right middle lobe is particularly susceptible to atelectasis; this is described as *middle lobe syndrome* or *Brock syndrome*. The right middle lobe bronchus is surrounded by lymph nodes that drain the right middle and lower lobes. The middle lobe syndrome was originally described in association with tuberculosis; however, it may be seen with other conditions such as CF and asthma. Patients having reduced lung expansion and lung recruitment associated with muscle weakness, splinting of the chest wall because of postoperative pain after thoracoabdominal surgery (**Figure 25-1**), hypoventilation due to narcotic medications, and musculoskeletal deformities are predisposed to developing atelectasis if there is poor airway clearance and pooling of secretions in the airways.

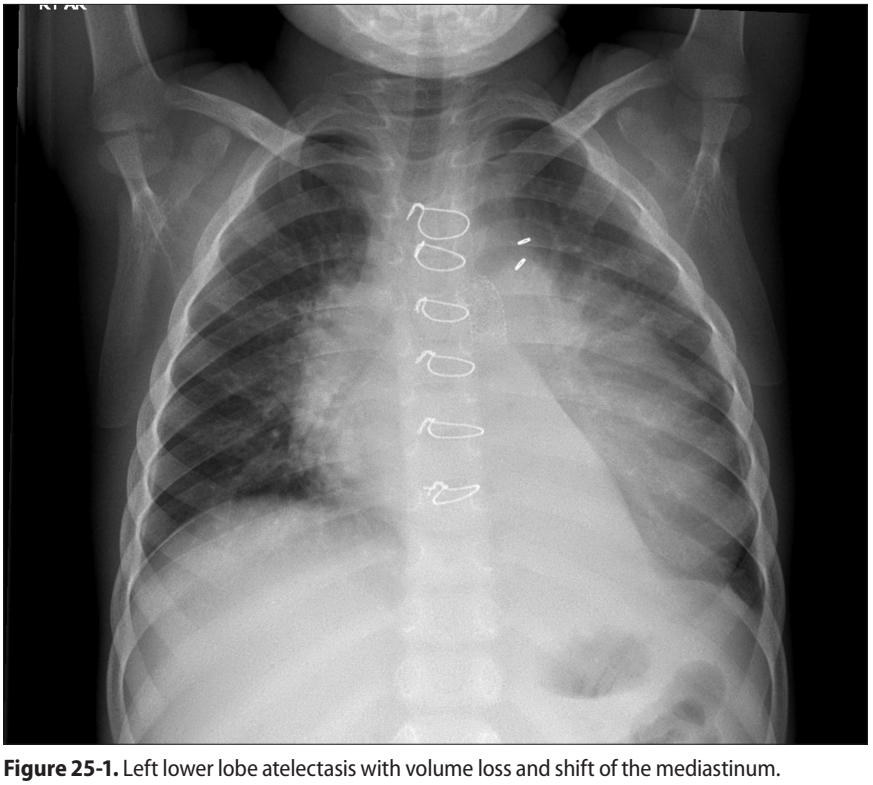


Figure 25-1. Left lower lobe atelectasis with volume loss and shift of the mediastinum.

Nonobstructive Atelectasis

The loss of contact between the visceral and parietal pleura is the primary cause of nonobstructive atelectasis. Normally, there is a balance between the factors responsible for the inward recoil of the lung and the outward recoil of the chest wall to reduce the potential for lung or alveolar collapse. In addition, surfactant protein produced by type II alveolar epithelial cells lowers the surface tension in the alveoli and prevents alveoli from collapsing. As alveolar volume decreases with expiration, surface tension increases to the extent that, without surfactant, the alveolus will collapse completely. Surfactant deficiency can lead to adhesive atelectasis. Dependent atelectasis is almost always present in patients receiving sedation for procedures such as computed tomography (CT) scanning unless measures such as endotracheal intubation and ventilation to maintain a large tidal volume are used. Atelectasis is also caused by compression of lung tissue owing to pleural effusion (pneumothorax, hemothorax, empyema, or chylothorax), space-occupying lesions of parenchyma, and hyperinflated adjacent lung parenchyma. Cicatrization atelectasis is caused by severe parenchymal scarring.

Clinical Features

Small areas of atelectasis often are detected only when a chest radiograph is obtained for other reasons. Microatelectasis, common in patients with neuromuscular disorders, may not be visible on chest radiographs. With larger areas of atelectasis, there may be tachypnea as the patient tries to compensate for decreased tidal volume by increasing the frequency of respiration. A child may grunt while attempting to create an auto-positive end-expiratory pressure, and sudden hypoxia may develop as evidenced by a sudden or rapid decrease in oxyhemoglobin saturation. Physical examination may not reveal any additional findings in children with small areas of atelectasis. In children with larger areas of involvement, such as lobar involvement or complete lung collapse, breath sounds are diminished, there is increased dullness on chest percussion, and a mediastinal shift may be present.

Diagnosis

Chest Radiography

Clinically unrecognized atelectasis may be revealed by a chest radiograph. There may be a displacement of fissures and opacification of the collapsed lobe. The site of obstruction will dictate the portion or area of the atelectasis, which can be the entire lung or 1 or more lobes (**Figure 25-2**). Other indirect signs, such as hilar displacement, mediastinal shift toward the side of collapse, loss of volume in the corresponding area or ipsilateral hemithorax, crowding of the ribs, compensatory hyperinflation of the adjacent area, or obliteration of the cardiac borders or diaphragm, may be visible on chest radiographs.

Examination of air bronchograms on chest radiographs may help determine whether proximal or distal airways are obstructed.

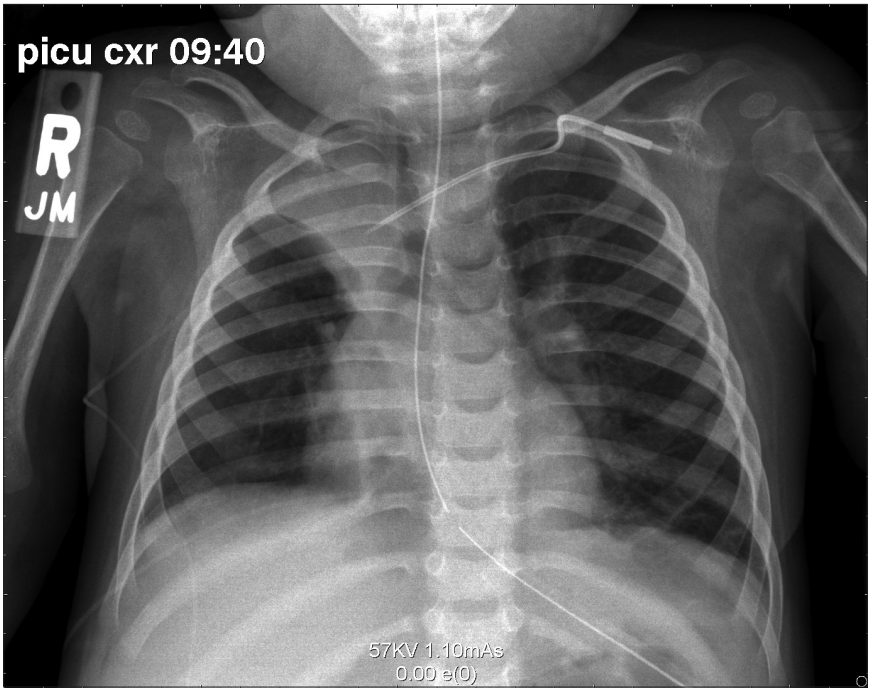


Figure 25-2. Right upper lobe atelectasis with volume loss.

Lung Ultrasonography

Lung ultrasonography has good sensitivity, specificity, and accuracy to diagnose postoperative atelectasis in children[14]; therefore, it has been suggested for use in diagnosing atelectasis in children with neuromuscular disorders.[15] Lung ultrasonography was found to be more effective than conventional therapies in preventing intraoperative atelectasis.[16]

Magnetic Resonance Imaging of the Lung

Magnetic resonance imaging of the lung is being tried in the diagnosis of various pulmonary disorders[17] and may be used to diagnose atelectasis.[18] In small children, for whom voluntary breath holding is not possible, sedation or general anesthesia has been used for a satisfactory examination. However, because of the risks associated with anesthesia, including dorsal atelectasis,

respiratory navigation (radiofrequency-tracking pulses to detect physical motion) during magnetic resonance imaging is being used[19] to obviate the need for sedation or general anesthesia.[20]

Computed Tomography

Chest CT may help evaluate airway compression, detect underlying disease, and reveal diffuse disease undetected with chest radiography. Because of the inherent additional risk of a patient developing atelectasis during general anesthesia, ultrafast chest CT using respiratory navigation during free breathing[21] is gaining wider acceptance at various centers in the United States. The best way to avoid iatrogenic atelectasis caused by sedation is by performing the examination with the child having undergone intubation and ventilation with high tidal volumes.[22]

Management

Some measures may prevent the formation of atelectasis (**Table 25-1**). These include aggressive and regular chest physical therapy (CPT) and postural drainage in patients with CF[23] and primary ciliary dyskinesia.[5] Patients with neuromuscular disorders, such as Duchenne muscular dystrophy,[6,7] may benefit from breathing exercises and preventive airway clearance techniques. Adequate pain management, early ambulation, and frequent position changes postoperatively to prevent splinting of the chest may reduce the incidence of atelectasis. Apart from some anecdotal reports, there is no evidence, such as double-blinded placebo-controlled trials, to support the routine use of dornase alfa hypertonic or normal saline, N-acetylcysteine, heparin, sodium bicarbonate, or bronchoscopy in patients with atelectasis. See **Figure 25-3** for steps in managing possible atelectasis.

Table 25-1. Preventive Measures to Reduce Atelectasis

Clinical Condition	Preventive Measures
Cystic fibrosis, primary ciliary dyskinesia	Chest physical therapy and postural drainage
Neuromuscular disorder	Use of cough assist device
Postoperative period	Chest physical therapy Pain control Early ambulation Frequent position changes Ultrasound-guided lung recruitment maneuver

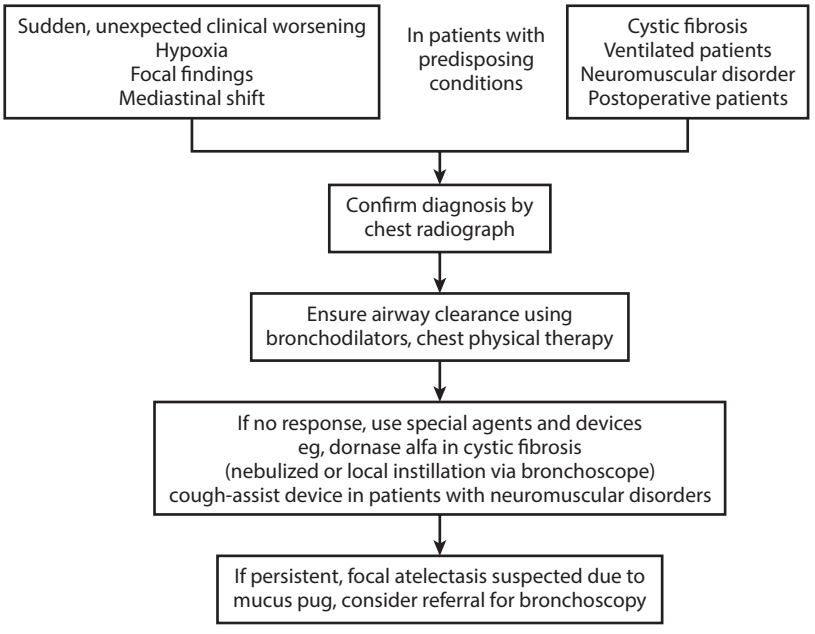


Figure 25-3. Management of suspected atelectasis.

Chest Physical Therapy

Although CPT has traditionally been the first-line therapy to prevent atelectasis, evidence for its efficacy is lacking.[24] In one study, postextubation CPT in neonates did not prevent postextubation atelectasis.[25]

Aggressive airway clearance is the attempt to clear mucus and secretions from the trachea and bronchial tree and includes nebulized or inhaled bronchodilators (β_2-agonists such as albuterol) followed by CPT and postural drainage. However, evidence is lacking to support using a bronchodilator as a component of an airway clearance regimen.[26] Chest physical therapy may be provided by using hand percussion and postural drainage or by using a mechanical method, the choice of which will depend on the underlying disorder. For example, the cough assist device used in patients with neuromuscular disorders[6] may not be appropriate for patients with CF who will be better served by a high-frequency chest wall oscillation device.[27] Other positive expiratory oscillation devices, such as the FLUTTER mucus clearance device (Axcan Scandipharm, Inc) or the acapella Vibratory PEP Therapy System (Smiths Medical), may also be used for airway clearance (see Chapter 55, Airway Clearance Techniques).

Intrapulmonary Percussive Ventilation

Intrapulmonary percussive ventilation is a form of CPT delivered by a percussive pneumatic device that delivers high-flow jets of gas to the airways by means of a pneumatic flow interrupter at a rate of 100 to 300 cycles per minute. The duration of percussion is controlled by the patient or the therapist. The driving pressure and peak airway pressure are adjustable. Intrapulmonary percussive ventilation maintains lung volume in a state of partial inspiration while the airways are internally percussed. It has been used in patients with CF and neuromuscular disorders.[28,29]

Recombinant Human DNase

Dornase alfa is a recombinant human DNase that when nebulized or directly instilled into the airways reduces the viscoelasticity of purulent secretions, especially in patients with CF. The Cystic Fibrosis Foundation recommends regular use of dornase alfa by children with CF, 6 years or older, with moderate to severe lung disease.[27] There have been reports of successful use of bronchoscopically administered dornase alfa for the treatment of lobar atelectasis in patients with CF,[30] but prospective controlled trials are lacking (see Chapter 55, Airway Clearance Techniques). Evidence is lacking to support its use in the neonatal or pediatric intensive care unit with non-CF causes of atelectasis or other lung diseases.

Oximetry and Blood Gas Measurement

Atelectasis may be associated with a decrease in oxyhemoglobin saturation or evidence of hypoxia on a blood gas profile.

When to Refer

For bronchoscopy:

- Bronchoscopy with therapeutic lavage should be considered when obstruction due to a mucous plug is considered to be causing atelectasis and there is no response to noninvasive airway clearance.[6]
- Patients with CF with persistent lobar atelectasis may benefit from lavage with local administration of recombinant human DNase.[28]
- Atelectasis caused by a foreign body requires bronchoscopy.

When to Admit

- Massive atelectasis
- Hypoxia
- Suspected foreign body

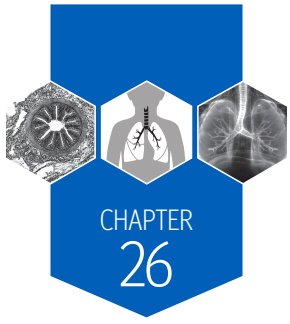
key points

- Extrinsic compression of the airways or lung tissue and intrinsic airway obstruction are some of the common causes of atelectasis.
- Clinically unrecognized atelectasis may be diagnosed by using chest radiography.
- Appropriate preventive measures to assist effective cough, airway secretion mobilization, and drainage by means of CPT and postural drainage may help prevent development of atelectasis.
- Atelectasis may be associated with a decrease in oxyhemoglobin saturation or evidence of hypoxia on a blood gas profile.

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Respiratory Disorders Associated With Systemic Inflammatory Diseases

Paul C. Stillwell, MD, FAAP
Eric D. Zee, MD

Introduction

The lungs are at risk for involvement in systemic inflammatory disorders because of their enormous vascular network, both systemic and pulmonary; extensive immunologic network; and vast structural framework. Systemic inflammatory diseases such as collagen vascular (or rheumatic) diseases,[1,2] vasculitidies,[3,4] and granulomatous diseases[5] may all have respiratory system involvement. Because most of these systemic diseases occur relatively infrequently in children, much of what we know about the lung involvement is extrapolated from adult literature. With national and international registries for pediatric-specific diseases, there is a growing body of information regarding the pediatric experience.

Systemic inflammatory diseases may present with a limited number of organs involved or multiple organ systems involved. Frequent constitutional complaints include fevers, malaise, fatigue, and arthralgias. Lung involvement might be an initial presenting feature, or the lungs may become involved as the primary underlying disease process evolves. Common pulmonary complaints include cough, dyspnea, exercise intolerance, chest pain, and hemoptysis. The findings on the pulmonary examination will vary according to the type of lung involvement. With pleural effusions, the breath sound intensity is decreased, as is the percussion note. With interstitial disease and pneumonia, crackles are common. If pulmonary hypertension is present, the pulmonic component of the second heart sound may be accentuated. Examination of other systems may lend a clue as to the underlying diagnosis, such as the distribution of the arthritis, pattern and type of skin involvement, digital clubbing, peripheral edema, weakness, nasal deformity, and ocular involvement.

A plain chest radiograph is often the initial imaging, but high-resolution computed tomography (HRCT) of the chest or computed tomography angiography provides more detailed information regarding the nature of the respiratory involvement.[6,7] Ultrasonography is helpful in assessing pleural disease and effusions, particularly if there is concern for infection in the pleural space. While the radiographic patterns can be highly suggestive of a specific underlying diagnosis, there is considerable overlap between the systemic inflammatory diseases and the appearance of infectious complications of the inflammatory disease or its treatment. Therefore, the imaging pattern may be highly suggestive of a specific disease process, but it is seldom diagnostic without additional studies.

A pulmonary function test (PFT) can be an integral part of the evaluation as well as a noninvasive mechanism to follow the pulmonary disease progression or improvement. The spirometry pattern varies with the specific underlying disease and pulmonary involvement, but it commonly shows a restrictive pattern. Restriction should be confirmed with lung volume measurements rather than relying solely on the spirometric data. If restriction is documented, the respiratory muscle strength should be assessed with maximal inspiratory and expiratory pressures to be sure that the restriction is not from weakness. If bronchiectasis or bronchiolitis obliterans is present, there may be an obstructive pattern on the spirometry and air trapping evident on the lung volumes. The diffusing capacity is typically low unless alveolar hemorrhage has occurred, which elevates the diffusing capacity.

Flexible fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) is helpful in assessing airway anatomy and appearance as well as differentiating among infections, inflammation, and alveolar hemorrhage, which can be a presenting problem for several systemic inflammatory diseases. Transbronchial biopsy can be useful to identify the noncaseating granulomas in sarcoidosis, but the small tissue sample can often miss the most significant pathology in other diseases of this nature. Therefore, if lung tissue is needed for diagnostic purposes, a video-assisted thoracoscopic lung biopsy is usually preferred.

Diagnostic criteria are established for each of these diseases to help provide correct classification and to unify disease identification between institutions. Despite specific criteria, some patients do not fit perfectly into a disease category, and occasionally the specific disease will be recognized at a later date after evolution of the primary disease process. The pattern of organ involvement can vary widely within a specific disease process, so in addition to the clinical presentation, both imaging and laboratory investigation are usually required to establish the correct diagnosis. The use of a variety of

antibody and antigen markers as well as other pertinent laboratory tests frequently allows a specific and accurate diagnosis to be determined.[8,9] Pathologic examination of a tissue biopsy specimen can be very supportive when a disease-specific location and abnormal histologic appearance are present. Treatments for the primary disease process may cause a lung problem or risk for opportunistic pulmonary infection, further confounding the correct diagnosis.[10]

A multidisciplinary team often participates in the diagnosis and management of patients with systemic inflammatory diseases. Key members may include clinicians from rheumatology, pulmonology, infectious disease, intensive care, and nephrology. Pediatric surgery is often called on to obtain biopsy specimens. Other specialists may be valuable depending on the specific organ system affected. Because of the complexity of multisystem disease and the challenges in establishing a diagnosis, referral to an experienced specialist early in the disease process is appropriate. The decision regarding hospitalization is determined by the severity and acuity of the initial presentation and subsequently by the response to therapy and potential complications. Many of these disease processes seem to have an ethnic predisposition. Reasons for this are not well understood, with more research for some diseases than for others. Regardless, these diseases are clearly affected by socioeconomic factors, inequities, and barriers to care.[11]

Rheumatic Diseases

For most patients, the constellation of symptoms, examination findings, and laboratory study results allows for a specific categorization of the disease process.[8,9] However, some children have a constellation of rheumatic and dermatologic problems that do not fit easily into a discrete diagnostic category. These diagnoses are termed *mixed connective tissue diseases* or *overlap diseases*; they comprise features of systemic lupus erythematosus (SLE), systemic sclerosis, dermatomyositis, and juvenile idiopathic arthritis (JIA). These patients seem to have a similar risk for pulmonary involvement, with the same respiratory disease processes that occur in systemic sclerosis and dermatomyositis.

The uncommon conditions of systemic sclerosis (scleroderma) and idiopathic inflammatory myositis (dermatomyositis and polymyositis) are associated with a higher risk for pulmonary disease than the most commonly occurring pediatric rheumatic disease, JIA, in which pulmonary disease occurs relatively infrequently (**Table 26-1**).[12–16] In SLE, a relatively common rheumatic disease, diverse lung involvement occurs frequently (**Table 26-2**).[17,18]

Table 26-1. Relative Frequency of Rheumatic Diseases and Associated Pulmonary Disease

Characteristic	Systemic JIA	SLE	JSS		JDM
Incidence (per 10^5)	1	0.3–0.9	Unknown		0.2–0.4
Age at onset	Variable	Adolescence	Unknown		7 y
Antibody associations	None	ANA, anti-dsDNA	ANA, anti-Scl-70; anti-centromere (in CREST syndrome)		ANA, myositis-specific antibodies
Pulmonary involvement	+	+++	+++		++
Female-to-male ratio	1:1	4–5:1	≤ age 8 y	> age 8 y	2–4:1
			1:1	3:1	
Ethnic prevalence[a]	None	African American, Hispanic, Native American, Asian	African American, Native American		No

Abbreviations: ANA, antinuclear antibody; anti-dsDNA, anti-double stranded DNA; anti-Scl-70, anti-scleroderma-70 antibodies; CREST, calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia; JDM, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; JSS, juvenile systemic sclerosis; SLE, systemic lupus erythematosus; +, occasional occurrence; ++, common or significant; +++, quite frequent or very significant.

[a] Reasons for apparent ethnic prevalence are not well understood; these diseases are clearly affected by socioeconomic factors, inequities, and barriers to care.

Table 26-2. Common Pulmonary Involvement Associated With Collagen Vascular Disease

Pulmonary Involvement	JIA	SLE	MCTD	jSS	jDM	SjS
Pleuritis/effusion	+	+	++	—	—	—
ILD	+/–	++	+++	+++	+	+
DAH	—	+++	+	+	—	—
Abnormal PFT	+/–	+++	+	++	++	+
Abnormal D_{LCO}	—	++	++	++	++	+
Pneumonitis	+	+++	+/–	++	++	+
Weakness	—	—	+	++	++	—
Dysphagia/aspiration	—	—	—	+++	+++	—
PH	—	++	—	+++	+	+
PAP	+/–	—	—	—	—	—
Thrombosis/PE	—	++	—	—	—	—
Bronchiectasis	+	+	+	+	—	—
Other	MAS	—	—	—	—	LIP;NHL

Abbreviations: DAH, diffuse alveolar hemorrhage; D_{LCO}, diffusing capacity for carbon monoxide; ILD, interstitial lung disease; jDM, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; jSS, juvenile systemic sclerosis; LIP, lymphoid interstitial pneumonitis; MAS, macrophage activation syndrome; MCTD, mixed connective tissue disease; NHL, non-Hodgkins lymphoma; PAP, pulmonary alveolar proteinosis; PE, pulmonary embolism; PFT, pulmonary function test; PH, pulmonary hypertension; SjS, juvenile Sjögren syndrome; SLE, systemic lupus erythematosus; —, rare or infrequent; +/–, some occurrence; +, occasional occurrence; ++, common or significant; +++, quite frequent or very significant.

Juvenile Idiopathic Arthritis

Formerly known as *juvenile rheumatoid arthritis*, JIA is the most common rheumatologic disease of childhood.[12,13] It consists of 7 subtypes: oligoarthritis, rheumatoid factor (RF)–negative polyarthritis, RF-positive polyarthritis, systemic arthritis, psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis. The classification depends on clinical manifestations, articular and extra-articular involvement, number of joints affected, and RF and human leukocyte antigen (HLA)-B27 positivity.

Clinical Manifestations

Joint stiffness and swelling are the most common presenting symptoms. These symptoms tend to improve over the course of the day with increased activity and warm showers. Children with JIA can have worse symptoms in the morning and an abnormal gait (walking like an "old person"). Joint pain is typically mild and at times absent. Pulmonary-specific symptoms are relatively rare.[12]

Pulmonary Evaluation

Pulmonary involvement is more common with systemic JIA[13]; it is rarer in patients with polyarticular JIA. As with many other rheumatologic causes of pulmonary disease, serositis and pleuritis are the most common presentations. Clinical presentations most commonly include cough, dyspnea, chest pain (with or without pleurisy and effusion), and increased pulmonary infections. Rarer but more severe pulmonary-related findings of interstitial lung disease (ILD), alveolar proteinosis, and pulmonary hypertension are suggestive of uncontrolled systemic disease. Pulmonary function test abnormalities may precede the onset of arthritis. Pulmonary function testing, plain chest radiography, and HRCT can be helpful in the initial evaluation of pulmonary involvement (**Figure 26-1**). Bronchoalveolar lavage can be helpful in determining if an inflammatory process is present and in ruling out infection with neutrophils predominating. However, lung biopsy remains the gold standard.

Management

Historically, treatment consisted of nonsteroidal anti-inflammatory drugs (NSAIDs); first-line treatment has been transitioning to disease-modifying antirheumatic drugs (DMARDs).[12,13,19] NSAIDs are still used for shorter time frames (1–2 months) or when the diagnosis of JIA has not been firmly established. Systemic steroids are used less often for long-term treatment, given their adverse effects, although intra-articular glucocorticoids continue to be a common component of the treatment plan. Methotrexate has been the most common DMARD used in JIA. Other DMARDs include leflunomide and sulfasalazine. Biologic DMARDs include tumor necrosis factor inhibitors

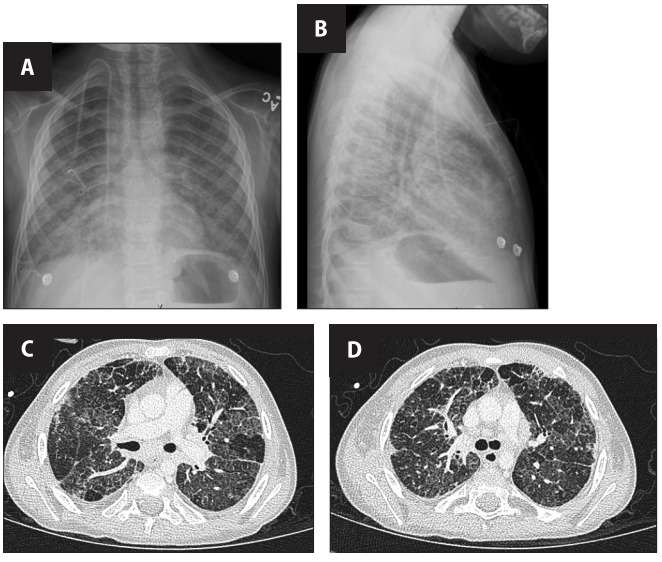


Figure 26-1. Seven-year-old with systemic juvenile idiopathic arthritis and secondary pulmonary alveolar proteinosis. Frontal (**A**) and lateral (**B**) chest radiographs and axial computed tomography images (**C**, **D**) show diffuse centrilobular interstitial thickening with ground-glass opacities.

such as etanercept, adalimumab, and infliximab; interleukin-1 (IL-1) receptor antagonist anakinra; interleukin-6 (IL-6) inhibitor tocilizumab; and T-cell co-stimulation inhibitor abatacept.[19]

New concerns have arisen regarding novel parenchymal lung disease in patients with JIA consisting of septal thickening and ground-glass opacities on CT scan, with pathologic changes of pulmonary alveolar proteinosis or endogenous lipoid pneumonia. A 2019 study suggested there was increased risk in children with Down syndrome; in those with young age of onset of JIA; and in those with exposure to IL-1 and IL-6 inhibitors, although severity might have been caused by the underlying disease process itself. Preliminary concern is for macrophage dysfunction as the etiology.[20]

Systemic Lupus Erythematosus

Systemic lupus erythematosus in children is a multisystem autoimmune disease with great variability of symptoms.[14,17] The diagnosis is based on the presence of at least 4 of 11 criteria from the American College of Rheumatology classification criteria, or more recently the Systemic Lupus International Collaborating Clinics Classification. Systemic lupus erythematosus rarely occurs before 5 years of age, and its incidence varies by sex and ethnicity; groups with a higher incidence include female, Hispanic, Black, Native American, and Asian individuals.[14]

Clinical Manifestations

Children with SLE can have more severe organ involvement with worse outcomes than adults. Many systems can be involved in children with SLE, including musculoskeletal (arthritis), skin (malar or photosensitive rash), neuropsychiatric (cognitive dysfunction, headaches), hematologic (cytopenia), cardiac (pericarditis, pericardial effusion, and premature atherosclerosis), renal (nephritis or nephrosis), and lung disease.

Pulmonary disease has a wide range of clinical severity, from asymptomatic PFT abnormalities[14,18] to severe life-threatening pulmonary hemorrhage.[21] Systemic lupus erythematosus–related lung disease consists of acute and chronic findings. Acute findings with chest pain and respiratory distress can revolve around serositis with pneumonitis and pleuritis. Simultaneous infectious pneumonia may complicate the clinical picture. Chronic findings consist of more severe disease, including pulmonary hemorrhage, pulmonary fibrosis, and pneumothorax.[21] Less common findings include diaphragmatic involvement (shrinking lung syndrome, phrenic nerve paralysis), vasculitis, chronic thromboembolic pulmonary hypertension with secondary antiphospholipid antibody syndrome, and pulmonary embolus. Pulmonary hypertension usually occurs late in the disease process and suggests poor prognosis; treatment with vasodilators (prostacyclins or inhaled nitric oxide) has not been shown to be effective. Chronic ILD also can present, with crackles and nonproductive cough; imaging often reveals scattered nodular densities. Cryptogenic organizing pneumonia is a rare complication.[21]

Pulmonary Evaluation

Plain chest radiographs help to differentiate the clinical patterns seen: pleurisy with effusion, pleuropericarditis with diaphragm thickening or elevation, and fibrosing alveolitis.[6] High-resolution computed tomography is indicated if the plain radiograph does not explain the symptoms and signs. Additional pulmonary investigations include bronchoscopy, bronchoalveolar lavage, and lung biopsy, especially to differentiate between SLE and infection.[21] Distinguishing lupus-induced pulmonary disease from infection can be a diagnostic challenge.

Pleural fluid in active SLE is exudative (protein > 3 g/dL, pH > 7.35), although it may be transudative on occasion. The fluid typically has an elevated white blood cell count (2,500–5,000 cells/mm^3) with mononuclear and lymphocyte predominance; LE cells may be present, and the positive antinuclear antibody titer is usually greater than the patient's serum titer.[22] Pulmonary function test results are abnormal in two-thirds of patients, with obstruction of small airways and decreased carbon dioxide diffusing capacity (D_{LCO}) the most prevalent complications.[21]

Management

Treatment for SLE should be handled in conjunction with a pediatric rheumatologist. NSAIDs provide symptomatic relief of mild pleuritis if the patient is not at risk for hemorrhage or experiencing decreased renal function. Hydroxychloroquine has also become a mainstay of therapy in decreasing rates of flare, organ damage, and thrombotic effects. Failure to respond may lead to a trial of an immunosuppressive agent or a biological response modifier, such as anti-CD19 monoclonal antibodies (rituximab) or an anti–B lymphocyte stimulator (belimumab).[19] Corticosteroids, including high-dose pulse therapy, are the treatment for severe acute pulmonary disease. Treatment may also be needed for specific processes, such as pulmonary hemorrhage and pulmonary hypertension. Patients with SLE often are immunocompromised, which increases their risk of developing pulmonary infections.[10,21]

Juvenile Dermatomyositis

Juvenile dermatomyositis (JDM) is an autoimmune disorder that occurs much less frequently than either JIA or SLE,[15,16] but it seems to be associated with a high risk of pulmonary involvement.[23] Although JDM occurs infrequently, it is one of the more easily identifiable of the systemic inflammatory myopathies.[24]

Clinical Manifestations

Nonspecific symptoms predominate, including malaise, fever, rash, and fatigue. Proximal muscle weakness and elevated muscle enzymes are frequently seen. It is important to be aware of musculoskeletal and cutaneous manifestations (heliotrope discoloration of the eyelids and Gottron papules); these can present before pulmonary involvement.[23] As many as one-third of patients will have pulmonary signs or symptoms sometime during the course of their disease.[23] Although the disease initially may be asymptomatic, the most common clinical manifestations are dyspnea and cough. Interstitial lung disease is commonly seen with JDM and is associated with significant morbidity. Because of proximal muscle weakness, patients may have impaired secretion control and increased susceptibility to pneumonia. They are also at risk for aspiration because of pharyngeal weakness. Children are also at risk for hypoventilation. Clinicians need to be vigilant for opportunistic lung infections secondary to immunosuppressive therapies.[10]

Pulmonary Evaluation

Pulmonary disease in JDM may occur less often than in adult disease. Anti-RNA synthetases, anti-Jo-1 antibody, and anti-MDA-5 are strong predictive factors in development of ILD. Rapidly progressive and fatal ILD with JDM has been associated with positive anti-MDA-5 antibody.[25] Pulmonary function testing is useful; even children without respiratory symptoms can have abnormalities, with restrictive pulmonary disease and reduced

diffusion capacity. High-resolution computed tomography has been less helpful in establishing the diagnosis in children. Children still may require a lung biopsy to establish the diagnosis of ILD.[1,23]

Management

Pharmacological treatment is centered around glucocorticoids combined at times with methotrexate or cyclosporin. For children with more severe disease or pulmonary involvement, high-dose pulse methylprednisolone has been used. There also have been case reports involving use of cyclophosphamide and rituximab.[19]

Juvenile Systemic Sclerosis

Localized scleroderma and juvenile systemic sclerosis (JSS) are thought to be 2 separate entities rather than a spectrum of the same disease process.[9,14,16] Juvenile systemic sclerosis is associated with hardening of the skin (morphea) and diffuse organ fibrosis and vasculopathy within the heart, lung, GI tract, and kidneys. It occurs in girls 3 times more commonly than in boys after age 8 years. Before 8 years of age, JSS is exceedingly rare and the incidence is similar for boys and girls.

Clinical Manifestations

Diagnostic criteria for JSS require skin thickening proximal to the metacarpophalangeal joints and at least 2 additional minor criteria consisting of specific organ involvement (including pulmonary fibrosis, decreased D_{LCO}, and pulmonary hypertension) and positivity to certain autoantibodies. Cardiopulmonary disease occurs in 30% to 50% of children with systemic sclerosis. It is a primary cause of morbidity and mortality.[26] Interstitial lung disease and pulmonary hypertension result from associated vasculopathy with endothelial damage.[26]

Pulmonary Evaluation

If possible, all patients should be screened with PFT, which can reveal reduced forced vital capacity, restrictive lung disease, and reduced diffusion capacity. Those with abnormal PFT results should undergo chest HRCT to evaluate for ground-glass appearance, pulmonary nodules, and bronchiectasis, as well as to reveal a nonspecific interstitial pneumonia pattern. Affected patients are at increased risk for aspiration secondary to dysphagia, esophageal dysmotility, and reflux.[26]

Management

Treatment for JSS depends on the organs affected. For the lung, cyclophosphamide is frequently used for ILD. Alternatively, mycophenolate mofetil and rituximab have also been used. For pulmonary hypertension, phosphodiesterase inhibitors, endothelin-1-receptor antagonists, and, if required, intravenous

prostacyclins may be used.[19] Lung transplantation may be necessary for those refractory to treatment.[26]

Mixed Connective Tissue Disease and Sjögren Syndrome

Mixed connective tissue disease (MCTD) and Sjögren syndrome are autoimmune diseases with immune dysregulation and multisystem organ involvement.[26,27] Clinically, they share many of the same features as SLE. The incidence and prevalence are not known but are thought to be lower than those seen with SLE.

Clinical Manifestations

Multiple aspects of the lung may be involved including airways, parenchyma, vasculature, and pleura.[6] For both entities, pulmonary-related symptoms depend on the presence of serositis culminating in chest pain, pleuritis, fibrosis, and pulmonary hypertension. Interstitial lung disease and organizing pneumonias have also been described.

Pulmonary Evaluation

Criteria for the diagnosis in children are not as rigorously validated as those in adults. The criteria for MCTD include either Raynaud phenomenon or hand and finger swelling in addition to high-titer anti-U1 RNP antibody and 1 sign from at least 2 of the following: SLE, systemic sclerosis, and polymyositis. No single laboratory test is diagnostic for MCTD. For Sjögren syndrome, earlier detection with anti-Sjögren syndrome A (Ro) and anti-Sjögren syndrome C (La) is possible.[9] Computed tomography of the chest can reveal ground-glass appearance with septal thickening and subpleural honeycombing. Pulmonary artery dilatations and pleural effusions also can be seen on CT.[6]

Management

Coordination between pediatric subspecialists is paramount. Treatment for MCTD is similar to that for SLE, with glucocorticoids, hydroxychloroquine, methotrexate, and NSAIDs. Serositis and pleuritis may require immunosuppressives such as cyclophosphamide. If pulmonary hypertension is present, prostacyclins and endothelin-1-receptor antagonists may also be needed.[26] For Sjögren syndrome, glucocorticoids continue to be a mainstay of therapy.[27]

Vasculitic Diseases

Granulomatosis With Polyangiitis

Granulomatosis with polyangiitis (GPA), formerly known as Wegener granulomatosis, is a rare necrotizing, granulomatous, small- to medium-sized vasculitis.[28–31] It has a pediatric incidence of 0.1 per 100,000 in the US population younger than 20 years, with involvement of the upper airways, lungs,

and kidneys. Pulmonary disease is associated with up to 75% of GPA cases.[1] The cause of GPA remains unknown.[31] In vitro studies show that cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA) interact with proteinase-3 (PR3) to activate proinflammatory pathways.[31]

Clinical Manifestations

To establish a diagnosis of GPA, a patient should have at least 2 of 4 predefined criteria (nasal or oral inflammation, abnormal findings on chest radiograph, abnormal urinary sediment, and granulomatous inflammation on biopsy), per the American College of Rheumatology.[32] The presence of any 2 or more criteria yields a sensitivity of 88% and a specificity of 92%.[29] More than 90% of patients with GPA initially seek medical attention for upper or lower airway symptoms.[33] Sinusitis is the most frequent presenting symptom, followed by fever, arthralgias, cough, rhinitis, and hemoptysis. In the upper airway, GPA is commonly associated with subglottic stenosis and nasal deformities (nasal septum perforation and saddle nose deformity).[28] Subglottic stenosis often occurs independently of other GPA symptoms. In the lower airway, tracheobronchostenosis is possible and can involve clinical symptoms of cough, hoarseness, stridor, dyspnea, and wheezing. Stenosis of the airways may require surgical intervention.[34] Diffuse alveolar hemorrhage and massive hemoptysis can be life-threatening conditions. Pulmonary fibrosis, pleurisy, and pneumothorax are less common.

Evaluation

Evaluation for GPA can be complicated. Routine laboratory test results are generally nonspecific, with increased generalized markers of inflammation. The diagnosis often can be established with elevated c-ANCA levels (detectable in 70%–90% of patients with active GPA), PR3-ANCA, and potentially kidney and lung biopsies.[35] Children should be monitored and evaluated for signs of upper airway and lower airway obstruction. Often part of presenting symptoms, pneumonia and sinusitis may also mask the diagnosis.[28,29]

Although one-third of chest radiographs in children with GPA show abnormalities, these children may be asymptomatic. Findings include densities, cavitation, and nodules, which become more severe over time without treatment. Less frequently, atelectasis, pneumothorax, pleural effusion, pulmonary hemorrhage, and mediastinal or hilar lymphadenopathy are found. Plain chest radiography can detect these abnormalities, but HRCT provides more detail, especially in detecting airway stenosis, pulmonary nodules, granulomas, and cavitations (**Figure 26-2**). Following a diffuse alveolar bleed, a septal thickening pattern, sometimes termed *crazy paving*, can be seen. Bronchoscopy may be necessary to evaluate airway lesions fully. Pulmonary function testing

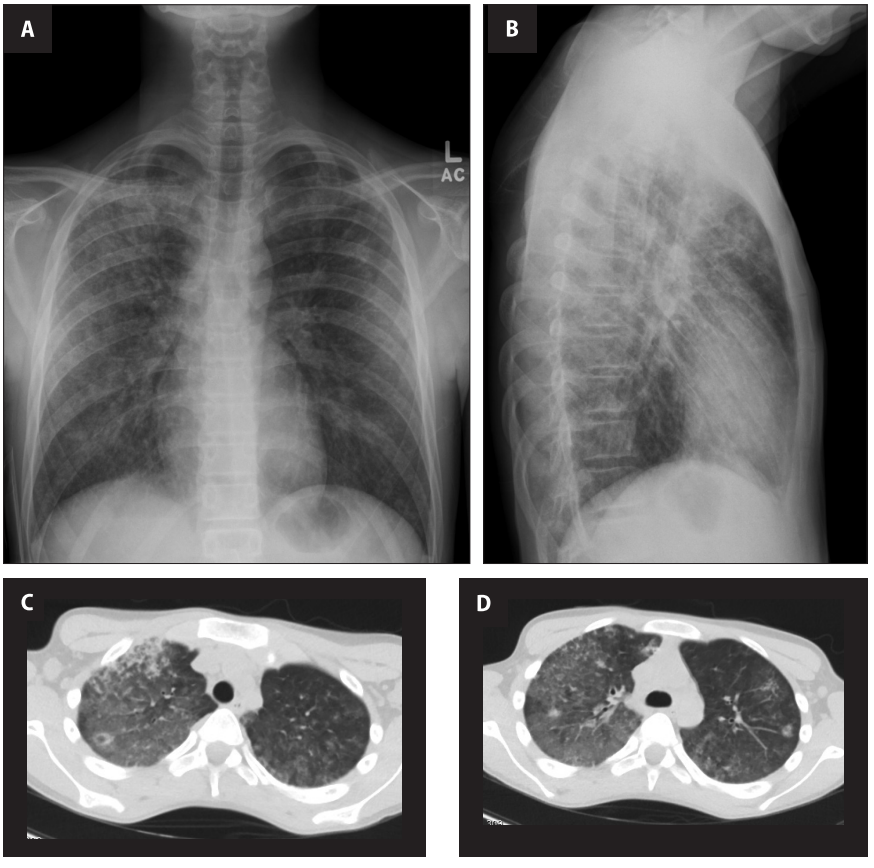


Figure 26-2. Radiograph (**A, B**) and chest computed tomographic scans (**C, D**) in a child with granulomatosis with polyangiitis; note the diffuse infiltrate, nodules, and granulomas.

reveals obstructive or restrictive lung disease as well as lower DLCO. Histopathologic evaluation with lung biopsy can reveal necrosis, vasculitis, and/or granulomatous inflammation.[35]

Management

Initial treatment with glucocorticoids and cyclophosphamide induces remission in more than 90% of patients.[35] This treatment may be continued for at least 1 year after disease control or remission and then gradually reduced. Alternatively, methotrexate or azathioprine may be used after an initial 4- to 6-month tapering course of cyclophosphamide.[35] Rituximab is a promising new option in both induction remission and maintenance therapies. Unfortunately, subglottic stenosis related to GPA does not usually improve with systemic medical treatment. Serial intratracheal dilation and injection of long-acting

glucocorticoids provide a safe and effective treatment, commonly mitigating the need for tracheostomy.[34] Clinicians should be aware of the risk of opportunistic infections. Prophylaxis against *Pneumocystis jiroveci* with trimethoprim-sulfamethoxazole is now commonplace for children undergoing treatment for GPA.[35]

Microscopic Polyangiitis

Microscopic polyangiitis (MPA) is another ANCA-positive systemic vasculitis that shares many of the same clinical and pathophysiologic features as GPA.[36] The great challenge of the MPA diagnosis is differentiating it from GPA. Given significant clinical overlap and lack of standardized definitions and distinct classification, diagnosing MPA has been difficult. It occurs at a slightly younger age than GPA, and girls are affected about 3 times more often than boys.[36] Previous classification systems have been inadequate; thus, rheumatologists have been validating new ways to identify MPA.[3,35]

Clinical Manifestations

The kidneys and lungs remain the most affected organs. Children can still present with tachypnea and hemoptysis, but, unlike GPA, pulmonary manifestations are typically less severe in MPA. Pathologically, MPA is differentiated from GPA by the absence of granuloma formations. Pulmonary nodules, fixed infiltrates, and cavitation are not seen in MPA; if present, they tend to steer the diagnosis toward GPA. Pleural effusions, along with fibrosis, septal thickening, and pneumothorax, are less common. Children with MPA frequently do not have sinusitis, subglottic stenosis, and tracheobronchomalacia, as seen in GPA.[3,29] More recent classification systems exclude upper airway disease and airway stenosis from the diagnosis of MPA.[3]

Pulmonary Evaluation

Typical of other types of vasculitis, markers of inflammation are elevated. pANCA/MPO-ANCA is often positive with MPA, and occasionally patients will test positive for both MPO-ANCA and PR3-ANCA; as many as one-quarter will have negative ANCA test results.[3] Radiographic evaluation of the chest can show effusions, fibrosis, and pneumothorax, but, overall, there are far fewer abnormalities compared to those in GPA.

Management

Treatment is similar to that for GPA. Corticosteroids with cyclophosphamide are often used for induction. Maintenance and remission therapy also includes DMARDs such as azathioprine, methotrexate, azathioprine, and rituximab. Other therapies may include plasmapheresis or intravenous immunoglobulin.[19,29]

Eosinophilic Granulomatosis With Polyangiitis

Eosinophilic granulomatosis with polyangiitis (EGPA; formerly known as Churg-Strauss syndrome) is an exceedingly rare condition in childhood that is characterized by development of eosinophilic vasculitis involving sinopulmonary and gastrointestinal tracts, heart, nervous system, and skin.[37] The disease is defined by pulmonary eosinophilic granulomatous inflammation of small- to medium-sized vessels, pneumonia, and necrotizing vasculitis with associated asthma and eosinophilia.[37] The cause of EGPA is unknown.[21] The incidence and prevalence in the pediatric population are unknown. The prominence of allergic features, such as elevated levels of serum immunoglobulin (Ig) E, and the presence of immune complexes, rheumatoid factor, and c-ANCA suggest an autoimmune origin.[31]

Clinical Manifestations

Eosinophilic granulomatosis with polyangiitis consists of 3 stages: asthma and rhinitis, tissue eosinophilia (including eosinophilic pneumonia), and extrapulmonary eosinophilic vasculitis.[37] Similar to many eosinophilic syndromes, constitutional symptoms, including fever, weight loss, and generalized myalgias, are common in EGPA. Prodrome is characterized by atopic disease, allergic rhinitis, and asthma. The eosinophilic phase includes blood eosinophilia and infiltration of multiple organs, especially the lung and gastrointestinal tract. Rarely, a life-threatening systemic vasculitis is associated with vascular and extravascular granulomatosis.

Pulmonary Evaluation

Because of its rarity in children, the incidence of pediatric EGPA is unknown. The diagnosis of EGPA in childhood remains challenging. A strong clinical suspicion coupled with pathologic confirmation can expedite the diagnosis. The diagnosis often is not established until the abdomen, heart, and nervous system become involved. Reports of EGPA occurring in children are limited and generally consist of single case reports. Asthma is almost always present in EGPA. Ear, nose, and throat disease includes chronic sinusitis and nasal polyps. Laboratory evaluation includes complete blood cell count with differential, c-ANCA, p-ANCA, and total IgE. Antineutrophil cytoplasmic antibodies are common but seem to have less specificity in children.[35,38] Pulmonary function testing has shown mostly obstructive disease, but restrictive and mixed lung disease patterns are possible. Bronchoalveolar lavage often shows eosinophil predominance. Chest radiograph abnormalities are common and consist of bilateral, nonsegmental alveolar or interstitial infiltrates. Computed tomographic chest findings include reticulonodular disease without cavitation (unlike GPA) and bronchial wall thickening, with less common findings of

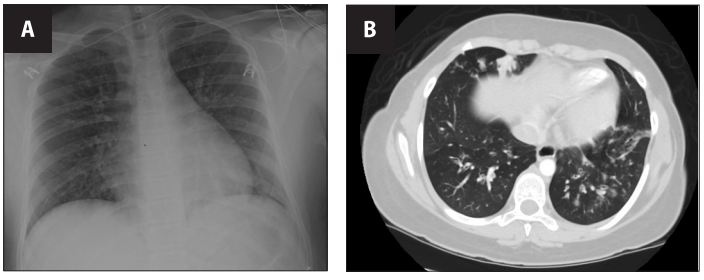


Figure 26-3. Fourteen-year-old with eosinophilic granulomatosis with polyangiitis and hemoptysis; note the reticulonodular disease on the radiograph (**A**) and corresponding computed tomographic scan (**B**) of the chest.

ground-glass opacities and tree and bud patterns (**Figure 26-3**).[37] A biopsy to evaluate for an eosinophilic inflammatory process or vasculitis remains the gold standard for diagnosis.[38]

Management

Corticosteroids are the mainstay of treatment, often with striking results.[35] Although cytotoxic agents, such as cyclophosphamide, do not improve survival rates, their use is associated with a reduced incidence of relapse. Other successful therapies have included intravenous Ig infusions, azathioprine, methotrexate, interferon-α, infliximab, and mepolizumab. Laboratory markers, such as serum eosinophils, often normalize within 2 weeks of treatment initiation. Clinical improvement can also be seen within 2 to 4 weeks, but often residual respiratory symptoms may require the continuation of low-dose prednisone therapy for longer periods. Since immunosuppressive therapies increase the risk of opportunistic infection, prophylaxis with trimethoprim-sulfamethoxazole should be provided.[35]

Anti-glomerular Basement Membrane Disease

Anti-glomerular basement membrane (AGBM) disease, previously known as Goodpasture disease, is an organ-specific small vessel vasculitis causing rapidly progressive glomerulonephritis and alveolar hemorrhage. Immunoglobulin G antibodies to the α-3 chain of type IV collagen deposit in the basement membranes of both the renal and pulmonary circulation.[39]

Clinical Manifestations

It is an uncommon cause of pulmonary-renal syndromes in children (**Table 26-3**). Rarely, alveolar hemorrhage occurs in the absence of renal involvement; it is more common to have renal disease without alveolar

Table 26-3. Most Common Alveolar Hemorrhage Syndromes

Characteristic	SLE	GPA	MPA	AGBM	EGPA
Blood markers	ANA, anti-dsDNA	c-ANCA	p-ANCA	Anti-GBM antibody	Eosinophilia
Renal disease	+++	+++	+++	+++	+
Skin involvement	+++	+	+	–	+
ENT involvement	+	+++	+	–	++
Arthritis	+++	++	+	–	–
Radiographic findings	ILD, hemorrhage	Nodules, cavities, hemorrhage	ILD, hemorrhage	Hemorrhage	Increased peribronchial markings

Abbreviations: –, rare occurrence; +, occasional occurrence; ++, common or significant; +++, quite frequent or very significant; AGBM, anti-glomerular basement membrane; ANA, antinuclear antibody; anti-dsDNA, anti-double stranded DNA; c-ANCA, cytoplasmic antineutrophil cytoplasmic antibody (also antiprotease antibody); EGPA, eosinophilic granulomatosis with polyangiitis; ENT, ear, nose, and throat; GPA, granulomatosis with polyangiitis; ILD, interstitial lung disease; MPA, microscopic polyangiitis; p-ANCA, perinuclear antineutrophil cytoplasmic antibody; SLE, systemic lupus erythematosus.

hemorrhage. Although alveolar and renal manifestations occur concomitantly, alveolar hemorrhage may occur prior to the onset of renal disease.

Pulmonary Evaluation

The diagnosis is established by the presence of circulating anti-glomerular basement membrane antibodies or linear immunofluorescent deposits of IgG on the renal basement membrane, which also can be seen on the alveolar basement membranes should a lung biopsy be performed.[39] This immunofluorescence pattern is less consistent on lung biopsy compared to renal biopsy. The linear pattern differentiates AGBM disease from immune-complex deposits causing the renal disease. In up to 30% of patients with AGBM disease, the ANCA may also be positive in addition to the AGBM antibodies (so-called double positive); MPO-ANCA is more common than PR3-ANCA.

Management

The goals of therapy are to remove the circulating antibodies, prevent the production of more antibodies, and attempt to identify and resolve any triggering agent. Initial treatment with plasmapheresis is often successful at removing the circulating AGBM antibodies. Intravenous methylprednisolone, cyclophosphamide, and, more recently, rituximab are used for immunosuppression. Survival should be anticipated, but prognosis is guarded if end-stage renal disease is present; renal transplantation may be necessary.[39]

Henoch-Schönlein Purpura (IgA Vasculitis)/ Kawasaki Disease/Polyarteritis Nodosa

The most common vasculitidies in children are Henoch-Schönlein purpura, Kawasaki disease, and polyarteritis nodosa.[40,41] Henoch-Schönlein purpura involves the small vessels, while Kawasaki disease and polyarteritis nodosa are predominantly medium vessel diseases. Takayasu arteritis is a granulomatous arteritis predominantly affecting the aorta and its major branches. Pulmonary involvement with these more commonly occurring vasculidities in childhood is extremely uncommon.

Granulomatous Lung Disease

Most of the granulomatous lung diseases in pediatrics are caused by infections (**Box 26-1**) and are discussed elsewhere in this book or elsewhere in this chapter (**Table 26-3**).[5] This section will focus on noninfectious, systemic inflammatory diseases with granulomatous pathology.

The chest radiographs or CT images often reveal nodules and adenopathy, which raises concern for malignancy. While malignancy is exceedingly rare when assessing a child with pulmonary nodules, the risk of cancer should be considered. Small nodules and nodules with calcification are unlikely to be malignant and can be observed, but larger or growing nodules without a determined etiology should be biopsied or excised.

Sarcoidosis

Sarcoidosis is a multisystem disease of unknown etiology.[42] Sarcoidosis is a granulomatous response to an unknown antigen or antigens characterized by a T lymphocyte infiltration, granuloma formation, and distortion of normal microarchitecture. These noncaseating granulomas have a core composed of activated macrophages (epithelioid cells), multinucleated giant cells, and CD4 type 1 helper T lymphocytes. Angiotensin-converting enzyme is produced by the activated macrophages in the granuloma. In adults, pulmonary involvement occurs in approximately 85% of patients; pulmonary involvement may be slightly less common in children. In the United States, sarcoidosis is more prevalent and more severe in the African American population. Socioeconomic factors, barriers to care, and occupational exposure are all implicated in racial disparities. Furthermore, certain medications may be better tolerated than others but are inaccessible because of insurance coverage rules. For example, corticosteroids may be associated with significant adverse effects, but steroid-sparing medications may not be as readily covered. Inequitable

Box 26-1

Differential Diagnosis of Granulomatous Lung Disease

Noninfectious Causes

- Autoimmune disease
  - Primary systemic vasculitidies
    - Granulomatosis with polyangiitis
    - Eosinophilic granulomatosis with polyangiitis
  - Systemic lupus erythematosus
  - Inflammatory bowel disease (Crohn disease)
  - Primary biliary cirrhosis
- Bronchocentric granulomatosis
- Primary immunodeficiencies
  - Chronic granulomatous disease (see Chapter 53, Pulmonary Complications of Immunologic Disorders)
  - Common variable immune deficiency
  - Hypogammaglobulinemia
- Histiocytosis X
- Hypersensitivity pneumonitis
  - Farmer's lung
  - Bird fancier's lung
- Neoplasms
  - Carcinomas
  - Sarcomas
  - Lymphomas
- Sarcoidosis (and necrotizing sarcoidosis)
- Drug-induced granulomas

Infectious Causes

- Viruses
  - Epstein-Barr virus
  - Herpes
  - Rubella
  - Cytomegalovirus
  - Measles
  - Coxsackie B
  - Parainfluenza
- Fungi
  - *Histoplasma*
  - *Aspergillus*
  - *Coccidioides immitis*
  - *Blastomycosis*
  - *Cryptococcus*
- Protozoa
  - *Toxoplasma*
  - *Leishmania*
- Metazoa (*Schistosoma*)
- Bacteria
  - *Yersinia*
  - *Borrelia*
  - *Brucella*
  - *Mycobacteria*
    - Mycobacterium tuberculosis
    - Mycobacterium leprae
    - Nontuberculous mycobacteria

access to medications and therapies results in potentially negative impacts on quality of life.[43]

Clinical Manifestations

Symptoms may be absent or sparse and include cough, dyspnea, and fatigue.[42] The diagnosis is often delayed and requires documentation of granulomatous involvement of at least 2 organ systems. A tissue biopsy should be performed from the most easily accessible site. Sarcoidosis is a diagnosis of exclusion, and alternative explanations such as fungal infection, mycobacterial infection, and lymphoma must be excluded. An elevated angiotensin-converting

enzyme (ACE) level is not pathognomonic of sarcoidosis. The ACE testing sensitivity is fair but not specific. The positive predictive value is higher but with a less helpful negative predictive value.

Pulmonary Evaluation

Pulmonary function testing may show a restrictive pattern with impaired diffusion capacity, but an obstructive pattern may also be present, as well as bronchial reactivity.[42] Radiographically, pulmonary involvement is identified by bilateral hilar adenopathy; interstitial infiltrates and pulmonary nodules may also be seen. Progression to end-stage fibrotic disease is possible but not frequent in children. Bronchoalveolar lavage is not a reliable tool to establish the diagnosis of sarcoidosis, although it is commonly performed at the time of bronchoscopy for transbronchial biopsy; noncaseating granulomas are found in more than 90% of biopsy specimens. Lymphocytosis on BAL may be present, with a T cell CD4:CD8 ratio elevated above 3.5. The ACE level also is often elevated in BAL fluid, as are several cytokines. The primary utility of BAL in sarcoidosis is to exclude fungal, mycobacterial, atypical mycobacterial infection, or other infectious processes as the explanation for the patient's symptoms and radiographic findings.

Treatment

Management of children with sarcoidosis depends on presentation, clinical picture, and number and severity of organ systems involved. Rarely, asymptomatic children with hilar adenopathy may not need to be treated. Treatment should be considered for children with multisystem disease, dyspnea, worsening lung function, and worsening radiologic findings. Corticosteroids remain the mainstay of treatment. For pulmonary disease, 6 to 18 months of therapy may be reasonable, but no time course has been well established for other organ systems. Immunosuppressives include methotrexate, hydroxychloroquine, azathioprine, cyclophosphamide, and infliximab. There is no guideline regarding optimal follow-up in children.[42]

Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (LCH) encompasses conditions with abnormal differentiation and proliferation of mononuclear phagocytes.[44] It is considered a myeloid neoplastic disorder. The granulomatous lesions are most commonly found in bone, skin, the lungs, and the pituitary. It can occur as a single indolent lesion or as an aggressive multisystem disease. Children with liver, spleen, or bone marrow involvement are considered at high risk for a poor outcome, even with chemotherapy. In the past, isolated pulmonary involvement was labeled "eosinophilic granuloma," which occurred primarily in adolescent boys and young men and was associated with cigarette smoking.

Pathologically, the lung lesions start as discrete bronchiolocentric nodules with a mix of Langerhans cells, lymphocytes, eosinophils, and plasma cells. The

Langerhans cells stain positive for langerin, CD1a, E-cadherin, and S100. Electron microscopy reveals Birbeck granules in the Langerhans cells. As the lesions progress, they coalesce and form cysts, creating the risk of spontaneous pneumothoraces, which may be the presenting symptom.

Therapy for LCH is stratified based on the number of organ systems involved and the risk of mortality. For isolated pulmonary LCH, smoking cessation alone may be the only therapy required.

Inflammatory Bowel Disease

Crohn disease presents more frequently with extraintestinal manifestations than ulcerative colitis.[45] Case reports have identified pulmonary nodules in patients with inflammatory bowel disease, which raises concern regarding infection complicating the therapy for the underlying bowel disease. These pulmonary nodules are noncaseating epithelioid granulomas similar to those seen in sarcoidosis (**Figure 26-4**). Before treatment with tumor necrosis factor α blockers is initiated in patients with inflammatory bowel disease, they should be checked for latent tuberculosis infection. When the pulmonary nodules are related to the inflammatory bowel disease, they commonly respond to treatment of the bowel disease.[45]

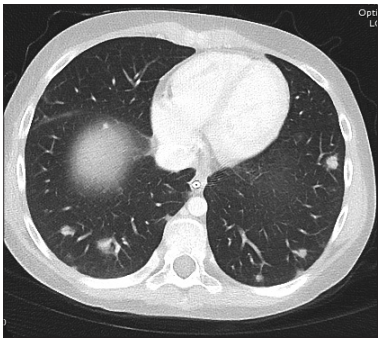


Figure 26-4. Pulmonary nodules incidentally found on a computed tomographic scan of the abdomen in a patient with Crohn disease.

key points

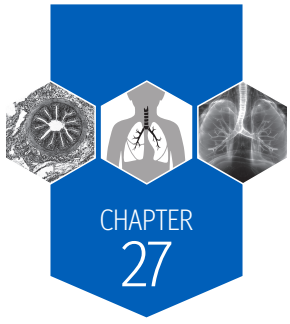
- Systemic inflammatory diseases may present with a limited number of organs involved or multiple organ systems involved. Lung involvement might be an initial presenting feature, or the lungs may become involved as the primary underlying disease process evolves.
- Initial respiratory symptomatology and constitutional complaints may be very similar through this very diverse collection of diseases.
- Diagnosis and management are often challenging and optimally include a multidisciplinary team from rheumatology, pulmonology, infectious diseases, intensive care, and nephrology.
- Results of pulmonary testing with chest radiography, chest CT, pulmonary function testing, and flexible fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) may be highly suggestive of a specific disease process, but these tests are seldom diagnostic without additional studies.
- Diagnostic criteria (clinical presentation, imaging, and laboratory investigation) are established for each of these diseases to help provide correct classification and to unify disease identification between institutions.

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CHAPTER
27

Interstitial Lung Disease

Pallav Halani, MD, FAAP
Timothy J. Vece, MD
Adrienne P. Savant, MD, MS

CASE REPORT 27-1

An infant born at 37 weeks had tachypnea, retractions, and hypoxemia at her 4-month checkup. She had a previous history of respiratory syncytial virus–negative bronchiolitis at 2 months of age; however, the patient's mother stated she never fully recovered from her previous illness. Because of her hypoxemia in the office, she was transferred to a local emergency department and administered an albuterol treatment that did not help. She was admitted to the general pediatric team, and a pulmonary consultation was obtained. Test results for viral respiratory pathogens were negative. Chest radiography was performed and showed only hyperinflation. A computed tomography scan of the chest showed ground-glass opacities in the right middle lobe, lingula, and paramedian portions of the upper and lower lobes bilaterally with sparing of the periphery. Results of genetic studies for surfactant protein mutations were negative. Lung biopsy results showed no evidence of clinically significant inflammation and clusters of bombesin-positive cells in the bronchioles, consistent with neuroendocrine cell hyperplasia of infancy. Supportive therapy was provided.

Introduction

The term *interstitial lung disease* (ILD) encompasses a group of rare, heterogeneous disorders characterized by diffuse pulmonary disease and disordered gas exchange.[1] Although a strict definition implies an abnormality of the interstitium, there are some diseases that have minimal interstitial defect but have pathological abnormalities in the airspaces and distal airway that are considered under the broad term of ILD.[2] For this reason, some authors prefer the term *diffuse lung disease* (DLD). In this chapter, *children's ILD* will be used to refer to children's diffuse and interstitial lung disease. Although individual children's ILD entities are rare, group estimates of disease prevalence range from 0.13 to 16.2 cases per 100,000, depending on disease definitions and inclusion criteria, which would make these ILDs nearly as common as cystic fibrosis in the United States.[3]

Previously, description and management of children's ILD were largely based on case reports and small series. The classification of children's ILD was fit to match adult classification schemes; however, there were clinically significant differences in clinical outcomes and responses to treatment,[4] leading to the recognition that new classifications were required (**Boxes 27-1** and **27-2**). Guidelines have been developed, with both the American Thoracic Society clinical practice guideline (ATS CPG) focusing on children younger than 2 years[5] and European protocols focusing on all childhood ages.[6]

The manifestations of these diseases are within a developing lung, leading to a more tailored, child-centered approach to care. This chapter focuses on the clinical presentation, pathophysiological characteristics, and diagnostic approach to children's ILD. Some of the common children's ILDs, management, and prognosis are also discussed.

Age at presentation results in varied clinical appearances, with distinctly different disorders in patients younger than 2 years and those aged 2 to 18 years. The severity of the disease at presentation correlates with prognosis.[7] Neonatal presentation often occurs shortly after birth in term infants who have substantial respiratory distress leading to rapidly progressive respiratory failure requiring mechanical ventilation. If an infant born preterm has respiratory distress that does not follow the anticipated course for their level of prematurity, children's ILD should also be considered.[6]

Presentation after the neonatal period is nonspecific, with a variety of pulmonary symptoms such as tachypnea, cough, wheeze, digital clubbing, hypoxia, retractions, and crackles; however, auscultation results may be normal.[6] Failure to thrive can also be seen as a comorbidity. Respiratory syncytial virus bronchiolitis that does not seem to resolve may be an indication of ILD.[6] In older children (2–18 years of age), in addition to these signs and symptoms, exercise-induced shortness of breath may be the presentation.

When a patient presents in a manner that suggests ILD, a systematic approach to evaluation is essential to distinguish between primary pediatric ILD and other conditions. A thorough medical history and physical examination will often provide clues to an underlying diagnosis. A family history is most likely to be positive in infants because many forms of ILD have a genetic basis.[8] In a retrospective analysis, 10% of case siblings were affected by similar diseases,[9] and up to 34% of patients had a family history of lung disease in another study.[10] It is also important to obtain information about exposures, such as to radiation, birds, or toxins. In one report, only 25% of the clinicians' initial diagnoses based on patient history were correct except in cases in which a history of a bird exposure led to a diagnosis of hypersensitivity pneumonitis.[2] A thorough review of systems, focusing on joints, skin, kidneys, sinuses, eyes, and nervous

system, may raise suspicion of known causes of ILD, such as collagen vascular diseases.[8] In addition, pulmonary hypertension, reflux, and aspiration should be excluded.[11] Testing should be tailored based on the patient's presentation and the severity of the respiratory disorder. Regardless of the presentation, common causes of the clinical symptoms should be excluded, such as cystic fibrosis, congenital or acquired immunodeficiency, congenital heart disease, bronchopulmonary dysplasia, pulmonary infection, primary ciliary dyskinesia manifesting with newborn respiratory distress, and recurrent aspiration.

Once the common diseases have been eliminated, the rubric of children's ILD can be applied if the patient has at least 3 of 4 criteria: (a) respiratory symptoms, (b) respiratory signs, (c) hypoxemia, and (d) diffuse radiographic abnormalities (**Box 27-3**).[5]

Box 27-1

Children's Interstitial Lung Disease More Prevalent in Infancy (Ages 0–2 Years)

Diffuse developmental disorders
- Acinar dysplasia
- Congenital alveolar dysplasia
- Alveolar capillary dysplasia with misalignment of pulmonary veins

Growth abnormalities reflecting deficient alveolarization
- Pulmonary hypoplasia
- Chronic neonatal lung disease
  - Prematurity-related chronic lung disease (bronchopulmonary dysplasia)
  - Acquired chronic lung disease in term infants
- Structural pulmonary changes with chromosomal abnormalities
  - Trisomy 21, others
- Abnormalities associated with congenital heart disease in children with normal chromosomes

Specific conditions of undefined cause
- Neuroendocrine cell hyperplasia of infancy
- Pulmonary interstitial glycogenosis

Surfactant dysfunction disorders
- Surfactant protein B (SFTPB) mutations
- Surfactant protein C (SFTPC) mutations
- *ABCA3* mutations
- Histological findings consistent with surfactant dysfunction disorder without yet recognized genetic cause

Derived from Kurland G, Deterding RR, Hagood JS, et al; American Thoracic Society Committee on Childhood Interstitial Lung Disease (chILD) and the chILD Research Network. An official American Thoracic Society clinical practice guideline: classification, evaluation, and management of childhood interstitial lung disease in infancy. *Am J Respir Crit Care Med.* 2013;188(3):376–394; and Deutsch GH, Young LR, Deterding RR, et al; Pathology Cooperative Group; ChILD Research Co-operative. Diffuse lung disease in young children: application of a novel classification scheme. *Am J Respir Crit Care Med.* 2007;176(11):1120–1128.

Box 27-2

Children's Interstitial Lung Disease More Prevalent in Childhood and Adolescence (Ages 2–18 Years)

Disorders of the normal host
- Infections and postinfectious processes
- Disorders related to environmental agents: hypersensitivity pneumonia, toxic inhalation
- Aspiration syndromes
- Eosinophilic pneumonias

Disorders of the immunocompromised host
- Opportunistic infections
- Disorders related to therapeutic intervention
- Disorders related to transplant and rejection
- Diffuse alveolar damage of unknown cause

Disorders related to systemic disease process
- Immune-related disorders
- Storage disease
- Sarcoidosis
- Langerhans cell histiocytosis
- Malignant infiltrates
- COVID-19 (COVID-ILD)

Disorders masquerading as interstitial lung disease
- Arterial hypertensive vasculopathy
- Congestive vasculopathy
- Lymphatic disorders
- Congestive changes related to cardiac dysfunction

Unclassified

Derived from Kurland G, Deterding RR, Hagood JS, et al; American Thoracic Society Committee on Childhood Interstitial Lung Disease (chILD) and the chILD Research Network. An official American Thoracic Society clinical practice guideline: classification, evaluation, and management of childhood interstitial lung disease in infancy. *Am J Respir Crit Care Med*. 2013;188(3):376–394; and Fan LL, Dishop MK, Galambos C, et al; Children's Interstitial and Diffuse Lung Disease Research Network (chILDRN). Diffuse lung disease in biopsied children 2 to 18 years of age: application of the chILD classification scheme. *Ann Am Thorac Soc*. 2015;12(10):1498–1505.

Box 27-3

Criteria for Diagnosis of Children's Diffuse and Interstitial Lung Disease

Presence of 3 of the following, in absence of an identified cause:
- Respiratory symptoms (cough, rapid and/or difficult breathing, and exercise intolerance)
- Respiratory signs (tachypnea, adventitious sounds, retractions, digital clubbing, and failure to thrive)
- Hypoxemia
- Diffuse abnormalities at radiography or computed tomography

From Kurland G, Deterding RR, Hagood JS, et al; American Thoracic Society Committee on Childhood Interstitial Lung Disease (chILD) and the chILD Research Network. An official American Thoracic Society clinical practice guideline: classification, evaluation, and management of childhood interstitial lung disease in infancy. *Am J Respir Crit Care Med*. 2013;188(3):376–394. © 2013 American Thoracic Society.

Pathophysiology

Interstitial lung disease is characterized by a pathological process affecting the interstitial space in the lung. In the normal lung, the interstitium, the area between the alveolar space and the capillary, is approximately 1 cell thick. However, in patients with ILD, this area becomes thickened. Diffusion of oxygen across the alveolus to the capillary is proportional to the thickness of the area. In patients with ILD, oxygen takes longer to diffuse across the thickened interstitium. This delay in diffusion leads to a compensatory increase in minute ventilation that is clinically manifest by tachypnea. Thus, tachypnea without desaturation is often the earliest symptom of ILD, especially in infants. When severe enough, the diffusion impairment cannot be overcome by increasing minute ventilation, and hypoxemia ensues.

The thickened interstitium likely occurs because inflammation leads to the deposition of connective tissue that forms areas of fibrosis. In some forms of ILD, there is little or no inflammation visible on lung histopathological studies, and treatment with anti-inflammatory agents does not consistently lead to clinical improvement. Thus, inflammation is not the sole mechanism for ILD. A second mechanism involves epithelial injury, leading to abnormal repair of the lung.[12] In children, the process of interstitial thickening is affected by age-specific lung growth and development. Children's lungs continue to grow beyond infancy, so alterations in normal growth occur from the underlying disease. In addition, genetic variations can modulate susceptibility and response to various injuries.[9]

Evaluation

The ATS CPG strongly recommends that diagnostic testing be performed to determine the exact form of ILD.[5] The order of diagnostic testing depends on the clinical presentation and severity. If the clinical presentation is more slowly progressive, a stepwise approach to diagnostic evaluation can be used. In addition to ruling out common diseases that manifest in a manner similar to that of ILD, this section will discuss specific evaluation of children's ILD, although the order of evaluation may vary for each patient.

Echocardiography

Pulmonary vascular disease and structural heart disease can masquerade as ILD; therefore, the ATS CPG strongly recommends an echocardiogram.[5] In addition, patients with ILD with pulmonary hypertension have a worse prognosis.[5]

Genetic Testing

Single gene defects can result in children's ILD, so genetic testing can help to provide a diagnosis, reduce or eliminate the need for invasive testing such as

lung biopsy, and provide prognostic information. However, results from genetic testing often take time, thereby limiting use in rapidly progressive cases, and interpretation is not always straightforward. Regardless, patients with a family history of ILD should undergo genetic testing.

Clinical presentation can guide genetic testing. For example, patients with refractory pulmonary hypertension and associated congenital abnormalities should be tested for the *FOXF1* deletions as a cause of alveolar capillary dysplasia, a weak recommendation from the ATS CPG.[5] Patients with hypothyroidism and/or neurological abnormalities, such as hypotonia and developmental delay, should undergo analysis for *NKX2.1* mutations, a strong recommendation from the ATS CPG.[5] Older children who present with children's ILD are strongly recommended to be assessed for surfactant mutations *ABCA3* and *SFTPC* and are weakly recommended to be assessed for receptors for granulocyte-macrophage colony–stimulating factor (GM-CSF), *CSF2RA,* and *CSFR2B*, along with serum levels for GM-CSF.[5] The ATS CPG strongly recommends newborns with children's ILD and severe, rapidly progressive disease or a family history be tested for genetic abnormalities associated with neonatal ILD, such as *SFTPB*, *SFTPC*, and *ABCA3*.[5]

Radiography

Radiographic evaluation of a child suspected of having ILD should begin with a chest radiograph. Although 10% of chest radiographs in adults with ILD can be normal, findings are usually abnormal in children with ILD.[2,4] The chest radiograph of a child with ILD (**Figure 27-1**) reveals diffuse pulmonary infiltrates or specific patterns described as reticular, nodular, ground-glass, or honeycombing.

To delineate parenchymal abnormalities further, a high-resolution computed tomography (HRCT) scan of the chest should be obtained (**Figure 27-2**). The ATS CPG weakly recommends obtaining a thin-section computed tomography (CT) scan of the chest at a center with expertise in pediatric chest CT and strongly recommends using the lowest radiation dose.[5] Computed tomography scans help to characterize the nature and distribution of the disease optimally. For some children's ILD diagnoses, the radiographic appearance can be diagnostic, thereby reducing the need for further diagnostic evaluation, but others have nonspecific findings that may provide guidance for further testing.[13] In a review of 20 children with ILD proved by means of biopsy, 56% of the confident first-choice diagnoses from HRCT were correct.[1,14] High-resolution CT scans of the chest can help evaluate the parenchyma of these children and help the surgeon determine the optimal site for biopsy.

In adults and older children, patients perform a voluntary breath hold at full inspiration and expiration during radiography. However, infants and young children cannot cooperate with breath holding, and respiratory motion

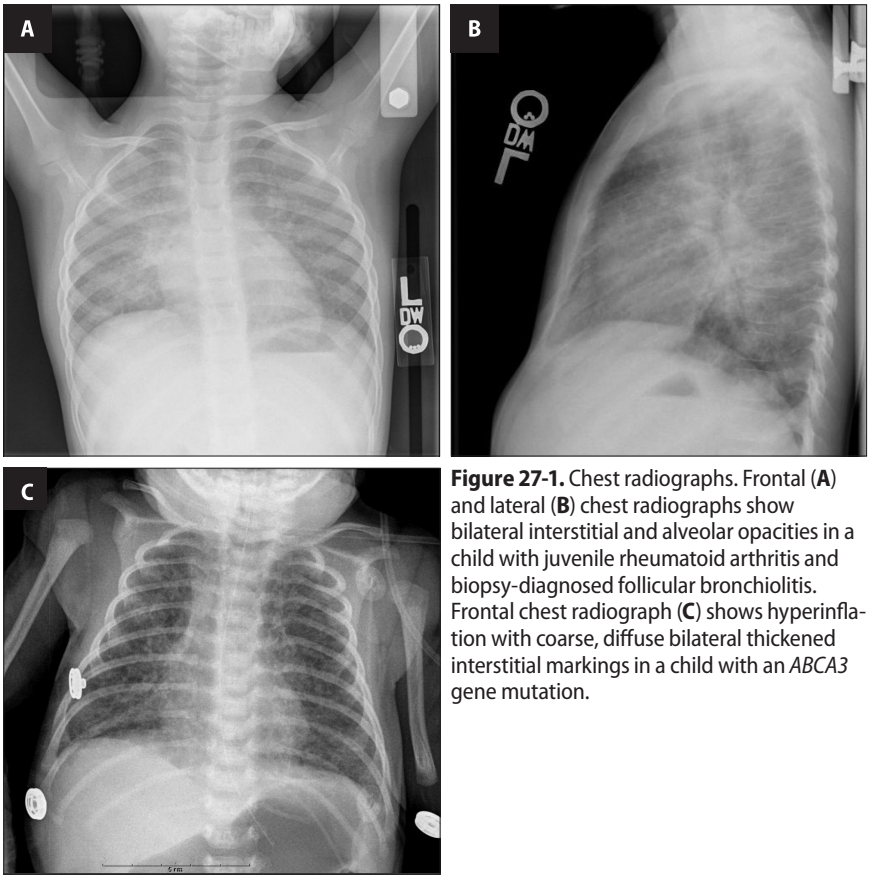


Figure 27-1. Chest radiographs. Frontal (**A**) and lateral (**B**) chest radiographs show bilateral interstitial and alveolar opacities in a child with juvenile rheumatoid arthritis and biopsy-diagnosed follicular bronchiolitis. Frontal chest radiograph (**C**) shows hyperinflation with coarse, diffuse bilateral thickened interstitial markings in a child with an *ABCA3* gene mutation.

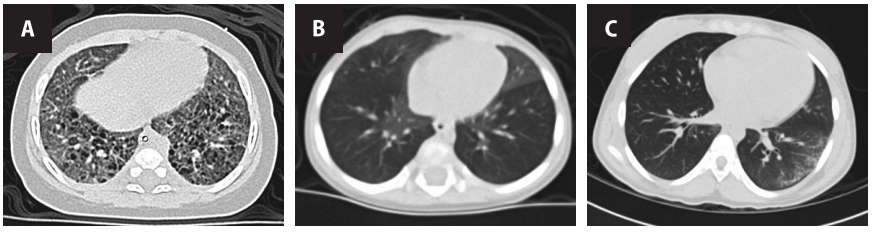


Figure 27-2. Axial high-resolution computed tomography images. **A**, Extensive diffuse ground-glass alveolar filling, with associated interstitial thickening. There are also multiple small- to moderate-sized cysts present within both lungs. **B**, Mosaic pattern with areas of denser and of more lucent lung in all lobes—the patient has abnormality in the *ABCA3* gene. **C**, Peripheral intralobular interstitial and interlobular septal thickening—this patient has juvenile dermatomyositis.

produces motion artifacts that limit the quality of the imaging study.[14] The alternative is to use anesthesia with intubation to obtain acceptable images. Long and colleagues[15] developed a method that uses sedation combined with controlled ventilation, as used in infant pulmonary function tests (iPFTs), to provide a controlled pause in respiration.[14] During this procedure, hyperventilation of a child with a face mask produces a respiratory pause that is long enough (6–12 seconds) to scan the entire lung. Images can thus be obtained at full inspiration at 25 cm H_2O and at full expiration at 0 cm H_2O. It is important to obtain high-quality scans, such as those obtained with controlled ventilation HRCT, because false-positive cases have been found with conventional scans.[14]

Radiographic findings for children's ILD can vary based on the specific illness. Patients with surfactant-related disorders may have ground-glass opacities and thickening of the interlobular septae.[13] In addition, the term *crazy paving* has been applied to the pattern seen in interlobular thickening.[16] Patients with *ABCA3* and *SFTPC* abnormalities also had parenchymal cysts.[5] Pathognomonic findings of neuroendocrine cell hyperplasia of infancy (NEHI) at chest CT include geographic ground-glass opacities located centrally in the right middle lobe and lingula.[17] (See **Figure 27-3**.) With a compatible clinical picture, chest CT scans are now considered sufficient to diagnose NEHI without performing lung biopsy.[18] Postinfectious bronchiolitis obliterans also has characteristic CT findings, including mosaic perfusion, vascular attenuation, and central bronchiectasis that are diagnostic and that correlate with the approximate clinical history.[19] Further specific radiographic evaluations for various forms of children's ILD continue to be investigated.

Physiological Testing

Pulmonary function tests are sometimes able to indicate functional patterns that aid in distinguishing different disorders and correlate with radiography

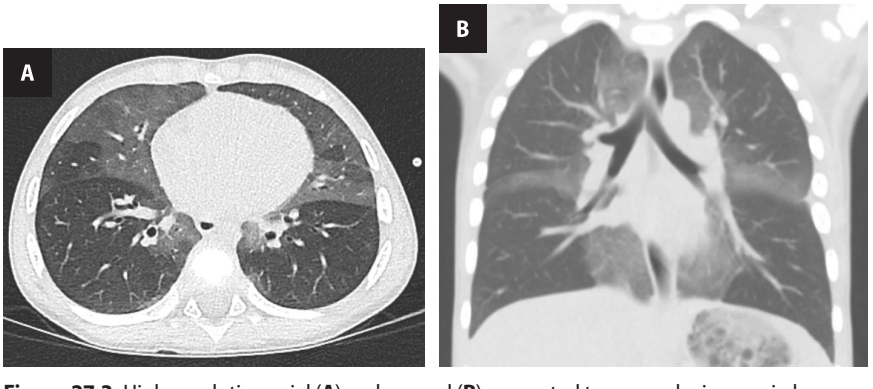


Figure 27-3. High-resolution axial (**A**) and coronal (**B**) computed tomography images in lung window demonstrate geographic ground-glass opacities with a right middle lobe and lingular predominance, as well as less confluent central involvement of the right lower, left lower, right upper, and left upper lobes.

Courtesy of Mariangeles Medina Perez, MD.

and histological findings.[1] Pulse oximetry and blood gas analysis are important to determine the degree of hypoxemia. Most patients will be normoxemic but may desaturate with sleep or exercise.[1] Exercise tolerance studies or evaluation of 6-minute walk distance may be of clinical use. Spirometry will reveal a pattern of restrictive lung disease, with decreased lung volumes sometimes with an obstructive component of air trapping.[1] Diffusion capacity will be low, although it may normalize when corrected for alveolar volume.[1]

Infant pulmonary function testing provides a physiological assessment and aids in diagnosis. The ATS CPG weakly recommends iPFTs for better characterization of physiological alterations.[5] Spirometry and plethysmography can now be used in infants at many major medical centers. Results from several reports show that iPFTs can help distinguish disease, correlate with radiographic and histological findings, and be used for assessment of therapy.[1,20] The usefulness of iPFTs in diagnosing ILD in infants is limited by the inability to perform this test routinely in patients who require ventilatory support and the limited number of centers that perform the test. To classify the characteristics of the various forms of ILD better, more iPFT data need to be obtained.

Bronchoalveolar Lavage

Pathological evaluation with bronchoalveolar lavage (BAL) is important to rule out infections and aid in the diagnosis of ILD. The entire aspirate is recovered and sent for cell count, infectious studies (microbiology and polymerase chain reaction–based assays), and lipid and hemosiderin stains. Cytological findings can support specific diagnoses, such as infections, aspiration, and pulmonary hemorrhage; alveolar proteinosis; lysosomal storage disorders; and histiocytosis.[1] In a prospective series of ILD cases, a specific diagnosis was determined from the BAL in 17% of cases.[21] When evaluated retrospectively, the diagnosis was determined in 30% of patients. Although the usefulness of BAL is limited, the ATS CPG weakly recommends BAL to exclude infection or airway abnormalities.[5]

Lung Biopsy

Lung biopsy is the gold standard in diagnosing ILD. Lung biopsies were well tolerated in one review, even during use of mechanical ventilation with extracorporeal membrane oxygenation, with no mortality and minimal morbidity.[22] The ATS CPG strongly recommends lung biopsy via video-assisted thoracoscopic surgery (VATS) in neonates and infants with children's ILD who have not had disease identified by means of other tests or when there is clinical urgency.[5] Even in small infants, VATS can dramatically reduce the morbidity associated with open thoracotomy.[5] A transthoracic procedure has a shorter operating time, a lower incidence of chest tube placement, and a shorter hospitalization,[23] although it requires a surgeon who is familiar with the technique. Current recommendations are to perform biopsies in more than 1 lobe, including 1 area that is clearly affected and 1 area that is newly evolving or

with an unaffected appearance on CT scans.[24] In a review of a small series of cases, there was no increase in complications when biopsy was performed in more than 1 lobe.[23]

Once the specimen has been obtained, proper processing of the tissue is critical for a comprehensive diagnostic evaluation. The ATS CPG recommends following published protocols to minimize improper handling and ensure uniform processing.[5] Tissue should be obtained for culture, light microscopy, immunohistochemistry (for surfactant proteins), and electron microscopy analyses. Useful stains include hematoxylin and eosin, trichrome, pentachrome, and periodic acid–Schiff with diastase.[24] Other immunostains, such as bombesin in NEHI and vimentin in pulmonary interstitial glycogenosis (PIG), have been described as diagnostic aids for specific causes of ILD. Electron microscopy shows distinctive type II cell abnormalities in specific surfactant gene mutations.[25] Other characteristic ultrastructural findings may indicate the presence of a metabolic disorder or PIG.[26]

Specific Diseases in Infancy

It is not practical to discuss all forms of children's ILD; however, a brief discussion of the newer entities, especially those that manifest in infancy, is provided here. Additional causes of children's ILD are continually being discovered and include coatomer-associated protein complex subunit α mutations leading to COPA syndrome, *FOXF1* mutations in alveolar capillary dysplasia with misalignment of the pulmonary veins, lipopolysaccharide-responsive beige-like anchor protein deficiency from mutations in the *LRBA* gene, *FLNA* mutations leading to abnormal filamin A, and *TMEM173* mutations leading to stimulator of interferon genes–associated vasculopathy with onset in infancy.[3,5,18,27]

Surfactant is a mixture of proteins and phospholipids that prevent atelectasis at end expiration. Both surfactant protein B and surfactant protein C are important in lowering the surface tension in the alveoli.[11] The ABCA3 protein is believed to play a role in surfactant processing and transport within the alveolar type II cell.[28] Transcription for surfactant proteins is under the control of the gene *NKX2.1*.[29] Once surfactant has been produced, it is cleared by macrophages under the control of GM-CSF. Mutations in any of these components can lead to ILD.

Surfactant protein B deficiency is a rare disorder, with clinical estimates of 1 per million live births.[11] These infants typically present within the first few hours after birth with respiratory failure. The neonates are clinically similar to infants with respiratory distress syndrome (RDS), except that they are born at term and the RDS does not resolve. The only treatment for these patients is lung transplant, without which the disease is fatal.[11]

Surfactant protein C deficiency has a variable manifestation. The onset of symptoms often occurs in term neonates who present with clinical symptoms

similar to those of RDS, but symptoms can occur later in childhood and even in adulthood, when manifestation is typical for later-onset ILD. Treatment is supportive, and many general ILD treatments have been used. Outcomes cover a wide spectrum, with some children requiring lung transplant and others improving enough over time that they no longer require supplemental oxygen.[11]

A deficiency of ABCA3 protein also has a varied manifestation and clinical outcome. ABCA3 deficiency manifests in the neonatal period with respiratory distress. Treatment is generally supportive. Outcome ranges from death in the newborn period to survival into the teenage years, with occasional survival until the patient's 20s or 30s.[28] Reports of children with mild disease suggest that some ABCA3 protein variants may lead to a milder course with prolonged survival.[28]

Mutations and deletions of *NKX2.1* have been seen in children with pulmonary disease, neurological findings (such as hypotonia), and hypothyroidism, with variable manifestations such that not all 3 organ systems are affected.[29] Because of the disruption of surfactant transcription, patients may present with severe respiratory distress in the neonatal period, but there is significant phenotypic variation, with neurological manifestations being subtle or occurring later in life.[30] Patients also can have recurrent infections.[30]

Patients with mutations in the receptors for GM-CSF, *CSF2RA*, and *CSF2RB* have pulmonary alveolar proteinosis in which surfactant accumulates in the alveoli.[31] Patients at any age can present with pulmonary symptoms of dyspnea; cough; fatigue; weight loss; and, less commonly, sputum production and fever.[31]

Pulmonary interstitial glycogenosis is a form of ILD that also manifests in the neonatal period and has been described in both term and preterm infants. There is an association with alveolar simplification, pulmonary hypertension, and structural heart disease.[32] These infants are typically tachypneic and hypoxic with crackles at physical examination and hyperinflation at radiographic evaluation. This illness is postulated to be caused by a developmental disorder of pulmonary mesenchymal cells, not an inflammatory or reactive process. Experts believe this is the same entity as cellular interstitial pneumonitis of infants. The long-term outcome is favorable in most patients.[26]

Neuroendocrine cell hyperplasia of infancy was referred to as *persistent tachypnea of infancy* before the characteristic histopathological findings were described.[33] Children with NEHI have an onset of symptoms usually in the first year after birth, with tachypnea, failure to thrive, and need for supplemental oxygen, but NEHI can manifest at later ages.[27] These patients have persistent tachypnea, hypoxia, and crackles. Radiographic evaluation reveals hyperexpansion of the lungs and characteristic CT findings. Treatment is mainly supportive, often including oxygen supplementation for several years. Neuroendocrine cell hyperplasia of infancy has a favorable outcome with a

waxing and waning course but slow and steady improvement, often over several years, with no known associated mortality.[33]

Management

Treatment of ILD is limited. The mainstay of treatment is supportive, specifically with oxygen. Most children with ILD have difficulty with diffusion of oxygen across the alveolar–capillary barrier and become tachypneic to maintain oxygen saturations. Administration of oxygen leads to less tachypnea.

If the underlying disease is known, then treatment toward the specific cause should help the lung disease. Additional therapeutic recommendations from both the Children's Interstitial Lung Disease Research Network and chILD-EU include maintaining adequate nutrition, treating underlying gastroesophageal reflux or aspiration during feeding, immunizing against respiratory pathogens, treating intercurrent illnesses aggressively, and avoiding environmental tobacco smoke and other pollutants.[5,6] Furthermore, patients may require treatment with noninvasive and invasive ventilation.[18]

Close attention to growth parameters is important because failure to thrive is a common complication of ILD. Many children with ILD have increased calorie needs because of tachypnea and inflammation, so they require close monitoring and, sometimes, interventions. In some cases, addition of supplemental oxygen will reduce tachypnea and improve weight gain, but many children need high-calorie formulas or supplemental feeding to augment caloric intake. Evaluation for supplemental enteral feeding via nasogastric or gastrostomy tube should be considered in addition to evaluation for other causes of failure to thrive, including aspiration and gastroesophageal reflux.

Infants and children with ILD are at risk of developing respiratory decompensation caused by viral respiratory infections. Many will have limited respiratory reserve and will require hospitalization for monitoring, hydration, and management of supplemental oxygen during such illnesses. Some, especially those with more severe forms of ILD, may require mechanical ventilation. Good communication between the primary care professional and the pulmonologist facilitates optimal care.

Beyond supportive care and disease-specific treatment, many modalities have been tried. Treatment effect can be judged by decreases in cough and dyspnea and by improvements in pulmonary function test results and saturation; however, radiographic changes do not occur quickly enough to follow frequently.[9]

Therapeutic agents for ILD can include immunomodulating agents, especially corticosteroids, which have a highly variable response. The ATS CPG states: "Given the limited evidence of a beneficial effect on clinical outcomes and the well-known side effects of immunosuppressive medications, the decision about whether or not to initiate trial of immunosuppressive therapy must be made on a case-by-case basis."[5]

Various immunomodulating treatment regimens have been used, ranging from daily oral doses to monthly intravenous pulses of steroids. The optimal dose, frequency, and duration of therapy, as well as when to initiate or discontinue therapy and the relative harm compared with adverse effects, remains unclear.[12] Therefore, using Delphi methodology, the European protocols developed consensus regarding treatment approaches for recommended dosages and response rates, as well as ongoing monitoring via improvements in physiological parameters.[6] Hydroxychloroquine therapy has been successful in the treatment of some cases, but the clinical response is highly variable. Other steroid-sparing agents have been tried, such as azathioprine, cyclophosphamide, methotrexate, cyclosporine, and intravenous immunoglobulin.[1] However, many reports of treatment are from case series that predate the current histological classification of pediatric ILD. There is a substantial need for research in this area.[18]

Azithromycin has also been used, although as with the remainder of children's ILD, evidence is limited, often via case reports.[34–37] Azithromycin not only is anti-infective but also has anti-inflammatory properties.[38] The European protocols included azithromycin in their treatment consensus.[6]

Lung transplant is an option for progressive ILD with respiratory failure. The ATS CPG strongly recommends referral to a pediatric lung transplant center for infants with severe, life-threatening disease.[5] Although the median post-transplant survival rate for children is 7.6 years,[39] some children survive much longer. Complications from lung transplant are common, with bronchiolitis obliterans being the most common, as well as hypertension, renal dysfunction, diabetes mellitus, and hyperlipidemia (see Chapter 42, Lung Transplantation). Infants who receive lung transplants for surfactant protein B deficiency have outcomes similar to those who receive transplants for other reasons.[40] There are some anecdotal reports of ILD recurrence in the transplanted lung.[12]

Prognosis

A prognosis based on clinical symptoms at initial evaluation can be determined using the severity of illness classification. The score includes the following elements: presence or absence of symptoms; saturations at rest, during sleep, or with activity; and evidence of pulmonary hypertension. The higher the score, the higher the probability of decreased survival, with each increase in score increasing the risk of death by an estimated 140%.[1,7]

The outcome for a child with ILD depends on the underlying cause. The higher the illness severity on the basis of symptoms at initial presentation, the higher the probability of mortality.[1] Pulmonary hypertension is the greatest predictor of mortality, with a 5-year survival of 38% compared with a 5-year survival of 64% in those without pulmonary hypertension.[7] In a retrospective study of diffuse lung disease in children younger than 2 years, only 30.2%

died, and 50% had ongoing pulmonary symptoms at follow-up; however, children with certain diseases, such as PIG and NEHI, had no mortality, whereas children with diffuse developmental disorders of the lung had 100% mortality.[10] It is important to have an accurate diagnosis before discussing the prognosis with the family.

When to Refer

Refer to a pediatric pulmonologist for the following:

- Hypoxia and tachypnea of unknown cause
- Radiographic findings of pulmonary ground-glass opacities
- Clubbing
- Chronic dry cough, tachypnea, dyspnea, retractions, cyanosis, clubbing, and failure to thrive in some combination
- Unexplained failure to thrive (found in two-thirds of children with ILD)[9,10]
- Unexplained exercise intolerance or frequent respiratory infections (crackles may or may not be present)

When to Admit

- Upper respiratory infection in a child with known ILD, especially with increasing hypoxemia
- Prompt evaluation for any change in the patient's baseline respiratory health, such as increased tachypnea or dyspnea or a reduction from baseline oxyhemoglobin saturation

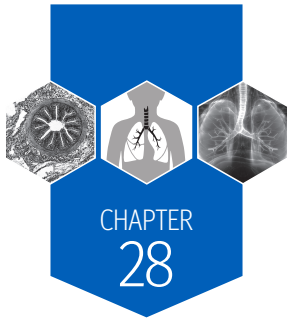
key points

- Interstitial lung disease is a rare, heterogeneous group of disorders, mainly pulmonary, and characterized by diffuse pulmonary disease with disordered gas exchange.
- Interstitial lung disease is any entity that results in derangement of the alveolar-capillary interface, often characterized clinically with tachypnea, crackles, hypoxemia, or diffuse infiltrates.
- Diagnosis is one of exclusion of known causes; lung biopsy is the gold standard.
- Treatment may include supportive therapy with oxygen supplementation, immunomodulating agents, or lung transplant, depending on the severity of the symptoms.
- Close monitoring of nutritional status, with appropriate intervention, is important.
- Outcomes vary widely, depending on the specific diagnosis, but are not uniformly fatal.

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Bronchopulmonary Dysplasia

Laurie C. Eldredge, MD, PhD
Susanna A. McColley, MD, FAAP

Introduction

History of Bronchopulmonary Dysplasia

Northway, Rosan, and Porter first described bronchopulmonary dysplasia (BPD) in 1967 as a severe respiratory distress syndrome (RDS) of late preterm infants who were treated with prolonged artificial ventilation and a life-sustaining high fraction of inspired oxygen (0.8–1.0).[1] In this landmark publication, Northway and colleagues described 4 stages of this chronic lung disease: acute RDS (stage 1), a period of regeneration (stage 2), and then progression to chronic disease (stages 3 and 4). Bronchopulmonary dysplasia was associated with substantial (59%) mortality from severe respiratory failure and pulmonary vascular disease with cor pulmonale. Despite the severity of BPD, Northway and colleagues highlighted that there was some reversibility of the condition with continued development of functional lung.[1] Catch-up growth with neoalveolarization takes place in childhood and throughout adolescence.[2] To model BPD for mechanistic studies, Northway and colleagues[3] also demonstrated that hyperoxia-induced lung injury in mice resembles histopathological aspects of BPD.

Since this original description of BPD, the survival of preterm infants has increased owing to significant advances in neonatal care, including the use of neonatal positive pressure ventilation (PPV), antenatal steroids, exogenous surfactant, and further honing of respiratory support strategies.[4]

BPD Epidemiology

Concordant with advances during the past 50 years, the incidence of BPD has increased as gestational age and birth weight of viable infants decrease. Extremely low gestational age newborns born at less than 28 weeks and extremely low birth weight (ELBW) infants born at less than 1,000 g are at

highest risk of developing BPD. However, even when separated according to gestational age, the rate of BPD is still rising.[5] For infants born at gestational ages 22 through 28 weeks across 26 centers in the Neonatal Research Network, the diagnosis of BPD increased from 32% (295 of 911) in 1993 to 45% (547 of 1,213) in 2000 (adjusted relative risk, 1.05 [95% CI, 1.04–1.06]) and then decreased to 40% (498 of 1,230) in 2008.[5] For 8 centers with complete data across 20 years, BPD increased from 2009 through 2012 for all gestational ages except for those born at 28 weeks: from 50% (130 of 258) to 55% (164 of 297) for infants born at 26 weeks and from 33% (103 of 312) to 40% (134 of 339) for infants born at 27 weeks.[5] Overall, nearly 50,000 extremely low gestational age newborns are born each year in the United States, and approximately 35% (18,000) of these children develop BPD.[6] Bronchopulmonary dysplasia rates are variable, however. Using a composite outcome of BPD or death, BPD rates varied from 17.7% to 73.4% between centers (interquartile range, 38.7%–54.1%) in a large retrospective study spanning 125 neonatal intensive care units (NICUs) in California.[7] Results from this study also demonstrated associations between BPD, lower Apgar scores, younger gestational age, lower birth weight, and male sex. Moreover, data from major cohort studies (Extremely Low Gestational Age Newborns, Canadian Neonatal Network, Korean Neonatal Network, Vermont Oxford Network, and Swiss Neonatal Network, as well as studies in China, Taiwan, and India) similarly demonstrated varied BPD prevalence of 11% to 50%, although cohort-specific differences in gestational age and birth weight also affected these numbers.[8–14]

BPD Definition

In 2001, a National Institutes of Health workshop developed a comprehensive clinical definition for BPD to include the requirement for supplemental oxygen for 28 days with further designation of mild, moderate, or severe disease according to respiratory support needs at 36 weeks' corrected gestational age (CGA) (**Table 28-1**).[15] However, in the era of a changing BPD pathophysiology with improved survival of extremely preterm infants that have severe alveolar and vascular hypoplasia, several changes to the definition have been proposed.[6] These changes delineate the clinical significances of noninvasive respiratory support such as continuous positive airway pressure (CPAP) or high-flow nasal canula with variable supplemental oxygen content. One strategy defines the need for invasive mechanical ventilation at 36 weeks' CGA as severe type 2 BPD.[16] More recently, Jensen and colleagues[17] proposed a severity-graded definition of BPD that predicted severe respiratory morbidity and mortality in 81% of study infants. On the basis of specific respiratory support needs at 36 weeks, BPD severity was defined as grade 1 (nasal cannula $\leq$2 L), grade 2 (nasal cannula >2 L or noninvasive positive airway pressure), or grade 3 (invasive mechanical ventilation).[17]

Table 28-1. Bronchopulmonary Dysplasia Definition With Severity Stratification

Bronchopulmonary Dysplasia Severity	Definition[a]	Relative Incidence[b]	Postdischarge Mortality[b]
None	O_2 treatment < 28 days and breathing room air at 36 weeks' PMA or discharge home, whichever comes first	23.10%	1.80%
Mild	O_2 treatment at least 28 days and breathing room air at 36 weeks' PMA or discharge home, whichever comes first	30.30%	1.50%
Moderate	O_2 treatment at least 28 days and receiving < 30% O_2 at 36 weeks' PMA or discharge home, whichever comes first	30.20%	2.00%
Severe (type 1)	O_2 treatment at least 28 days and receiving ≥ 30% O_2 or nasal CPAP/HFNC at ≥ 36 weeks' PMA	16.40% (all sBPD)	4.80% (all sBPD)
Severe (type 2)	O_2 treatment at least 28 days and receiving mechanical ventilation at ≥ 36 weeks' PMA		

Abbreviations: CPAP, continuous positive airway pressure; HFNC, high-flow nasal cannula; PMA, postmenstrual age; PPV, positive pressure ventilation; sBPD, severe BPD.

[a] Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med.* 2001;163(7):1723–1729. doi: 10.1164/ajrccm.163.7.2011060.

[b] Ehrenkranz RA, Walsh MC, Vohr BR, et al; National Institutes of Child Health and Human Development Neonatal Research Network. Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. *Pediatrics.* 2005;116(6):1353–1360. doi: 10.1542/peds.2005-0249.

Reprinted from Abman SH, Collaco JM, Shepherd EG, et al; Bronchopulmonary Dysplasia Collaborative. Interdisciplinary care of children with severe bronchopulmonary dysplasia. *J Pediatr.* 2017;181:12.e1–28.e1. doi: 10.1016/j.jpeds.2016.10.082. © 2017, with permission from Elsevier.

Pathophysiology

Jobe[18] describes BPD as "an injury syndrome superimposed on the essential lung growth and maturation (development) required for survival." The importance of lung maldevelopment in "new" BPD pathogenesis[19] has become even more important as the survival of extremely preterm and ELBW infants has increased (survival for 25–28 week preterm infants without major morbidity increased 2% per year between 1993 and 2012).[5]

The structure of preterm lungs makes them highly susceptible to alveolar and microvascular injury.[18] This immaturity, coupled with the need for life-sustaining but injurious therapies such as mechanical ventilation and supplemental oxygen, initiates pulmonary developmental arrest with disordered lung repair and remodeling (**Figure 28-1**).[6,18,19] Moreover, a complex combination of variables spanning the time from preconception to the postnatal years contributes to the risk of BPD development (**Figure 28-2**).[6] Prematurity and low birth weight are the strongest risk factors for BPD, with

additional risk factors of male sex, intrauterine growth restriction, patent ductus arteriosus, sepsis or infection, and maternal cigarette smoking.[20–23] Early respiratory support needs may predict BPD, as preterm infants with a respiratory severity score (product of mean airway pressure and fraction of inspired oxygen) of 6 or more on their 30th day after birth had worse survival

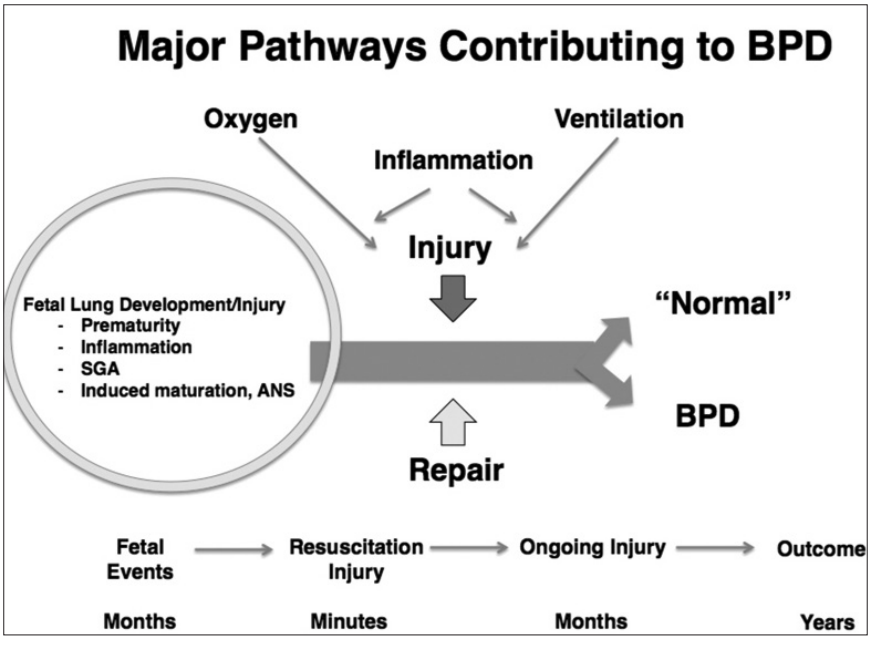


Figure 28-1. A diagram of some of the factors that can contribute to BPD. The focus is on how long development is modulated by multiple injuries and repair over time.

Abbreviations: ANS, antenatal steroids; BPD, bronchopulmonary dysplasia; SGA, small for gestational age.

From Jobe AH. Mechanisms of lung injury and bronchopulmonary dysplasia. *Am J Perinatol*. 2016;33(11):1076–1078. © Georg Thieme Verlag KG.

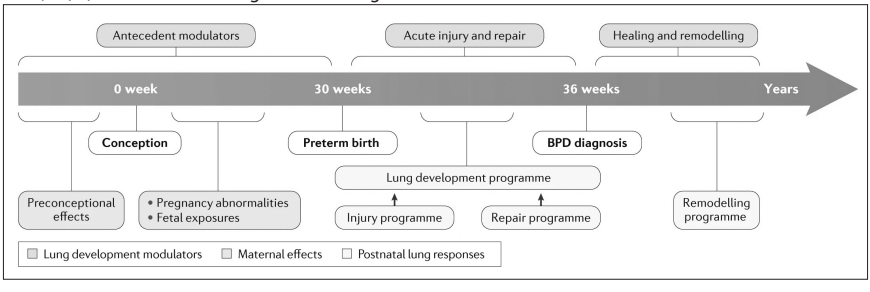


Figure 28-2. Timeline and stages of bronchopulmonary dysplasia (BPD). The timeline indicates variables that may modulate lung development, injury, and repair. Acute lung injury (days to weeks) progresses to chronic lung injury (weeks to years) and is coupled with lung repair and remodeling (months to years).

From Thébaud B, Goss KN, Laughon M, et al. Bronchopulmonary dysplasia. *Nat Rev Dis Primers*. 2019;5(1):78. © 2019 Springer Nature.

and longer ventilation courses.[24] Multicenter research studies are underway to characterize carefully the specific clinical signs and symptoms in infants who will develop severe BPD.

Inflammation plays a central role in BPD pathogenesis. Pro-inflammatory exposures in preterm infants, including exposure to supplemental oxygen,[25] mechanical ventilation, postnatal infections, and pulmonary overcirculation from a patent ductus arteriosus, increase the risk of developing BPD. Preterm infants may also be more susceptible to oxidative injury because of incompletely developed antioxidant enzyme defenses.[26] Inflammation in these infants is often systemic, and multiorgan cross talk may also play a role in BPD severity; for example, acute kidney injury has been associated with worse pulmonary outcomes in preterm infants.[27,28] Neonatal inflammation is pathogenic, but immune-mediated mechanisms driving BPD pathogenesis remain poorly understood.[29–35] Much of what is known about BPD development stems from animal models.[30,36] Hyperoxia-induced lung injury[37] recapitulates some of the histopathological aspects of BPD and allows for dissection of molecular pathways with genetically mutant mice. More than 60 genes affecting the response to lung injury have been characterized in mouse models of BPD.[6,38]

Prenatal inflammation from chorioamnionitis is present in 94% of placentas delivered between 21 and 24 weeks' gestation, compared with 3% to 5% of placentas delivered at term.[39] Chorioamnionitis has been associated with *Ureaplasma* species, among other genital mycoplasmas, but the pathogenic neutrophilic inflammation may also be sterile. Despite this correlation with preterm birth, authors of a meta-analysis of 59 heterogeneous studies involving more than 15,000 patients were unable to show a definitive association between chorioamnionitis and BPD once results were adjusted.[40]

While mechanical ventilation is a life-sustaining therapy for patients with immature lungs, ventilator-induced lung injury is a source of inflammation in the development of BPD.[41] Selecting the least injurious ventilation strategy possible is challenging because of changes in physiological characteristics as lung injury progresses. It is difficult to balance the risks of lung expansion and associated volutrauma (more injurious than barotrauma) with the risks of underexpansion and atelectrauma. Volutrauma is lung stretch injury resulting from localized overdistention of airways and alveoli.[42,43] Atelectrauma[42] is a lung injury caused by alveolar collapse at end expiration, seen in the setting of surfactant deficiency, as well as in inadequate inflation of an injured lung. Alveolar derecruitment leads to loss of functional residual volume.

Overall, it is difficult to predict which infants will develop severe BPD. Identification of useful biomarkers that predict BPD severity is challenging, in part, because of the variety of phenotypes and diseases that are grouped

together as the clinical diagnosis of BPD. Investigators in a published study of exome sequencing identified variants in immune-mediated and growth factor pathways in patients with BPD[44] as part of the multicenter Prematurity and Respiratory Outcomes Program. This study's results highlight the need for multicenter collaborative science to increase statistical power and generalizability of findings relevant to this heterogeneous disease.

Clinical Features

Bronchopulmonary dysplasia is a multifactorial and multicompartmental cause of pediatric respiratory failure.[45] It includes alveolar disease with associated hypoxemia and hypercarbia, lower airway obstruction due to structurally narrowed airways with superimposed airway inflammation, pulmonary vascular maldevelopment, and variable central injury.[46] Bronchopulmonary dysplasia parenchymal injury is heterogeneous and may include fibrosis, emphysema, and hypoalveolarization.[6]

To preserve minute ventilation, infants with BPD are tachypneic, with increased work of breathing. Respiratory support should be titrated to the patient to ensure adequate linear growth and neurodevelopment despite the abnormal respiratory mechanics and chronic respiratory demands.[16] Survivors of BPD have lifelong obstructive lung disease with reduced FEV_1 as adults[19,47] and are an emerging population of individuals with chronic obstructive pulmonary disease.[48] Patients with BPD, therefore, should be followed up longitudinally with consideration of pulmonary function testing and/or imaging.

Comorbidities

Infants with BPD frequently have feeding issues, including dysphagia, gastroesophageal reflux disease, and growth failure. Feeding, occupational and physical therapy, and gastrointestinal specialists may be needed as determined in the patient's medical home.

Tracheobronchomalacia (TBM) is a comorbidity that occurs most often in preterm infants who develop BPD and require prolonged PPV.[49,50] Because the airways are not functionally or structurally mature, positive pressure may distend the abnormally compliant airways and result in acquired or secondary TBM.[51] Pulmonary consequences of TBM include decreased intrathoracic airway flow, cyanotic episodes, difficulty weaning from PPV, and higher mortality.[49] Patients with BPD and TBM also have longer and more complicated hospitalizations, with increased need for tracheostomy, gastrostomy tube use, longer mechanical ventilation, and increased risk of developing oral feeding difficulties.[49,52]

In 2016, the American Heart Association (AHA) and American Thoracic Society (ATS) published guidelines for the diagnosis and management of pediatric pulmonary hypertension (PH).[53] Recommendations for infants with BPD include the following: (1) screening for PH in infants with established BPD (at 36 weeks' postmenstrual age [PMA] for preterm infants who require supplemental oxygen or positive pressure support or earlier in the presence of severe respiratory distress or high levels of ventilatory support, oligohydramnios, intrauterine growth restriction, or extreme prematurity); (2) evaluation and treatment of lung disease (hypoxemia, aspiration, and so on) in those with BPD-PH before starting PH medications; and (3) including cardiac catheterization for diagnosis, identification of other cardiac factors such as pulmonary vein stenosis, and acute vasodilator testing when evaluating for use of medication to treat PH. Treatment options for PH include supplemental oxygen, inhaled nitric oxide, and a variety of oral, inhalational, subcutaneous, and intravenous pharmacotherapies. The AHA/ATS and Pediatric Pulmonary Hypertension Network guidelines also recommend that a multidisciplinary team of neonatologists, pulmonologists, cardiologists, intensivists, and PH specialists should be involved in the care of patients with BPD-PH.[54] Because intermittent or prolonged hypoxemia can delay resolution of PH, oxygen saturation goals for patients with BPD are 92% to 94%.[53]

Systemic hypertension is common in infants with BPD.[55–57] Management includes use of a PMA-specific nomogram for blood pressure that indicates severe hypertension is blood pressure greater than the 95th percentile and requires pediatric nephrologic consultation. Blood pressure elevations may be severe enough to require pharmacological treatment in approximately one-half of patients.[55–57] The mechanisms involved in the development of systemic hypertension in patients with BPD are not fully understood but may include neonatal kidney injury,[27,28] as well as increased aortic thickness and systemic arterial stiffness.[58]

Respiratory Management

Prenatal, Perinatal, and Preventive

Management begins in the prenatal period to decrease the risk of preterm delivery, with maternal monitoring, interventions to decrease infection and preterm labor and delivery, and maximizing fetal growth and nutrition. Antenatal steroids are administered to accelerate lung development, with effects on alveolar epithelial cells, surfactant binding protein, and antioxidant production.[59] Preterm infants born to mothers who received antenatal steroids have improved rates of mortality, RDS, intraventricular hemorrhage (IVH), and necrotizing enterocolitis. However, antenatal steroids have not been shown

to decrease the risk of BPD developing,[59] possibly because of decreased total alveolar number,[60] which has been documented in preterm nonhuman primates whose mothers were treated with antenatal steroids. Resuscitation efforts in the delivery room progress with high oxygen concentration and positive pressure as needed for respiratory failure, according to well-researched Neonatal Resuscitation Program protocols.[61] Lung recruitment maneuvers in the delivery room have been abandoned because of increased mortality in the first 48 hours after birth.[62]

Noninvasive Respiratory Support

A meta-analysis of 30 trials found that mechanical ventilation is overall inferior to noninvasive strategies in primary outcomes of death and BPD at 36 weeks' CGA or secondary outcomes of death, BPD, IVH, and air leak.[63] However, because of advanced noninvasive ventilation strategies,[62–64] many extremely preterm infants no longer require intubation and mechanical ventilation and therefore do not acquire ventilator-associated lung injury.

Continuous positive airway pressure is an effective form of noninvasive support that has been popular since its development in 1973[65] and has had interval improvements in mask and cannula interfaces. High-amplitude bubble nasal CPAP (Seattle-PAP) allows for increased ventilation greater than that with other forms of CPAP.[66] Lung stretch induced by CPAP has been associated with improved lung growth after hyperoxic lung injury in animals.[67] Similarly, infants born at 32 weeks' gestational age or younger who required 24 hours or more of CPAP who received an additional 2 weeks of CPAP (compared with those with discontinuation of CPAP) had greater functional residual capacities, indicating improved lung volumes.[68]

Other noninvasive respiratory support modalities include neurally adjusted ventilatory assist[69]; noninvasive PPV; heated, humidified high-flow nasal cannula; and low-flow nasal cannula. More research is needed to determine the optimal noninvasive respiratory strategies, with the goal of decreasing the work of breathing and promoting growth and development in patients with BPD.

Surfactant improves lung compliance and uniformity of lung expansion, permits lower oxygen supplementation and ventilatory support, and protects against volutrauma in animal models. Less invasive surfactant administration (LISA),[70] during which surfactant is delivered with feeding tubes or vascular catheters by using laryngoscopes during CPAP-assisted breathing, has been used to realize the benefits of surfactant without the injury seen with invasive mechanical ventilation. Results from a randomized controlled trial (RCT) of LISA versus conventional surfactant delivery via endotracheal intubation showed LISA was associated with increased survival without major complications. In a meta-analysis of 30 RCTs, investigators compared noninvasive

ventilation and surfactant administration strategies within 24 hours after birth for infants less than 33 weeks' gestational age who had not undergone intubation, and the results showed that the use of LISA was associated with the lowest likelihood of the composite outcome of BPD or death at 36 weeks' PMA.[63] Therefore, preterm infants often benefit from exogeneous surfactant without invasive mechanical ventilation.

Invasive Mechanical Ventilation

Despite the use of noninvasive PPV, 44.7% of ELBW infants require some invasive mechanical ventilation within the first 7 days after birth.[71] For preterm infants who require invasive ventilation, the goal is to provide adequate gas exchange while minimizing lung injury. Preterm infants with RDS, before BPD is diagnosed, have poorly compliant lungs, but the lung disease is relatively homogeneous. A gentle ventilation strategy is used to minimize ventilator-associated lung injury with minimal peak pressures, adequate positive end-expiratory pressure, and faster rates.[16] In a Cochrane review of 20 randomized trials, compared with neonates receiving pressure-limited ventilation, neonates receiving volume-targeted ventilation had reduced rates of death or BPD, pneumothorax, and duration of ventilation.[72]

Approximately 16% of infants with BPD require mechanical ventilation at 36 weeks' CGA and therefore have severe BPD.[73] Data have not solidified the superiority of a specific mode of ventilation for established BPD, and there is considerable center-to-center variability in local ventilation practices.[74] Determination of optimal ventilation strategies for BPD is an important and open research question for future multicenter studies.

Specific Ventilation Strategies for Patients With Severe Type 2 BPD

With careful multidisciplinary care, infants with severe type 2 BPD (those requiring invasive mechanical ventilation at 36 weeks' PMA in comparison with those with severe type 1, who require noninvasive ventilation) will progress through 4 stages of BPD: unstable (high fraction of inspired oxygen, low ventilation/perfusion state), transitional, pro-growth, and convalescence.[75] As infants progress through these stages, different phenotypes become apparent, including restrictive (tachypnea due to hypoplasia), obstructive (lower airway obstruction and 74% likelihood of bronchodilator responsiveness), and mixed (obstructive and restrictive).[76] A high tidal volume, long inspiratory time, and low rate strategy from multiple centers of excellence support these infants with heterogeneous lung disease and severe BPD (**Figure 28-3**).[6]

Chronic Mechanical Ventilation

The typical disease course of BPD is slow, steady improvement in lung disease and weaning of respiratory support over time. A small number of patients with BPD do not wean from invasive ventilation and develop severe

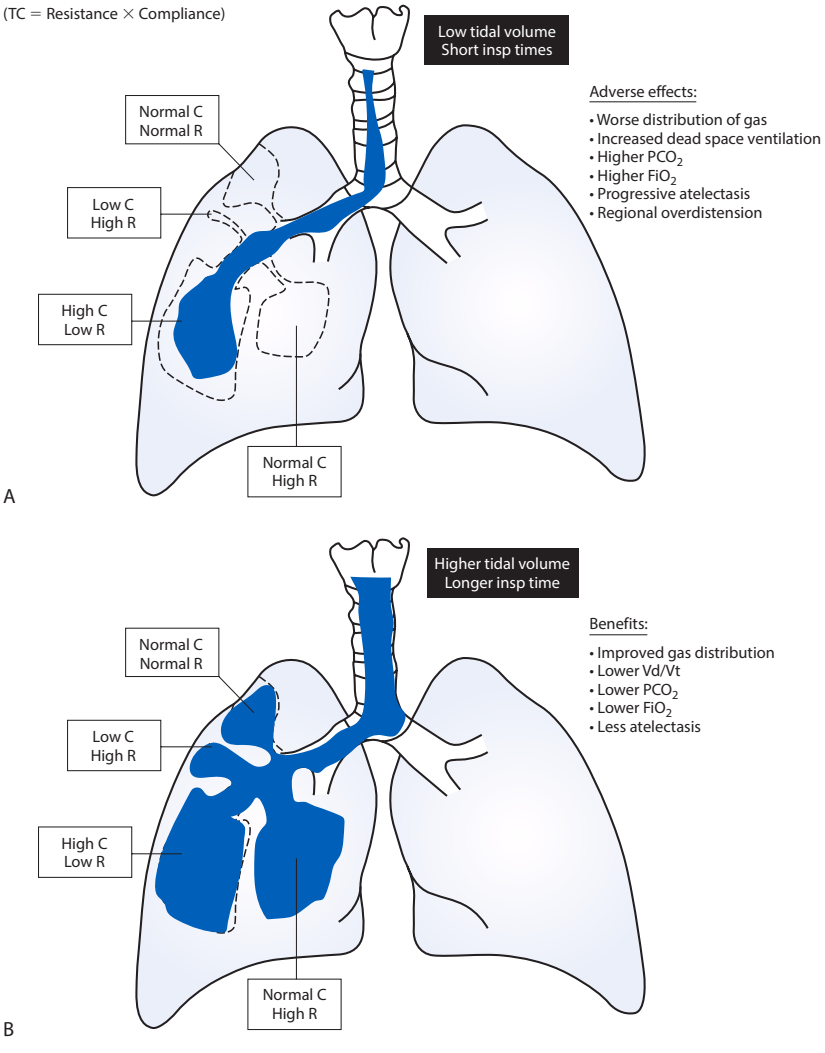


Figure 28-3. Alternative ventilation strategies in the treatment of heterogeneous lung disease and severe BPD.

Abbreviations: C, compliance; FiO_2, fraction of inspired oxygen; R, resistance; V_D, dead-space ventilation; V_T, tidal volume.

Reprinted from Abman SH, Nelin LD. Management of the infant with severe bronchopulmonary dysplasia. In: Bancalari E, Polin RA, eds. *The Newborn Lung: Neonatology Questions and Controversies*. 2nd ed. Elsevier Saunders; 2012:407–425. © 2012, with permission from Elsevier.

type 2 (Abman criteria) or grade 3 (Jensen criteria) BPD. These patients are more prevalent in the NICU because of prolonged hospitalizations, accounting for 41% of patients with severe BPD at 36 weeks' CGA.[77] Patients with severe BPD as well as TBM are more likely to require and benefit from tracheostomy and long-term ventilation.[49] Tracheostomy promotes improved neurodevelopment in infants with severe BPD and can facilitate transition to chronic mechanical ventilator care at home or in a pediatric chronic ventilatory care facility.[78] Management for these patients requires a multidisciplinary team,[78] and a standardized discharge process can decrease hospital length of stay.[79] An ATS clinical practice guideline recommends generalist and subspecialist comanagement for these patients, in addition to the presence of an awake, trained caregiver at all times and standardized equipment for monitoring, emergency response, and airway clearance.[80] A comprehensive medical home is also essential for longitudinal and coordinated care for these patients.

Medications

In a study in 3,252 infants with severe BPD hospitalized at 43 centers, there was a median of 30 (interquartile range, 17–45) medication exposures per infant, with marked center–center variation.[81] Most of these medications have unclear efficacy and safety in patients with BPD. Thiazide and loop diuretics,[82] although commonly used in the inpatient setting to improve lung compliance, have not been shown to improve preterm infants' clinical outcomes, such as duration of mechanical ventilation, NICU length of stay, or rates of BPD. In addition, diuretics (especially furosemide) are associated with comorbidities such as sensorineural hearing loss,[83] nephrolithiasis,[84] and metabolic bone disease.[85] Therefore, diuretic use should be sparing, such as in patients who cannot be weaned from positive pressure despite mild fluid restriction.

Interventions to minimize lung injury in patients with BPD, and the level of evidence supporting their use, are summarized in **Table 28-2**. Systemic corticosteroids have been frequently used as effective anti-inflammatory agents to prevent and treat BPD. Enthusiasm for steroids waned because of association with serious adverse effects, including hypertension, hyperglycemia, adrenocortical axis suppression, poor weight gain, gastrointestinal perforation, and adverse neurodevelopmental outcomes.[86] However, evidence supports the use of corticosteroids when there is a high risk of developing BPD,[87] although this risk may be difficult to determine. Steroid administration practices vary considerably across centers.[77] Inhaled corticosteroids (flunisolide, beclomethasone, budesonide, dexamethasone, fluticasone) have the benefits of less systemic toxicity but with uncertain efficacy. A meta-analysis including 16 trials found that inhaled corticosteroids were associated with a statistically significant reduction in death or BPD at 36 weeks' PMA,[88]

although long-term data were not available. A promising approach combines surfactant and budesonide. A multicenter RCT of 265 very low birth weight infants with severe RDS compared outcomes of administration of surfactant and budesonide versus administration of surfactant alone and found that the surfactant and budesonide group had a statistically significant decrease in mortality and the incidence of BPD, as well as lower levels of intratracheal cytokines interleukins 1, 6, and 8 in tracheal aspirates at 12 hours of age.[89]

Results from a 2018 meta-analysis of 4 studies (3 with intramuscular delivery and 1 with oral delivery) demonstrated that vitamin A supplementation was associated with reduced BPD in ELBW survivors at 36 weeks' CGA, but there was no reduction in death, oxygen use at 28 days after birth, duration of mechanical ventilation, IVH, retinopathy of prematurity, or necrotizing enterocolitis.[90] Vitamin A is essential for normal lung growth and maintenance of respiratory tract epithelium.[91,92]

Caffeine is a methylxanthine used to treat apnea of prematurity. Caffeine reduces the risk of BPD developing in very low birth weight infants and is associated with improved survival without neurodevelopmental disability at 18 to 21 months of age, but it is not known whether caffeine affects longer-term pulmonary outcomes.[93,94]

Inhaled bronchodilators such as albuterol and ipratropium treat increased airway resistance and are often used in patients with BPD and/or patients who were born preterm with chronic wheeze or cough. In a study in 110 patients with severe BPD during their initial hospitalization, pulmonary function test results demonstrated that 74% of patients with obstruction and 63% of patients with a mixed obstructive and restrictive phenotype were bronchodilator responsive (2–8 puffs albuterol).[76] Another review of 21 studies in preterm-born children aged 5 years and older found improvements in FEV_1 after short-term administration of bronchodilators.[95] Although there are no studies showing long-term benefits of inhaled bronchodilators in BPD, they may be helpful in select patients with an obstructive phenotype and/or with viral illnesses causing lower airway obstruction.

Inhaled nitric oxide can be effective for treating established BPD and symptomatic PH. Chronic PH secondary to BPD is managed according to AHA and ATS pediatric pulmonary hypertension guidelines.[53]

Studies to evaluate long-term effects of therapies, such as inhaled bronchodilators, diuretics, and steroids, in patients with BPD are retrospective and underpowered. Further research on respiratory treatments for these patients is needed.

Table 28–2. Interventions to Minimize Lung Injury in Preterm Infants

Intervention	Rationale	Level of Evidence	Clinical Implications
Caffeine	Reduced time on ventilator leading to less lung damage	High quality: large RCT with long-term follow-up	Use in extremely preterm infants with apnea of prematurity
Less invasive surfactant administration	Avoids the risks associated with endotracheal intubation	Low quality: small RCTs, imprecise estimates of safety and efficacy	Very promising, but more research required
Vitamin A	Low levels seen in preterm infants; vitamin A required for normal lung growth	Moderate quality: meta-analysis suggests a small reduction in rates of death or BPD	Depends on local incidence of BPD; trade-off between the modest reduction in BPD and acceptability of intramuscular treatment
Dexamethasone	Reduced inflammation allowing earlier extubation	Moderate quality: meta-analyses and meta-regression of numerous small trials	Low-dose, short courses that are useful for infants receiving ventilation at highest risk of developing BPD
Hydrocortisone	Avoids adverse neurodevelopmental effects of dexamethasone	Moderate quality: small RCTs, imprecise estimates of safety and efficacy	Promising, but more research into neurodevelopmental outcomes is required
Steroids administered with surfactant	Better distribution of steroids and reduced systemic effects	Low quality: small RCTs, imprecise estimates of safety and efficacy	Very promising, but more research is required

Abbreviations: BPD, bronchopulmonary dysplasia; RCT, randomized controlled trial.

Adapted from Thébaud B, Goss KN, Laughon M, et al. Bronchopulmonary dysplasia. *Nat Rev Dis Primers*. 2019;5(1):78. © 2019 Springer Nature.

Longitudinal Care for Patients With BPD

Infants with moderate to severe BPD (requiring respiratory support at 36 weeks' CGA) have prolonged hospitalizations after birth. Interdisciplinary teams consisting of pulmonologists; neonatologists; cardiologists; nurses; respiratory therapists; dieticians; physical, occupational, and speech therapists; and social workers are helpful for coordinated discharge and outpatient plans.[16,96]

The European Respiratory Society published a guideline in 2019 outlining long-term management of BPD in children. The authors recommended the following: (1) lung imaging only in patients with severe BPD or recurrent admissions; (2) lung function monitoring with pulmonary function testing; (3) individualized advice on child care attendance; (4) treatment with bronchodilators for subgroups

such as those with severe disease, asthma symptoms, recurrent admissions, and/or exercise intolerance; (5) no long-term treatment with steroids; (6) allowing patients to outgrow their diuretics gradually; and (7) saturation targets of 90% to 95%.[97] An example of imaging in a patient with severe type 2 BPD is in **Figure 28-4**.[16] In 2021, the American Thoracic Society also published a guideline[98] for outpatient management of post-prematurity respiratory disease (PPRD), a more inclusive diagnosis defined by prematurity and chronic respiratory symptoms. The guidelines address the outpatient use of medications (bronchodilators, inhaled steroids, and diuretics) and diagnostics (swallow studies, bronchoscopy, polysomnography, and CT imaging) in patients with PPRD.

Oxygen supplementation may be required throughout hospitalization and continued after discharge. New oxygen guidelines recommend higher saturation goals than those used previously because of the SUPPORT (Surfactant, Positive Pressure, and Oxygenation Randomized Trial) trial findings of increased mortality with oxygen saturation less than 90%.[99,100] Titrating oxygen therapy to avoid extremes of low or high saturations and unnecessary exposure to inflammatory oxygen is still an active research question,[101] but additional guidance has emerged with new ATS guidelines for home oxygen therapy.[102] Standardized protocols for home oxygen weaning are being evaluated.[103]

Nutritional maximization plays an essential role in neonatal growth and development, and early undernutrition is linked with increased BPD. Early aggressive protein and calorie administration improves pulmonary outcomes.



Figure 28-4. Imaging in severe type 2 bronchopulmonary dysplasia. Anterior-posterior chest radiograph (left) and coronal computed tomography scan (right). Cystic lung disease is apparent on the computed tomography scan.

Reprinted from Abman SH, Collaco JM, Shepherd EG, et al; Bronchopulmonary Dysplasia Collaborative. Interdisciplinary care of children with severe bronchopulmonary dysplasia. *J Pediatr*. 2017;181:12.e1–28.e1. doi: 10.1016/j.jpeds.2016.10.082. © 2017, with permission from Elsevier.

Lung growth is proportional to linear and somatic growth,[104] and linear growth should be maintained as respiratory support is weaned. Patients with BPD should be followed up regularly with a dietician who partners with the pediatrician and/or pediatric pulmonologist.

The Future of BPD

Bronchopulmonary dysplasia is the most common morbidity after preterm birth. Research is critical to understand the variety of phenotypes within the broad clinical definition of BPD and to develop targeted therapies. The Bronchopulmonary Dysplasia Collaborative is a multicenter group of clinicians with the goal of improving the care of patients with severe BPD through research and standardization of team-based care.[16]

key points

- Bronchopulmonary dysplasia remains a common cause of neonatal morbidity and mortality, and BPD rates are increasing.
- Prematurity and gestational age are the largest risk factors for the development of BPD.
- Advanced noninvasive ventilation techniques allow for avoidance of invasive surfactant administration and mechanical ventilation in many preterm infants.
- Patients with severe type 2 BPD have unique physiological characteristics with high airway resistance treated with specific ventilator strategies.
- Longitudinal care of infants with BPD requires a multidisciplinary approach with a medical home that facilitates frequent evaluation and monitoring.
- More research is needed to establish a more precise diagnosis for BPD, investigate underlying pathophysiological mechanisms of severe BPD, and target inflammatory pathways with future therapies.

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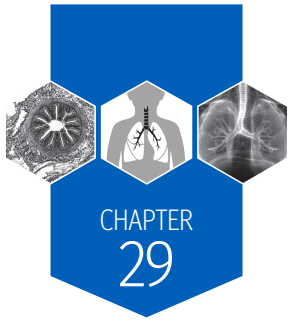
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Pleural Effusion (Noninfectious)

Girish D. Sharma, MD, FAAP, FCCP

Introduction

Pleural effusion is defined as an excessive amount (> 10–20 mL) of fluid in the pleural space and is the result of excessive filtration or defective absorption of accumulated fluid. Normally, there is a balance between the influx and outflow of fluid from the pleural space, resulting in a very small amount (0.1–0.2 mL/kg) of sterile, colorless fluid.[1] Nearly 90% of the amount of pleural fluid filtered out of the arterial end of the capillaries is reabsorbed at the venous end. The remaining 10% of the filtrate is returned via the lymphatic system. The final direction of fluid transport depends on the balance between filtration and absorption forces.[2]

The balance depends on several factors, including capillary filtration or hydrostatic pressure, capillary oncotic pressure (mainly due to albumin), pleural capillary hydrostatic pressure, and pleural fluid oncotic pressure. Normally, capillary hydrostatic or driving pressure is higher than pleural hydrostatic pressure, and pleural oncotic pressure is lower than capillary oncotic pressure, which results, along with lymphatic drainage, in no net accumulation of pleural fluid. Alterations in fluid dynamics may occur with changes in hydrostatic or oncotic pressure in the capillaries and the pleural cavity. Variants of pleural effusion include empyema or pyothorax, hemothorax, and chylothorax, which are due to collections of pus, blood, and lymph, respectively, in the pleural space.

CASE REPORT 29-1

A 4-year-old boy with nephrotic syndrome developed sudden respiratory distress, hypoxia while breathing room air, and abdominal distention. Laboratory test results showed hyponatremia and anemia, and a chest radiograph (**Figure 29-1**) showed density in the lower lobes. A pleural effusion is suspected.



Figure 29-1. Bilateral pleural effusions, moderate on the left side and smaller on the right side, in a 4-year-old boy with nephrotic syndrome.

Courtesy of E. Comiskey, MD, Rush University Medical Center.

Fluid Characteristics

On the basis of its chemical characteristics, pleural fluid can be transudative (due to congestive heart failure, atelectasis, or hypoalbuminemia) or exudative (due to pleuropulmonary infections, circulating toxins, systemic lupus erythematosus, rheumatoid arthritis, sarcoidosis, tumor, or pulmonary infarction). Fluid characteristics, such as protein concentration and the ratio of lactate dehydrogenase (LDH) between pleural fluid and plasma, can help determine whether the pleural fluid is an exudate or a transudate (**Table 29-1**).[2] Another way of describing pleural fluid is based on causative factors such as hemorrhage or malignancy.

Table 29-1. Pleural Fluid Characteristics to Differentiate Between Transudates and Exudates

Characteristic	Transudate	Exudate
Protein level	< 3 g/dL (< 30 g/L)	≥ 3 g/dL (≥ 30 g/L)
Pleural fluid LDH versus serum LDH (upper level of serum LDH)	< 2/3	≤ 2/3
Pleural fluid: serum protein	< 0.5	≥ 0.5
Pleural fluid: serum LDH	< 0.6	≥ 0.6

Abbreviation: LDH, lactate dehydrogenase.

Box 29-1

Causes of Pleural Effusion According to Type of Fluid

Causes of transudative pleural effusion	Causes of exudative pleural effusion
Hypoalbuminemia	Parapneumonic effusion (most common cause in children)
Congestive heart failure	Pancreatitis
Atelectasis	Collagen vascular disorders (rheumatoid arthritis, systemic lupus erythematosus)
Nephrotic syndrome	Tuberculosis
Cirrhosis	Sarcoidosis
Peritoneal dialysis	Trauma (esophageal perforation, after cardiac surgery)
Myxedema	Malignancy
Constrictive pericarditis	Pulmonary embolism
	Radiation pleuritis
	Meigs syndrome and pseudo-Meigs syndrome
	Yellow nail syndrome

Transudative Pleural Effusion

Disequilibrium between hydrostatic and oncotic forces results in ultrafiltration of plasma in the pleural space, causing transudative pleural effusion. Increased microvascular pressure is the mechanism in congestive heart failure; increased perimicrovascular pressure, in atelectasis; and decreased oncotic pressure, in hypoalbuminemia (see **Box 29-1** for a list of causes). Because of the systemic nature of disorders causing transudative pleural effusion, pleural effusion tends to occur bilaterally.

Exudative Pleural Effusion

Exudative pleural effusion can be caused by pleural or pulmonary inflammation, impaired lymphatic drainage from the pleural space, or transdiaphragmatic movement of inflammatory fluid from the peritoneal space. Infectious pleural effusions tend to occur unilaterally.

Hemorrhagic Pleural Effusion

Hemorrhagic pleural effusion can be caused by trauma to the heart, the great vessels, and the chest wall; postpericardiotomy syndrome; hemorrhagic disorders such vitamin K deficiency; Henoch-Schönlein purpura; and malignancy. Hemothorax has been reported with congenital cystic adenomatoid

malformation.[3] Patients with hemorrhagic pleural effusion, depending on the amount of bleeding, may have a reduced hematocrit level. Hemothorax should be suspected if pleural fluid hematocrit is more than 50% of peripheral blood hematocrit.

Pleural Effusion Associated With Malignancies

In malignancies such as lymphomas and Hodgkin disease, pleural effusion can be caused by impaired pleural lymphatic flow secondary to pleural involvement and thoracic duct obstruction. Enlarged mediastinal lymph nodes, fibrosis, thickening of parietal pleura, and obstruction of the thoracic duct can result in exudative pleural effusion.[2] Pleural metastasis may result in increased permeability or obstruction of the pleural lymphatic vessels, in turn resulting in pleural effusion. Radiation-induced pleural fibrosis and malignancy-associated hypoproteinemia may also contribute to pleural effusion. Meigs syndrome is a triad of ascites, pleural effusion, and benign ovarian fibroma and has been reported even in prepubertal children. Presence of an ovarian tumor other than a fibroma, ascites, and pleural effusion is called *pseudo-Meigs syndrome*. The prognosis in Meigs syndrome is good because most tumors are benign.

Chylous Pleural Effusion (Chylothorax)

Chyle is lymphatic fluid enriched with fat secreted by intestinal cells. In children, chylothorax is usually a postoperative complication of cardiac and thoracic surgery; other causes are thrombosis of the subclavian vein and malformation of the pulmonary or thoracic lymphatic system as described in trisomy 21 and Noonan syndrome.[4] Congenital chylothorax, the most common cause of pleural effusion in the newborn, is reported to occur in 1 in 10,000 live births.[5]

Characteristics of chylous pleural fluid are milky appearance with triglyceride levels greater than 97.4 mg/dL (1.1 mmol/L), with minimal oral fat intake; total cell count greater than or equal to 1,000 cells/μL (1×10^9/L); and lymphocytic fraction greater than 80%.[6] In cases caused by postoperative complication, there is a relationship between the time congenital chylothorax is diagnosed and initiation of oral fat intake. A delay in oral feeding may delay the appearance and diagnosis of chylothorax.

Clinical Presentation

The presentation of pleural effusion ranges from an incidental radiological finding to symptoms of respiratory distress and hypoxia requiring urgent treatment and removal of fluid. The degree of dysfunction and associated clinical picture is determined by the amount and rate of fluid collection, nature of the underlying disorder, and patients' cardiopulmonary reserve. With a very small collection, no obvious change may be apparent; larger collections limit lung inflation and may result in imbalance and decoupling of the normally

Box 29-2

Drugs Associated With Pleural Effusion

- Amiodarone
- Bleomycin
- Dantrolene
- Hydralazine
- Methotrexate
- Methysergide
- Mitomycin
- Nitrofurantoin
- Procainamide
- Procarbazine
- Quinidine

balanced inward recoil of the lung and outward recoil of the chest wall, which further deflates the lung. This imbalance may result in compressive lung atelectasis; ventilation/perfusion mismatch; hypoxemia; or a clinical picture of a pleural space–occupying lesion, such as physical examination showing chest wall bulge and mediastinal shift with corresponding radiological changes. Inspiratory muscles are placed at a mechanical disadvantage, which may compromise inspiratory efforts.

The clinical picture of a patient with pleural effusion depends on the underlying disease, amount of pleural effusion, and rate at which the fluid accumulates in the pleural space. Many patients with pleural effusion may not have symptoms related to pleural effusion.

It is important to obtain a history of the drugs implicated in the cause of pleural effusion. These include drugs that have been associated with lupus syndrome and others that may cause pleural effusion (**Box 29-2**). The following sections discuss some of the symptoms.

Chest Pain

Transudative pleural effusion is not associated with chest pain because there is no inflammation of pleura in the disorders associated with transudates (**Box 29-1**). Involvement and inflammation of parietal pleura, because only parietal pleura has pain fibers, may result in pleuritic chest pain, which is present or gets worse during inspiration or coughing. Usually the pain is localized and coincides with the affected area of the pleura. The pain may be mild or severe and is stabbing or sharp in nature. At times, the pain may be referred to the abdomen or ipsilateral shoulder because of common nerve supply. The pain may decrease in severity as the quantity of pleural effusion increases because increased quantity of fluid between 2 layers of pleura prevents rubbing of the 2 surfaces against each other.

Dyspnea

Dyspnea, or shortness of breath, may be the most common presenting symptom. Mechanical inefficiency of respiratory muscles stretched by outward movement of the chest wall and downward movement of the diaphragm results in dyspnea. Dyspnea indicates a large amount of pleural fluid collection. Underlying lung disease can also contribute to dyspnea.

Cough

Mild nonproductive cough is a less common symptom of pleural effusion. Distortion of the lung may cause cough, but an underlying lung disorder may also cause cough.

Physical Findings

Pleural rub may be the only finding in the early stages when the fluid amount collected in the pleural space is very small. Pleural rub is present throughout the respiratory cycle, loudest at end inspiration and early expiration. It disappears when the patient holds their breath.

With increasing amounts of fluid, there may be decreased breath sounds, increased dullness at percussion, decreased tactile fremitus, and egophony. Large amounts of fluid are associated with contralateral mediastinal shift. There may be fullness of intercostal spaces over the pleural effusion area. Ipsilateral mediastinal shift may be present when there is endobronchial obstruction by a foreign body or tumor.

Pleural effusion rarely may be associated with yellow nail syndrome (slow growing and discolored nails), lymphedema, or chronic recurrent pleural effusion.

Diagnostic Studies

Laboratory Studies

Conservative management with observation of the patient for complications may be reasonable in cases of pleural effusion associated with congestive heart failure, viral pleurisy, and postoperative pleural effusions. Thoracentesis should be considered in patients with unexplained pleural effusion when fluid quantity is sufficient to allow a safe procedure. Blood cell counts, erythrocyte sedimentation rate, and C-reactive protein level estimation help to confirm or rule out an infective or inflammatory cause for pleural effusion. The results of pleural fluid analysis for pH and serum glucose, LDH, protein, triglyceride, and electrolyte levels, as well as microbiological studies, are associated with different causes and used to differentiate between exudate and transudate (**Table 29-1**).[7]

Chest Radiography

Chest radiography helps to confirm the diagnosis of pleural effusion. Radiographic features of pleural effusion are related to several factors,[3] including the amount of fluid, whether the fluid is free or loculated, presence of adjacent parenchymal lung disease, and position of the patient relative to the x-ray beam. A small amount of fluid (<200 mL) may be detected as only blunting of the costophrenic angle. A larger amount of fluid appears as homogeneous

density with a concave superior border on an upright posteroanterior (PA) view or lateral view. This meniscus sign may not be present when the radiograph is obtained with the patient supine, as in a portable radiograph, and only a nonspecific haze over the affected hemithorax may be visible because of the fluid layers in the posterior area. In still larger fluid collections, the whole hemithorax may be opacified, and there may be evidence of mediastinal shift to the opposite side. The fluid may extend into major or minor fissures and appear as thickened fissures on chest radiographs obtained in the PA or lateral view. A subpulmonic pleural effusion with fluid between the inferior surface of the lung and superior margin of the diaphragm may appear as apparent elevation of the corresponding dome of the diaphragm. Lateral displacement of the apex of the diaphragm, increased space between the air bubble of the gastric fundus and the superior margin of apparent diaphragm, absence of the lower lobe vessels normally visualized overlying the diaphragm on PA radiographs, and sharp angulation of the anterior portion of the apparent diaphragm may also be seen.[8]

Ultrasonography

Ultrasonography is effective for visualization of effusion and determining whether the fluid is free flowing or loculated, and it may also be used to guide thoracentesis.[9] Ultrasonography can also help differentiate between solid mass and effusion.

Computed Tomography

Unless an underlying mass is a concern, computed tomography (CT) of the chest may not be necessary to diagnose a simple pleural effusion. Nevertheless, CT with contrast material may provide additional information, such as underlying lung parenchymal information, necrotizing pneumonia, atelectasis, hilar adenopathy, and lung abscess. It may also have a role in cases of complicated effusion or those unresponsive to therapy.

Magnetic Resonance Imaging

Conventional pediatric chest magnetic resonance imaging (MRI) for diagnosing pleural effusion[10] and its modified version, dynamic contrast-enhanced MRI,[11] for diagnosing chylothorax have also been proposed. However, conducting the MRI may be associated with multiple issues, such as difficulty in transporting the patient to the MRI facility because it may mean interrupting monitoring and other ongoing therapies, need for sedation and anesthesia, and risk of dorsal atelectasis during general anesthesia.

In cases in which conventional chest radiography or ultrasonography is not helpful in confirming the diagnosis of pleural effusion, use of the respiratory navigator (use of radiofrequency pulses to detect physiological motion) during MRI may be considered.[12,13]

Management

Treatment of nonbacterial pleural effusion is primarily treatment of the primary disorder (**Box 29-3**). Refer to Chapter 21, Complications of Pneumonia, for the treatment of bacterial pleural effusion, such as parapneumonic pleural effusion.

Box 29-3

Treatment for a Pediatric Patient With Nonbacterial Pleural Effusion

- **Document the presence of pleural effusion.**
- **Suspect pleural effusion in the presence of clinical disorders likely to be associated with it, such as nephrotic syndrome, hypoalbuminemia, and congestive heart failure, and postoperative cardiothoracic cases.**
- **Take a history and conduct a physical examination for symptoms such as chest pain, dyspnea, and cough and the presence of physical signs such as pleural rub, decreased breath sounds, increased dullness, and mediastinal shift.**
- **Confirm the presence and estimate the quantity of pleural effusion by means of chest radiography, ultrasonography, or computed tomography.**
- **Investigate for possible causes of the pleural effusion (blood cell counts, erythrocyte sedimentation rate, C-reactive protein levels).**
- **Use thoracentesis to diagnose the type of fluid (transudate vs exudate) and possible cause.**
- **Use thoracentesis when pleural effusion compromises the patient's respiratory status; bacterial causes of pleural fluid, such as empyema, tuberculosis, and malignancy, may require thoracentesis for diagnostic and therapeutic reasons.[8]**
- **Apart from thoracentesis for diagnostic purposes and to relieve respiratory distress, treatment of the underlying disorder should be the goal of therapy.**

Thoracentesis

Thoracentesis may be considered therapeutic or diagnostic.

Therapeutic Thoracentesis

Thoracentesis is indicated to relieve dyspnea in patients with large effusions[8] and to prevent development of complicated parapneumonic effusions. As a general rule, thoracentesis can be performed safely when the thickness of the pleural fluid layer at lateral decubitus chest radiography is more than 10 mm or loculated fluid is identified at ultrasonography or chest CT. Administering supplemental oxygen during thoracentesis can prevent hypoxemia as a complication of the procedure. It is important to withdraw enough fluid to improve the dyspnea without withdrawing too much fluid and too rapidly, which can cause reexpansion pulmonary edema and pneumothorax.[9] A small and clinically nonsignificant pneumothorax may be present after thoracentesis. The

pneumothorax, if large, may manifest with increased respiratory distress, oxygen requirement, and clinical signs (see Chapter 30, Pneumothorax and Pneumomediastinum) and can be confirmed with chest radiography.

Diagnostic Thoracentesis

Diagnostic thoracentesis is performed in patients with effusion with no clear cause. The fluid can be tested to differentiate between transudates and exudates (**Table 29-1**). The fluid can be examined for physical characteristics, such as color, specific gravity, triglyceride levels, and chylomicron levels. Other tests can be used to help diagnose a specific cause of pleural effusion; these include total and differential blood cell counts, LDH levels, pH, protein levels, glucose levels, Gram stain, mycobacterial studies, fungal stain and culture, and cytological testing.[8] Levels of amylase more than twice the levels of serum amylase suggest pancreatic disease, such as acute pancreatitis, pancreatic pseudocyst, and malignancy. Esophageal rupture also increases amylase levels in pleural fluid.

Management of Chylous Pleural Effusion

Chylous pleural effusion may be either acquired (postoperative) or congenital. Usually, initial therapy for postoperative chylothorax is pleural space drainage, use of medium chain triglyceride oil, fat-free oral feeding, or enteric rest with total parenteral nutrition. Chylous effusions often persist for weeks. In neonates with congenital chylothorax refractory to conservative management, octreotide, a somatostatin analogue, administered as an intravenous infusion (1 mcg/kg/h, gradually increased to 10 mcg/kg/hr)[14] may reduce production and accumulation of fluid.[15] However, gastrointestinal intolerance, necrotizing enterocolitis, and transient hypothyroidism have been reported as adverse effects.[15,16] Investigators in a 2017 retrospective study of chylothorax in neonates reported no advantage of octreotide over a regimen of nothing by mouth and total parenteral nutrition.[17] Surgery in the form of pleurodesis of leaking lymphatic vessels and ligation of the thoracic duct is usually indicated if the effusion persists after more than 4 weeks of conservative treatment.[4,18]

Prognosis and When to Refer

The prognosis depends on the cause of pleural effusion, the rate of fluid collected, and the quantity of fluid collected. Small pleural effusions detected accidentally on chest radiographs and not associated with clinically significant findings may not require major intervention, such as pleural drainage. Pleural effusions with a large amount of rapidly collecting fluid and clinical signs, especially respiratory distress, hypoxia, and mediastinal shift, require more aggressive therapy and referral for possible surgical intervention for drainage. Failure of conservative therapy and delay in initiation of specific therapy may result in complications, such as respiratory failure.

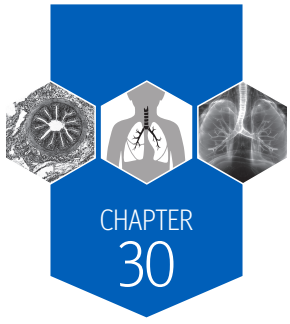
key points

- Nonbacterial pleural effusion should be suspected when a patient with underlying disorders, such as nephrotic syndrome, hypoalbuminemia, or congestive heart failure, or postoperative cardiothoracic cases, develops respiratory distress, increased oxygen requirement, and clinical signs of effusion.
- A small pleural effusion may manifest as only an incidental finding at chest radiography.
- Rapidly collecting large pleural effusions with respiratory distress require therapeutic thoracentesis.
- Pleural effusions with no obvious underlying cause require diagnostic workup, including diagnostic thoracentesis, investigations for the possible underlying cause, and treatment according to the cause.

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Pneumothorax and Pneumomediastinum

Danna Tauber, MD, MPH

Pneumothorax

Pneumothorax occurs when air enters the pleural space by means of a leak in the parietal or visceral pleura. Pneumothorax can be spontaneous or traumatic. Traumatic pneumothorax is the result of blunt or penetrating trauma to the chest wall or an unintended injury from a medical procedure. Spontaneous pneumothorax does not have a preceding trauma and can be categorized further as primary or secondary spontaneous pneumothorax. In primary pneumothorax, there is no known underlying lung disease that would lead to air leak. Apical blebs of unknown cause can be seen at the time of surgery or computed tomography (CT).[1] Secondary pneumothorax occurs as a complication of underlying lung disease, such as asthma or cystic fibrosis. Data are limited on the exact incidence of spontaneous pneumothorax in the pediatric population, but it appears to be higher between the ages of 13 and 16 years.[2] Primary spontaneous pneumothorax typically occurs in patients who are tall or asthenic and more commonly in male patients.[3,4] Smoking increases the risk of pneumothorax.[5] **Box 30-1** contains a list of causes of pneumothorax.

CASE REPORT 30-1

A 16-year-old adolescent presented to the emergency department with a 2-day history of right-sided chest pain. The only other symptom was shortness of breath on exertion. He has been in previously good health, is active, and participates in sports. The pain started when he was sitting quietly in the evening. His vital signs were normal except for a respiratory rate of 18 breaths/min. Oxygen saturation in room air was 97%. Physical examination revealed a tall and thin youth with a normal chest configuration. The chest examination findings were normal, and findings from auscultation of the heart and lungs were negative. A chest radiograph revealed a small pneumothorax on the right. He was observed in the emergency department for 4 hours, during which time computed tomography (CT) was performed. The CT scan confirmed the pneumothorax and showed small apical blebs in both lungs. He was discharged home with no intervention, and arrangements were made for follow-up radiography in 2 days.

Box 30-1

Causes of Pneumothorax

Traumatic
- Penetrating or blunt chest trauma

Iatrogenic
- Mechanical ventilation (barotrauma)
- Central vein catheterization
- Procedures on airways: intubation, endoscopy, transbronchial biopsy
- Laparoscopic procedures
- Percutaneous biopsies

Primary spontaneous
- Asthenic body habitus
- Idiopathic
- Cocaine or marijuana inhalation

Secondary spontaneous
- Airway disease: asthma, cystic fibrosis
- Postinfection: measles, *Pneumocystis jirovecii* pneumonia, tuberculosis, necrotizing pneumonia or abscess, parasitic (ecchinococcal)
- Interstitial lung disease: sarcoidosis, Langerhans cell histiocytosis
- Connective tissue disease: Marfan syndrome, Ehlers-Danlos syndrome, rheumatoid arthritis, systemic lupus erythematosus, polymyositis, dermatomyositis
- Malignancy: lymphoma, metastasis
- Aspiration: foreign body, meconium
- Catamenial pneumothorax

Congenital malformations

Pathophysiology

The exact mechanism for pneumothorax remains unclear but is thought to involve an interplay of a few factors. One proposed mechanism suggests that large increases in transpulmonary pressure can cause alveolar distention with high pressure gradients leading to alveolar rupture. Subpleural blebs then form that can rupture directly into the pleural space. Another suggested mechanism is that there is direct injury from underlying lung disease to the visceral pleura that then leads to pneumothorax. There is a negative pressure within the pleural space, relative to the alveoli, which helps keep the pleural space intact. Spontaneous pneumothorax occurs when the visceral pleura is ruptured. Traumatic pneumothorax may involve the parietal pleura (air entering from the outside), visceral pleura (air entering from the lungs), or both. Tension pneumothorax develops when air enters the pleural space during inspiration but cannot exit during exhalation. This situation will lead to

collapse of the affected lung and shift of the mediastinum away from the affected side. Tension pneumothorax is uncommon following primary spontaneous pneumothorax but is a potential risk after traumatic pneumothorax and secondary spontaneous pneumothorax, especially in patients who are receiving positive-pressure–assisted ventilation. Air enters the pleural space with each breath and is unable to escape so that the mediastinum becomes shifted to the other side. Hypoxia results, and hemodynamic changes lead to shock and death within a short period (sometimes minutes) if the pneumothorax is not treated.

Clinical Features

The most common symptom of pneumothorax is the sudden onset of chest pain. Additional symptoms include tachypnea, dyspnea, tachycardia, and cyanosis. The volume of air in the pleural space, the suddenness of onset, and the degree of respiratory compromise from underlying lung disease determine the severity of symptoms. Pain can be localized to the retrosternal space or to the ipsilateral shoulder or can be generalized pleuritic pain. Physical examination findings include decreased breath sounds, decreased chest wall movement, and increased resonance during percussion on the affected side. In cases of tension pneumothorax with shift of the mediastinum, the trachea will be displaced, as will the point of maximal cardiac impulse. Air moving from areas of lower resistance can create subcutaneous emphysema in the neck, upper extremities, abdominal wall, and peritoneum. If the pneumothorax is small or is picked up as an incidental finding on a chest radiograph, the patient will frequently be asymptomatic.

Diagnostic Tests

Pneumothorax is most frequently diagnosed by means of chest radiography. The characteristic findings at radiography are air in the pleural space outlining the visceral pleura (pleural line) and hyperlucency and attenuation of vascular and lung markings on the affected side (**Figures 30-1** and **30-2**). Chest CT can depict bullae and blebs in patients with recurrent pneumothorax and in cases in which the radiograph is inconclusive.[6,7] Blood gas measurements can reveal hypoxemia, but hypercapnia is not typically seen in cases of pneumothorax without underlying chronic lung disease.[1] Electrocardiography can demonstrate changes in amplitude of the QRS complex and the cardiac axis in cases of severe tension pneumothorax when there is mediastinal shift.

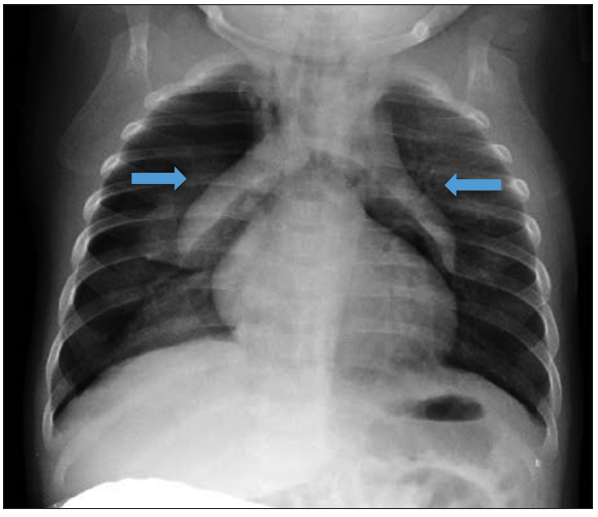


Figure 30-1. Anteroposterior radiograph showing the spinnaker sail (angel wing) sign (arrows) in a patient with pneumomediastinum and pneumothorax.

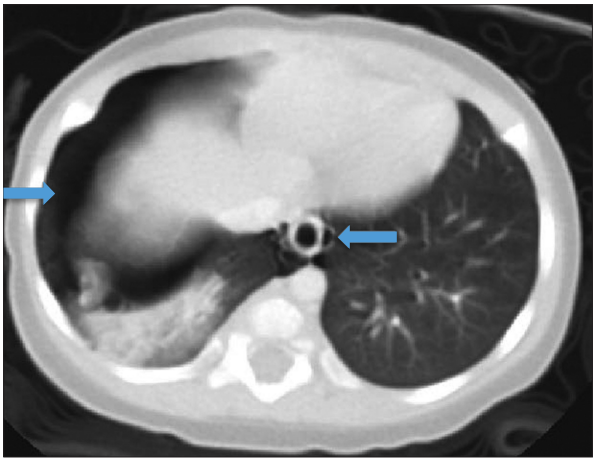


Figure 30-2. Axial computed tomography scan revealing both paraesophageal air and pneumothorax in the same patient seen in Figure 30–1.

Management

Treatment choice depends on a number of factors, including degree of respiratory distress, pneumothorax size, pneumothorax cause, and the presence of underlying lung disease. The goals of treatment are removal of air from the pleural space and prevention of recurrence.[1,8] Treatment options include observation with or without supplemental oxygen; needle aspiration; chest tube placement; pleurodesis; and, in some cases, surgical resection of blebs if present. A few recent studies have been published on management of pediatric spontaneous pneumothorax, but pediatric-specific guidelines are not currently available.[9–11]

Minimal Symptoms: Observation With or Without the Use of Supplemental Oxygen

In patients without respiratory distress and a small pneumothorax (<2 cm [0.79 inches] distance between chest wall and lung at the apex), simple observation can be instituted.[12,13] In a younger child, hospitalization is advisable. Supplemental oxygen can be used during this period of observation. The rate of resorption of air from the pleural space is increased with the use of supplemental oxygen.[14] The increased alveolar oxygen tension creates a large gradient between capillary and pleural gas partial pressure of nitrogen, resulting in faster resorption of intrapleural air (known as *nitrogen washout*). Use of 100% oxygen via a nonrebreathing face mask has been suggested, although this should not be continued for a long period. In the older child, observation may be on an outpatient basis. The exception is traumatic pneumothorax because of the potential for tension pneumothorax. Most cases of traumatic pneumothorax should be treated with a chest tube, especially if positive-pressure ventilation is used.

Patients With Symptoms

Needle Aspiration

Patients with symptoms with a small or large pneumothorax will need to have the air evacuated, which may be accomplished with needle aspiration. A large-bore intravenous catheter is attached to a large syringe with a 3-way stopcock. Air is aspirated until no more can be drawn off. If air continues to be withdrawn, this means that there is a persistent air leak, and tube thoracostomy should be performed. If no more air can be aspirated, then the stopcock is closed and the catheter is taped to the chest wall. After 4 hours of observation, chest radiography should be performed. If there is sufficient lung re-expansion, then the catheter can be removed and the patient observed. If the pneumothorax remains the same size or larger, then the patient requires chest tube placement. Published success rates vary, although they point to a higher success rate in small pneumothoraces.[9] A 2020 study[10] looked at needle aspiration for children presenting with their first primary spontaneous pneumothorax. The authors recommended that needle aspiration be used as a test and that those in whom needle aspiration fails go on to early video-assisted thoracoscopic surgery (VATS).

Thoracostomy Tube

Thoracostomy tube placement has been the initial treatment of choice for pediatric patients with symptoms with large primary or secondary pneumothoraces, for younger children, or for those with recurrent spontaneous pneumothorax.[15] Tube placement involves the use of a 1-way Heimlich valve or water seal device to prevent re-accumulation of air. In guidelines from the American College of Chest Physicians,[15] half of the panel members recommended clamping of the tube 4 hours after the last evidence of an air

leak, and the other half recommended never clamping a chest tube. To avoid developing tension pneumothorax, a bubbling chest tube should never be clamped. Repeat chest radiography should be performed 5 to 12 hours after the last evidence of an air leak in preparation for removal of the tube.

Pleurodesis

Pleurodesis is performed in cases of recurrent pneumothorax. It can be achieved chemically or surgically. Chemical pleurodesis involves injection of a sclerosing agent, such as talc, tetracycline, doxycycline, autologous blood patches, or fibrin glue, at the time of thoracostomy tube placement. Surgical pleurodesis is favored over chemical pleurodesis for persistent air leak.[16] The literature supports both mechanical pleurodesis achieved by direct abrasion with gauze or laser or chemical pleurodesis with talc or doxycycline at the time of surgery to prevent recurrent pneumothoraces.[15]

Surgical Intervention

Surgery is indicated to treat persistent air leaks and to prevent recurrence. Surgery involves stapling or oversewing ruptured blebs (bullectomy) or tears in the visceral pleura and resection of abnormal lung tissue if present. Surgery can be performed via a mini thoracotomy, open thoracotomy, or VATS, with VATS being the preferred method by many surgeons. The American College of Chest Physicians recommends surgical intervention at the time of the first occurrence of a secondary spontaneous pneumothorax[15] and at the second occurrence of a primary spontaneous pneumothorax.[17]

Prognosis

Data are limited regarding the prognosis after spontaneous pneumothorax in children. Results from one reported series showed a 37% incidence of recurrent spontaneous pneumothorax.[18] In pediatric patients undergoing surgery, the reported risk of recurrence was 6% to 9%.[19,20] In another study,[21] the authors found that patients who underwent VATS-directed bullectomy and pleurodesis at the first presentation of spontaneous pneumothorax had a 29% recurrence rate compared with 0% in the group of patients undergoing VATS on the second occurrence. Although there is not yet consensus in the literature regarding the best treatment strategy for initial presentation of spontaneous pneumothorax, patients and caregivers should be made aware of the risk for recurrence.[22]

Pneumomediastinum

Pneumomediastinum is defined as the presence of air in the mediastinum. Cases of pneumomediastinum can be further subdivided into spontaneous or secondary pneumomediastinum. Spontaneous pneumomediastinum does not have an identifiable source. Secondary pneumomediastinum occurs in children with asthma or foreign body aspiration and after chest trauma due to

endotracheal or endoesophageal procedures, mechanical ventilation, cardiac catheterization, or thoracic surgery. Spontaneous pneumomediastinum is a rare condition in young children. However, because of respiratory infections, there is a peak incidence between 6 months and 3 years of age.[23,24] Spontaneous pneumomediastinum is mostly seen in older children and adolescents, with reported incidences of 1 in 800 to 1 in 42,000 patients presenting to a hospital emergency department.[25] Stack and Caputo[23] found an incidence of spontaneous pneumomediastinum in 0.3% of 12,000 children presenting to a pediatric emergency department with asthma. Most investigators report a slightly higher incidence in male patients.[25,26]

Pathophysiology

Alveolar rupture occurs owing to excess pressure (from overdistention) in the alveolus compared with the surrounding tissue. The air leaks into the interstitial tissues toward the hilum along the peribronchial and perivascular sheaths. The air then spreads toward the mediastinum; the cervical region; the upper limbs; and, in some cases, the retroperitoneum, peritoneum, spine, pericardium, and pleura.[25] In some cases of spontaneous pneumomediastinum, a trigger can be found, which often includes asthma, emesis, intense physical activity, inhalation drugs, and situations involving a strong Valsalva maneuver (eg, coughing, screaming).[26] Pneumothorax may accompany the pneumomediastinum.

Clinical Features

Patients typically present with retrosternal chest pain with radiation to the shoulders, back, and arms. The pain is worsened with deep inhalation. Other presenting symptoms include sore throat, dyspnea, swelling of the neck, torticollis, dysphagia, and abdominal pain. Physical examination findings include subcutaneous emphysema and the classic Hamman sign, which is a precordial systolic crepitation or crunching sound at auscultation of the chest. Esophageal perforation must be excluded in cases of spontaneous pneumomediastinum that occur after severe and violent emesis.[25]

Diagnostic Tests

The diagnosis of spontaneous pneumomediastinum can be confirmed with chest radiography. A number of specific radiographic findings are seen in pneumomediastinum.[25,27] The spinnaker sail or angel wing sign (**Figure 30-1**) is created by air lifting the thymus off the heart and major vessels. The continuous diaphragm sign is caused by air collecting between the diaphragm and the pericardium. The vertical lucent streak is seen on the left side of the heart because of air outlining the parietal pleura. Additional radiographic findings include thoracic and cervical subcutaneous emphysema and associated pneumothorax. If esophageal perforation is suspected, then radiography

with contrast material should be performed, which can be combined with CT. Esophageal endoscopy can also be used to identify cases of perforation or radiotransparent foreign body. Electrocardiography can show diffuse microvoltage, depressed ST interval, T-wave inversion, and axis deviation, depending on the size and location of the pneumomediastinum.[25]

Management

In most cases, spontaneous pneumomediastinum is benign and resolves in 3 to 15 days without further sequelae.[28] Management is usually supportive, including rest, analgesia, and treatment of the underlying condition, if present. Patients are advised to avoid maneuvers that lead to forceful exhalation (measure of lung function, physical activity, and playing of wind instruments) for a few months after the episode. As with pneumothorax, the use of nitrogen washout with 100% inspired oxygen is frequently used; however, efficacy has not been conclusively established.[29,30] Follow-up radiographs are not necessary.[25] Recurrence of spontaneous pneumomediastinum is rare but is likely linked to either the underlying diagnosis of asthma or a repeat of the causal situation (emesis, strong Valsalva maneuver) that led to the first pneumomediastinum.

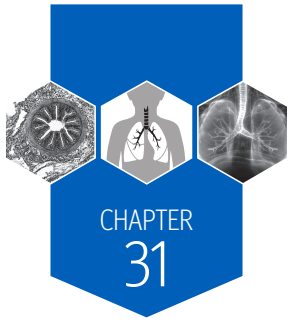
key points

- Pneumothoraces manifest with the sudden onset of severe chest pain.
- Treatment of pneumothoraces depends on the size of the pneumothorax and degree of respiratory distress, with small pneumothoraces being treated with observation or supplemental oxygen and larger pneumothoraces requiring thoracotomy tube placement.
- Further evaluation with chest CT is indicated with recurrent pneumothorax.
- Most cases of pneumomediastinum in children are spontaneous and occur during an asthma exacerbation or after a strong Valsalva maneuver; the course is typically benign, and treatment is supportive.
- Tension pneumothorax is a potentially life-threatening emergency requiring immediate attention.

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Pulmonary Hemorrhage

Evans M. Machogu, MBChB, MS, FAAP
Karen Z. Voter, MD, FAAP

Introduction

Pulmonary hemorrhage is an acute episode of bleeding from the upper or lower respiratory tract, including the trachea, bronchi, bronchioles, and alveoli. The onset can be characterized by hemoptysis, which is the expectoration of blood during coughing. Hemoptysis is uncommon in children, so it is important to consider the possibility of pulmonary hemorrhage in children with cough, hypoxemia, or respiratory distress in the setting of anemia. Although most episodes of hemoptysis are mild and short-lived, they cause anxiety among parents and patients. Furthermore, there is the possibility that the hemoptysis indicates a severe underlying condition or a potential for life-threatening bleeding.

A report of "coughing up blood" may indicate the presence of blood from the upper airway (nose and pharynx) or the lower airway, lung, or gastrointestinal tract, or it may be spurious and related to expectoration of saliva tinted with colored food or drink. A history sorting out the presence or absence of cough, possible foreign body exposure, underlying infection, nasal or pharyngeal trauma, and recent food consumption may help. Many people with pulmonary bleeding report the sensation of gurgling or bubbling in an area of the lung. A physical examination of the nose, pharynx, and mouth should be performed to look for signs of bleeding that would direct attention to the upper airway. Evidence of crackles, increased work of breathing, or localized wheezing would direct attention to causes of bleeding in the lower airways. Studies, including chest radiography, may help to localize the bleeding.

Etiology

There are multiple causes of hemoptysis in children.[1] Most cases of airway bleeding are from irritation of the airway mucosa (**Box 31-1**). Irritation of the airway mucosa from infection or trauma should trigger assessment for pneumonia, bronchitis, or foreign body aspiration, especially in children with underlying conditions, such as cystic fibrosis (CF). Bleeding from a tracheostomy is characteristic of airway irritation, which can occur from dried secretions when there is inadequate humidification, minor suction trauma when a suction catheter is placed too deeply in the airway, or mechanical trauma from the tracheostomy tube itself. Airway bleeding from infection may also be related to mucosal irritation.

Increased pressure within the vasculature is another cause of bleeding (**Box 31-1**), which is seen in children with congenital heart disease or congenital vascular anomalies such as arteriovenous malformations.[2] Pulmonary hypertension from any cause can increase the risk for bleeding. Bronchial arteries are under systemic pressure, and bleeding from these vessels may be massive. Hemorrhage into the alveoli is more unusual than other causes of airway bleeding. Alveolar hemorrhage is seen in children with autoimmune disorders, such as granulomatosis with polyangiitis (GPA), formerly known as Wegener granulomatosis; microscopic polyangiitis; or systemic lupus

Box 31-1

Results of Select Studies of the Causes of Airway Bleeding

Godfrey Chart Review[a]

- Upper airway bleeding—29%
- Tracheostomy complications—18%
- No cause—18%
- Other causes—35%

Batra and Holinger Chart Review[b]

- Infectious causes—29%
- Tracheostomy complications—14%
- No cause—21%
- Other causes—36%

Batra and Holinger Bronchoscopy Studies[b]

- Blood clots—37%
- Purulence—21%
- Mucosal inflammation—21%
- Tracheal abrasion—11%
- Granulation tissue—5%
- Bronchial mass—5%

Coss-Bu Chart Review[c]

- Cystic fibrosis—65%
- Congenital heart disease, including ventricular septal defect, truncus arteriosus, complex cyanotic heart disease, transposition of the great arteries, atrioventricular canal, tetralogy of Fallot—16%
- Other causes—18%

[a] Godfrey S. Pulmonary hemorrhage/hemoptysis in children. *Pediatr Pulmonol.* 2004;37(6):476–484.

[b] Batra PS, Holinger LD. Etiology and management of pediatric hemoptysis. *Arch Otolaryngol Head Neck Surg.* 2001;127(4):377–382.

[c] Coss-Bu JA, Sachdeva RC, Bricker JT, Harrison GM, Jefferson LS. Hemoptysis: a 10-year retrospective study. *Pediatrics.* 1997;100(3):E7.

erythematosus (SLE). Fungal infections are more likely than bacterial infections to cause alveolar bleeding. Idiopathic pulmonary hemosiderosis is diagnosed when bleeding occurs without an identified cause.

General Evaluation of a Child With Pulmonary Hemorrhage and Hemoptysis

The first step in evaluating hemoptysis is to determine the site of bleeding. It is important to be aware that bleeding sources can occur from the upper airway or gastrointestinal tract, although those processes will not be discussed here. It is helpful to estimate the amount of bleeding because children with large amounts of hemorrhage are likely to need hospitalization and rapid diagnostic and therapeutic intervention.

The physical examination should initially focus on the degree of respiratory distress present, which would include tachypnea or tachycardia, as well as any increased work of breathing or fever. Regardless of the cause of the bleeding, the most common finding at auscultation is crackles. These may be localized in the context of a single focus of bleeding or can be diffuse if there is a nonfocal process such as capillaritis.

It is important to differentiate between a single episode of hemoptysis and repeated, possibly undiagnosed, episodes. Aspects of the history that can be helpful would include evidence of other bleeding problems (including clinically significant or recurrent epistaxis), recurrent or chronic respiratory or sinus symptoms, anemia, skin rash, jaundice, and renal disorders. Individuals with an acute episode of hemoptysis may have evidence of infection, such as fever, malaise, or cough. It is important to ask about foreign travel or use of medications (oral contraceptives, warfarin, aspirin) that can affect the risk of thrombosis or bleeding. The environmental history should include specific questions about areas of water damage or mold in the home environment.[3] Parents may notice dampness or a moldy smell. If the parents acknowledge water damage or a moldy smell, inquire about the child's exposures to floods and chronically water-damaged, moldy environments. The social history may suggest risk for abuse.

Imaging and Laboratory Evaluation

Individuals with known underlying processes such as a tracheostomy, bronchiectasis, or congenital heart disease may need only a focused evaluation (**Table 31-1**). Evaluating hemoptysis in children without underlying cardiorespiratory problems can be more involved (**Table 31-2**).

Laboratory evaluation may help determine the cause of bleeding. If the child can expectorate sputum, this can be analyzed for the presence of infection. A complete blood cell count (CBC) can help determine the amount of blood loss

and the likelihood of infection. Clinically significant anemia may suggest repeated episodes of bleeding or an acute, severe episode of bleeding. Clotting studies can be helpful to determine whether an underlying coagulopathy, vitamin K deficiency, or medication adverse effect is present. A chest radiograph may help discriminate between focal or diffuse processes and localize a particular site of bleeding. In some situations, a computed tomography (CT) scan may be helpful to determine whether a focal endobronchial lesion, diffuse interstitial process, or arteriovenous malformation is involved.

Table 31-1. Evaluation of Airway Bleeding in the Setting of a Preexisting Condition

Preexisting Condition	Probable Cause of Bleeding	Evaluation and Treatment
Tracheostomy	Dried secretions	Improve humidification
	Purulent secretions	Culture secretions, antibiotics
	Granulation tissue in airway Mucosal erosion	Ear, nose, throat, or pulmonary referral Visualize airway Alter suction protocol Consider new tracheostomy tube size
Cystic fibrosis Bronchiectasis	Infection or exacerbation	Antibiotics, airway clearance
	Coagulopathy	Check clotting studies Vitamin K supplementation
	Central line clot Pulmonary embolism	Ultrasonography or dye study to evaluate the line Remove central line Consider anticoagulation
	Massive hemorrhage (> 240 mL/day)	Interventional radiology for dye study of the bronchial arteries Embolization of tortuous arteries Decreased airway clearance and inhaled hypertonic saline for a few days
Infection	Bacterial Fungal Tuberculosis Leptospirosis	Sputum culture Chest radiography Consider bronchoscopy
	Foreign body	Chest radiography Consider bronchoscopy
Congenital heart disease	Pulmonary hypertension Previous surgical repair Collateral vessels	Chest radiography Cardiology evaluation, consider echocardiography or catheterization

Table 31-2. Evaluation of Airway Bleeding in the Absence of Preexisting Conditions

Evaluation	Finding	Possible Diagnosis
History Physical examination	Fever	Infection, autoimmune process
	Weight loss	Autoimmune process
	Skin rash (butterfly, vasculitis)	Autoimmune process
	Skin rash (petechiae)	Infection, autoimmune process
	Jaundice	Infection (leptospirosis)
	Nasal or sinus fullness or inflammation	Autoimmune process (GPA)
	Arthralgias or arthritis	Autoimmune process (systemic lupus erythematosus, GPA)
	Localized crackles	Can be any process but may suggest focal infection, foreign body, or idiopathic cause
	Diffuse crackles	Autoimmune process, capillaritis
Sputum	Blood mixed with purulent sputum	Infection
Chest radiograph	Normal	Bleeding from a different site Foreign body Infection Cleared episode of idiopathic pulmonary hemosiderosis
	Focal	Foreign body Infection Autoimmune Idiopathic cause
	Diffuse	Autoimmune Idiopathic cause
Computed tomography scan (chest)	Vascular abnormalities	Arteriovenous abnormalities
	Interstitial prominence	Autoimmune process
	Alveolar filling	Infection Localization of blood
Computed tomography scan (sinus)	Mucosal thickening	Autoimmune process (GPA)
Urinalysis	Blood or protein	Autoimmune process

Abbreviation: GPA, granulomatosis with polyangiitis.

Bronchoscopy may be important to localize the site of hemorrhage. Cardiac evaluation with either echocardiography or catheterization may be indicated, especially if there is a history of previous cardiac disease. Ongoing bleeding from tortuous bronchial arteries can be localized and treated with dye studies and embolization of these vessels, usually by an interventional radiologist. In some cases, lung biopsy is indicated to determine whether there is evidence of capillaritis, immune complex deposition, or pulmonary hypertension. Susarla and Fan[4] suggested considering lung biopsy in any child with diffuse alveolar bleeding of unknown cause.

General Management

Minor amounts of bleeding from infection, airway dehydration, or trauma can often be managed on an outpatient basis if the cause of the bleeding is established and a treatment plan initiated. In the case of clinically significant pneumonia or exacerbation of bronchiectasis, intravenous (IV) antibiotics may be indicated. If the cause of the hemoptysis is unknown, further evaluation with CT scanning, bronchoscopy, cardiac assessment, or lung biopsy may be needed. It is important to consider the availability of the studies to determine whether admission or referral to specialists is indicated. Hemoptysis requires a prompt evaluation because of the risk of increased bleeding, as well as the sometimes transient nature of the findings. If the cause of the bleeding is not known, it is important to consider the risk of additional, sometimes massive, bleeding in the decision about hospitalization.

Massive hemorrhage can be managed with endotracheal intubation and mechanical ventilation to raise the pressure in the airways. Transfusion of packed red blood cells may be indicated to stabilize the patient. If tortuous vessels are suspected, embolization of the vessels can promptly stop the bleeding.

Causes of Hemoptysis

Pulmonary Hemorrhage Due to Infection

Infection in the lower respiratory tract is the most common cause of hemoptysis. In most cases, hemoptysis is mild and lasts less than 24 hours. In otherwise healthy children, bacterial infections can cause irritation and friability of the airway mucosa. There may be some streaking of the sputum in bacterial tracheobronchitis or pneumonia, but true hemoptysis or massive hemorrhage is rare in previously healthy children. Common infectious causes include bacterial or viral pneumonia, bronchitis, pulmonary tuberculosis, pharyngitis or laryngitis, and lung abscess. Features of the history and physical examination that suggest an infection include fever, cough, diminished appetite or activity level, jaundice (leptospirosis), and exposure to other people who have

been sick. There may be localized or diffuse crackles, depending on the extent of the infection.

A CBC may be helpful in determining the amount of blood loss and the likelihood of infection. A chest radiograph can be helpful in assessing if the lesion is focal, but it can be difficult to distinguish infection from blood in the lungs. Opacity on a chest radiograph that resolves quickly is more likely to be blood than infection.

Treating the infection usually results in resolution of the bleeding. Worldwide, tuberculosis is probably the infection most associated with pulmonary bleeding. Bleeding due to tuberculosis results from either endobronchial infection or cavitary lesions.

CASE REPORT 31-1

A 19-year-old woman with cystic fibrosis has evidence of moderate lung disease. She has needed intravenous antibiotics approximately twice yearly. She has been able to continue her daily routine with airway clearance, inhaled bronchodilators, inhaled deoxyribonuclease, and antibiotics inhaled every other month.

She was sitting quietly watching TV when she noticed the abrupt onset of a gurgling sensation in her right upper lung field. She coughed up approximately 1 cup of bright red blood. She was brought to the emergency department, where she had 2 more episodes of massive hemoptysis.

Evaluation included a chest radiograph with a new opacity in the right upper lobe. Her hematocrit was 29% (0.29). Her coagulation study results were normal. She started on bed rest and oxygen and was administered vitamin K. She was brought to the interventional radiology department, where an angiogram demonstrated tortuous bronchial arteries in both upper lobes. The radiologist embolized the tortuous vessels, and the patient was admitted for observation. She continued on bed rest, and airway clearance measures were stopped for 24 hours, then gradually resumed. She was discharged 3 days later with instructions to resume her usual routine gradually.

Cystic Fibrosis and Bronchiectasis

Clinical Features

Cystic fibrosis and non-CF bronchiectasis can be associated with either small or massive amounts of bleeding. Small volumes of blood are seen relatively frequently and are associated with infection and friability of the airway mucosa. As the infection progresses, there can be invasion into the airway with erosion into a bronchial artery. Massive hemoptysis is defined as blood loss of greater than 240 mL per day and can be rapid enough to be life-threatening.

Evaluation and Imaging

Sputum can be cultured to determine the cause of the infection so appropriate antibiotics are initiated. A new infiltrate on the chest radiograph may help with localization of the bleeding and can help determine whether pneumonia is present. Clotting studies can be helpful to determine whether an underlying coagulopathy, vitamin K deficiency, or medication adverse effect is present. Individuals with CF are at risk for vitamin K deficiency because of the malabsorption of fat-soluble vitamins and for coagulopathy if there is associated liver disease.

Management

The Cystic Fibrosis Foundation developed guidelines for treatment of hemoptysis in patients with CF in 2010, and this document was reviewed and reaffirmed in 2019.[5] If there is clinically significant bleeding in a child with CF, it may be worth stopping or using less vigorous methods of airway clearance for a day or 2 to minimize the risk of massive hemoptysis. If a patient is receiving inhaled hypertonic saline or oral nonsteroidal anti-inflammatory medications, they should be stopped, at least during a clinically significant bleeding episode. Administering vitamin K can be helpful in cases of coagulopathy. If the patient has a central line or has been inactive, the possibility of a thrombus and pulmonary embolism must be considered. If a patient is receiving bilevel positive airway pressure ventilation, it should be withheld during episodes of massive hemoptysis.

Massive hemoptysis in this setting is usually related to erosion into a bronchial artery. The most definitive treatment of bleeding from tortuous vessels is embolization of the arteries, which interventional radiologists perform with the use of fluoroscopy. A catheter is introduced into the bronchial arteries from the aorta, and dye is infused to try to isolate the individual bleeding artery, which is then embolized. Many radiologists will embolize any bronchial artery that appears tortuous because of the risk of recurrent bleeding. Although most patients tolerate the procedure well, there are risks of embolizing vessels that may supply other organs, including the spinal cord.

Tracheostomy

Clinical Features

Trauma to the airway is a common cause of bleeding in patients with a tracheostomy. Abrasion of the airway mucosa with either the tip of the tracheostomy tube or suction catheter can cause small amounts of bleeding. Repeated episodes of these abrasions can stimulate the formation of granulation tissue, which can be friable. Bleeding is worsened with dry secretions, and maintaining adequate humidity is critical to controlling bleeding. Humidification of secretions in children with a tracheostomy can be increased with use of a mist collar, heat and moisture exchanger (HME) device, or frequent nebulized

saline treatments. Massive bleeding in the presence of a tracheostomy may indicate erosion into the mucosa. Rarely, erosion into an anterior innominate artery has caused massive hemoptysis.

Evaluation and Imaging

Children with bleeding through a tracheostomy are likely to have localized bleeding in the central airways. Thick or discolored secretions with small amounts of blood may indicate an infection. A chest radiograph may be helpful in determining whether pneumonia is present. Secretions can be cultured to determine the possible role of infection. Large amounts of blood or persistent bleeding should be evaluated by visualizing the airway mucosa via bronchoscopy, which can help identify areas of mucosal disruption, granulation tissue, or erosion into the airway, which are potential causes of bleeding. Massive bleeding episodes are sometimes preceded by smaller bleeding episodes, referred to as *sentinel bleeds*.

Management

Bleeding caused by airway infection will usually respond to antibiotics. Small amounts of blood with suctioning are likely to be related to dehydration of the secretions. It is important to review the humidification and suctioning techniques. The tracheostomy should always have some source of humidification. Short-term management of dehydrated secretions can include nebulized or instilled saline. If the child is also receiving ventilation, the temperature of the humidification system may need to be adjusted to allow for maximal humidification. The airway should be suctioned primarily to clear the tracheostomy tube, not the lower airways. Limiting the depth of the suctioning will minimize the risk of damage to the airway mucosa. If granulation tissue has already become established, the child may need surgical evaluation. Massive bleeding is a clinical emergency that requires surgical intervention.

Child Abuse

Trauma can be a cause of bleeding even in patients who do not have a tracheostomy. Southall et al[6] found evidence of bleeding from the nose or mouth in infants who had been under covert surveillance for evaluation of an apparent life-threatening event that was suspected to be caused by nonaccidental suffocation. Child abuse should be considered as a cause of reported hemoptysis in children in whom no other cause is discovered.

Cardiac Abnormalities

Clinical Features

Bleeding related to cardiovascular problems can arise in several situations. A thrombus or pulmonary embolism may occur, especially in the setting of a clotting disorder or the use of oral contraceptives in women. Pulmonary hypertension can be associated with pulmonary hemorrhage, especially if the

vessels have become tortuous or collateral vessels have developed.[7] Pulmonary hypertension can develop from many causes, including uncorrected congenital heart disease (Eisenmenger syndrome), as well as other cardiac, pulmonary, or systemic autoimmune processes. Those who have undergone surgical repair of congenital heart disease may have leak from aneurysms at the site of the previous repair. In some cases, such as with cor triatriatum, the congenital anomaly is not suspected before the hemoptysis.[8] Arteriovenous malformations in the lungs can be seen in patients with hereditary hemorrhagic telangiectasia or hepatopulmonary syndrome and can be a cause of hemorrhage as well.[9]

Evaluation and Imaging

Individuals with known congenital heart disease or pulmonary hypertension require reassessment of the pulmonary vasculature. Chest radiography or CT scanning may help localize areas of aneurysms or arteriovenous malformations. These patients are usually seen by a cardiologist, who should be involved in the evaluation and management of the bleeding. Many of these patients will need echocardiography as well as catheterization of the vessels to identify possible sites of bleeding. Patients with pulmonary hypertension without a previously known cardiac, pulmonary, or systemic cause will need a thorough evaluation to establish a diagnosis.

Management

Medications to decrease pulmonary hypertension may be helpful, but, in some cases, surgical intervention is required to stop the bleeding. If pulmonary hypertension is identified in the absence of congenital heart disease, more evaluation is indicated to determine possible underlying causes. If arteriovenous malformations are identified, embolization may be performed at the time of cardiac catheterization.

Autoimmune Pulmonary Hemorrhage

Clinical Features

Diffuse alveolar hemorrhage is less common than other forms of pulmonary hemorrhage but can be life-threatening. It can be seen in association with pulmonary capillaritis in such processes as GPA, microscopic polyangiitis, Goodpasture syndrome, and SLE.[10,11] Other rare causes of capillaritis have included autoimmune hepatitis, Crohn disease, and drug reactions. The cause of disrupted capillaries is frequently autoimmune in nature.[12]

Evidence that the process is chronic includes poor growth and anemia. The presence of a rash suggesting one of the collagen vascular diseases should prompt further autoimmune evaluation. Petechiae can be related to the presence of autoimmune vasculitis but may also be associated with bleeding disorders or infection. Nose and sinus involvement in a patient with pulmonary hemorrhage suggests the possibility of GPA. Swelling and inflammation of characteristic joints can be seen with autoimmune disorders, including SLE.[13]

Evaluation and Imaging

Evaluation of these autoimmune causes of pulmonary bleeding includes tests to find evidence of autoimmune dysfunction, including CBC (to look for evidence of chronic anemia), Coombs test (to look for evidence of hemolysis), screening for evidence of hematuria and proteinuria, and levels of antineutrophil cytoplasmic antibodies and myeloperoxidase and proteinase 3 antibodies. Chest radiography may show a bilateral alveolar filling pattern. If the bleeding is occult, bronchoalveolar lavage can be used to evaluate for hemosiderin-laden alveolar macrophages, which would indicate the presence of blood in the airways or alveoli. Diffuse bleeding at bronchoscopy is also useful in excluding localized causes of hemorrhage. Many collagen vascular disorders have associated renal involvement, so urinalysis may aid in the diagnosis. Other laboratory evaluations useful in diagnosing collagen vascular diseases include erythrocyte sedimentation rate and levels of C-reactive protein, antinuclear antibodies, specific extractable nuclear antigens, antineutrophil cytoplasmic antibodies (which can have either perinuclear or cytoplasmic patterns), D-dimer, von Willebrand factor antigen, antiglomerular basement membrane antibodies, and antiphospholipid antibodies. The final diagnosis may require a lung biopsy to help confirm disruption of the pulmonary capillaries.[4]

Management

Most autoimmune disorders respond to anti-inflammatory medications, although the treatment course may last months or years. These medications may include corticosteroids, rituximab, cyclophosphamide, azathioprine, methotrexate, hydroxychloroquine, and IV immunoglobulin. Initial therapy of alveolar hemorrhage with high doses of IV methylprednisolone is usually successful in controlling the bleeding. Treatment often begins with high-dose pulse steroids with 30 mg/kg methylprednisolone daily for 3 days, followed by a taper to daily oral steroids. Susarla and Fan[4] describe the use of IV methylprednisolone 2 to 4 mg/kg/day divided every 6 hours as an initial therapy for alveolar hemorrhage. As the bleeding stops, the corticosteroids can be tapered to either prednisone or methylprednisolone 0.5 to 1 mg/kg every other day. An alternative is pulse IV methylprednisolone 30 mg/kg (maximum 1 g) infused over 1 hour daily for 3 consecutive days repeated monthly.[4] After the initial bleeding has subsided, therapy for the underlying disease is likely to decrease the risk of recurrent bleeding. Some patients may need ongoing therapy with corticosteroids for months to control exacerbations of hemorrhage.

Idiopathic pulmonary hemosiderosis is diagnosed when no other autoimmune disease is identified. It can respond to steroids but is not typically treated with the other immunomodulatory medications.

CASE REPORT 31-2

A 10-year-old boy returns for follow-up of his pulmonary hypertension and history of pulmonary hemorrhage. He was born at 26 weeks' gestation and subsequently had bronchopulmonary dysplasia diagnosed. Although he was discharged from the neonatal intensive care unit at 3 months of age, he developed hypoxemia requiring long-term oxygen therapy at 7 months of age. At the age of 14 months, he had an acute deterioration with respiratory distress and hypoxemia and was admitted to the hospital for evaluation and treatment. The evaluation included the following:

1. Cardiac catheterization, which revealed suprasystemic pulmonary hypertension, right ventricular diastolic dysfunction, clinically significant right pulmonary vein desaturation, atrial septal defect (right-to-left shunting), and diffuse pulmonary interstitial disease
2. Bronchoscopy, which revealed diffusely hemorrhagic and friable bronchial tissue

He was treated with intubation and mechanical ventilation. He developed bright red blood from the endotracheal tube and was treated with increased pressure on the ventilator. Lung biopsy results revealed changes consistent with idiopathic pulmonary hemosiderosis. Allergy testing revealed sensitivity to milk, eggs, and peanuts.

He was treated with high-dose intravenous methylprednisolone and inhaled nitric oxide. He required numerous transfusions to maintain his hemoglobin level. He gradually improved, tapered off inhaled nitric oxide, and was ready for discharge 2 months after admission. Prednisone was tapered over approximately 2 years and was increased with subsequent viral infections. He had 1 episode of subsequent pulmonary hemorrhage, approximately 6 months after his admission, but otherwise has not had evidence of further bleeding. He maintains a milk-, egg-, and peanut-free diet. He continues with nighttime oxygen and sildenafil to treat his pulmonary hypertension but is able to attend school and participate in activities, including physical education.

Idiopathic Pulmonary Hemorrhage and Hemosiderosis

Clinical Features

Idiopathic pulmonary hemorrhage is characterized by alveolar bleeding without capillaritis. This bleeding tends to be recurrent, and when no underlying cause for repeated episodes of diffuse alveolar hemorrhage is determined, the condition is referred to as *idiopathic pulmonary hemosiderosis*. Lung biopsy results in these patients generally demonstrate erythrocytes and hemosiderin-laden alveolar macrophages but no inflammation of the capillaries. Acute idiopathic pulmonary hemorrhage (AIPH) of infancy is a more acute variation of pulmonary bleeding that was first described in a Cleveland-based study, associated with indoor exposure to molds, including

Stachybotrys chartarum.[14] Young infants often present without frank hemoptysis, and the diagnosis can be suspected in the presence of respiratory distress, opacities on chest radiographs, and anemia. Although the causal association between exposure to mold and AIPH in infants is being further evaluated, the Cleveland study, additional case series, case reports from independent sources, and basic scientific studies in animal models have provided evidence of plausibility.[15] Clinicians should be aware of the high mortality of acute pulmonary hemorrhage and ensure that infants are not returned to moldy home environments. Results from epidemiological studies suggest that exposure to secondhand cigarette smoke may be an additional risk factor.[16]

Evaluation and Imaging

The appearance of an acute episode of pulmonary hemorrhage on a chest radiograph is similar to that of pneumonia; however, the infiltrates are more transient and tend to resolve in 1 to 2 days. Repeated testing of hemoglobin and hematocrit can be useful in determining the severity of the bleeding. Many of these children will need bronchoscopy and bronchoalveolar lavage to document the presence of alveolar bleeding. Care should be taken in children with active bleeding because there is some risk of accelerated bleeding after bronchoscopy.

Management

Idiopathic pulmonary hemosiderosis has been associated with a poor prognosis in the past, but aggressive anti-inflammatory therapy has improved this prognosis, with recent 5-year survival rates greater than 80%.[4]

The American Academy of Pediatrics recommends that parents of infants with AIPH try to find and eliminate sources of chronic moisture and mold growth before the child returns to the home. Avoidance of exposure to secondhand cigarette smoke is always recommended, but especially in cases of AIPH.[17]

Other Causes of Hemoptysis

Malignancy is a common cause of airway bleeding in adults. Although the occurrence of airway tumors is much lower in children, between 2% and 6% of children with hemoptysis have masses.[4,18] These include endobronchial lesions such as carcinoid, adenoma, mucoepidermoid tumor, metastases, teratoma, carcinoma, and pseudotumor.[19,20] Some airway lesions, such as carcinoid and hemangioma, are highly vascularized, and caution should be used when obtaining biopsy samples, especially through a flexible bronchoscope.

Obstruction of an airway by an endobronchial lesion will usually produce atelectasis visible on a chest radiograph. It is important to differentiate atelectasis from infiltrate by means of radiography to determine the appropriate evaluation. The presence of an airway obstruction will need further evaluation with CT scanning or bronchoscopy. Bronchoscopy will allow differentiation of

a foreign body from an airway mass. Determining the cause of the mass will require pathological evaluation.

The location and pathological characteristics of the airway mass will determine the management. Some lesions can be removed through the bronchoscope, but other lesions may require surgical removal of the affected lobe.

key points

- Pulmonary bleeding can arise from a number of causes, ranging in importance from minor irritations and infections to life-threatening hemorrhage.
- In many cases, the bleeding is related to an underlying condition and can easily be evaluated and treated. Other times, the cause is more elusive and will require careful radiological, bronchoscopic, and pathological evaluation to determine the cause of the bleeding.
- Identify the location of the bleeding.
- Evaluate expected complications of known problems, such as tracheostomy, CF, bronchiectasis, and congenital heart disease.
- Evaluation of the child's home is sometimes indicated to assess whether it is a water-damaged or moldy environment.
- Consider new problems:
  - Acute or chronic infection, foreign body aspiration
  - Pulmonary hypertension, pulmonary embolism, or thrombosis
  - Arteriovenous malformation
  - Autoimmune disorder, idiopathic diffuse alveolar hemorrhage
- Diligently work to establish the diagnosis via coagulation status evaluation, imaging, sputum culture, bronchoscopy, echocardiography or cardiac catheterization, lung biopsy, and autoimmune evaluation.
- Treatment begins with stabilizing the patient, if necessary (including intubation and/or transfusion, if necessary).
- Specific treatment depends on the cause of the bleeding and may include antibiotics, humidification, cardiac or thoracic surgery, or long-term anti-inflammatory medications.
- Treat the underlying condition:
  - Embolization of bronchial arteries for massive bleeding
  - Anti-inflammatory therapy for autoimmune disease

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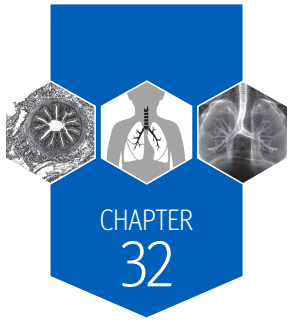
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CHAPTER
32

Development and Maturation of Sleep

Madeleine Grigg-Damberger, MD

Piaget[1] thought play was the major "work" of children, while sleep is the principal behavior state of infants and young children. Sleep has long been recognized as the predominant behavioral state of the fetus, neonate, and young infant, where important developmental work happens.[2] Neonates born preterm spend 97% of the time sleeping, and infants born term sleep 14 to 18 hours per 24 hours.[3–7] By age 2 years, the average child has spent 10,000 hours asleep compared to 7,500 hours awake.

The more time infants spend sleeping is thought to reflect the essential role sleep plays in early fetal and neonatal brain development.[8] The percentage of sleep time spent in rapid eye movement (REM) sleep is far greater in infants: 80% of sleep time when preterm, 50% at term, decreasing to 30% by age 1 year, and reaching adult percentages of 20% to 25% of sleep time spent in REM by ages 3 to 5 years. Before age 2.5 years, brain development is characterized by exuberant neuroplasticity, ongoing synaptogenesis, and increasing myelination, and most of this occurs during REM sleep.[8–12] Whereas, after age 2.5, sleep functions involve stabilizing brain network connectivity, increasing white matter integrity, and optimizing synaptic efficiency; these occur preferentially in non-rapid eye movement (NREM) sleep.[10]

Reduced time spent in REM sleep during early infancy has been shown to have lasting effects on later neurocognitive functioning.[13–15] In a prospective study of 81 infants born preterm, less REM sleep time in infants (32 to 36 weeks' postmenstrual age [wPMA]) was associated with poorer developmental outcomes on the Bayley II Scale of Infant and Toddler Development at 6 months.[13] The infants who had longer periods of sustained sleep, more time spent in REM sleep, and more periods of REM sleep with rapid eye movements had better cognitive outcomes.

In 2015, the National Sleep Foundation[16] published updated age-related sleep duration recommendations for children: 14 to 17 hours for babies aged 0 to 3 months; 12 to 15 hours for infants aged 4 to 11 months; 10 to 13 hours for preschoolers aged 3 to 5 years; 9 to 11 hours for schoolchildren aged 6 to 12 years; and 8 to 10 hours for teenagers (13 years or older). In 2016, the

American Academy of Sleep Medicine[17] published (and the American Academy of Pediatrics endorsed) age-related sleep duration recommendations for children: infants ages 4 to 12 months should sleep 12 to 16 hours per 24 hours (including naps); children aged 1 to 2 years should sleep 11 to 14 hours per 24 hours (including naps); children aged 3 to 5 years should sleep 10 to 13 hours per 24 hours (including naps); children aged 6 to 12 years should sleep 9 to 12 hours per 24 hours; and teenagers aged 13 to 18 years should sleep 8 to 10 hours per 24 hours.

Unfortunately, such recommendations are too often ignored. Insufficient sleep is common in children at all ages. In 2018, the Centers for Disease Control and Prevention[18] surveyed 52,500 US schoolchildren and adolescents and found that 63% of children aged 6 to 12 years and 93% of those aged 13 to 18 years reported sleeping less than 9 hours on school nights; 30% of adolescents averaged 7 hours, 23% averaged 6 hours, 13% averaged 5 hours, and 8% averaged 4 hours or less.

Insufficient sleep in adolescence can alter the ultimate developmental trajectory of brain and behavior. Final brain development occurs across adolescence and young adulthood (usually complete by age 25 years). The last parts of the brain to develop are the medial prefrontal cortex (PFC) and anterior cingulate cortex. The PFC is most involved in attention, behavior, judgment, moral reasoning, planning, executive decision-making, cognitive control, and flexibility. The PFC is the part of the brain most vulnerable to sleep loss.

Late bedtimes and sleep restriction in adolescents can impact final remodeling of cortical circuitry for adult decision-making, cognition, impulse control, social interaction, and regulation of emotion.[19,20]

How much sleep is too little for optimal final brain development in adolescents? A 2011 survey of 15,364 US high school students found that the 17% who sleep less than 5 hours per night were more likely to report various negative outcomes compared to those sleeping 8 hours or more per night.[21] High school students who reported sleeping 7 hours or less on school nights were more likely to report several injury-related risk behaviors (infrequent bicycle helmet use, infrequent seatbelt use, riding with a driver who had been drinking, drinking and driving, and texting while driving) compared with students who sleep 9 hours on school nights.[22]

This chapter provides a brief review of the development and maturation of sleep in typically developing infants, children, and adolescents.

Emergence of Sleep as a Distinctive Behavior State

Fetal ultrasonographic studies show rest-activity cycles by 20 to 24 weeks' gestational age (wGA).[8,23] By 24 to 25 wGA, these cycles last 40 to 60 minutes and are unrelated to those of the mother. As early as 25 wGA, rudimentary

sleep cycling, characterized by periods of rapid eye movements (suggestive of active/REM sleep) and periods without them, are observed. Recordings of fetal electroencephalogram (EEG) on infants born extremely preterm show activity that consists of bursts lasting less than 60 seconds alternating with quiescent periods (interburst intervals [IBIs]) lasting 20 to 25 seconds. This EEG activity is called *tracé discontinu*. At this gestational age, the fetus exhibits alternating periods of activity and rest, but variations in EEG are inconsistently associated with behavior.[24] Painful stimulations during handling provoke limb-withdrawal movements, which cause muscle artifacts on EEG but no change in the EEG.

By 28 to 29 wPMA, 3 behavioral states are identifiable: active/REM sleep, quiet/NREM sleep, and active wakefulness. Active/REM sleep is best (and perhaps only) identified by the presence of rapid eye movements, absent in quiet/NREM sleep. The EEG is more "continuous" with more runs of EEG activity now lasting up to 160 seconds, and IBIs shorter (≤30 seconds). Infants this age spend very little time awake (≤3%), identified by open eyes and crying.[8,24,25] Reactivity (change in EEG in response to varying forms of sensory stimuli, including pain) is still inconstant and variable in expression.[24]

The EEG begins to help distinguish wakefulness from active/REM and quiet/NREM sleep by 30 to 31 wPMA: continuous during active/REM sleep, discontinuous in quiet/NREM sleep. The IBIs during quiet/NREM sleep are shorter (≤20 seconds). Periods of quiet wakefulness are rare. Reactivity of the EEG to sensory stimuli is now observed, characterized by the appearance of delta EEG activity.

The EEG is continuous in both wakefulness and active/REM sleep at 32 to 35 wPMA (distinguished so these 2 states [wakefulness and active/REM] can only be identified by behavioral [not the EEG] correlates).[26]

Behaviors in preterm (and later term) infants that, when observed, are suggestive of active/REM sleep are (1) eyes closed with rapid eye movements; (2) irregular respiration (sometimes with periods of tachypnea or periodic breathing); and (3) a myriad of movements tend to occur (such as sucking, facial grimaces, clonic jaw jerks, fine limb muscle twitches, tremors, intermittent stretching, and large athetoid limb movements). Behaviors that suggest quiet/NREM sleep in infants are (1) closed eyes, not moving; (2) regular respiration; (3) reduced movements relative to wakefulness with occasional startle and periodic sucking. Identifying wakefulness, particularly quiet wakefulness, is especially difficult in preterm infants.[27]

At 32 wPMA, the EEG in quiet/NREM sleep remains discontinuous with periods of no EEG activity (interburst intervals) which normally last up to 15 seconds at 32 wPMA, and up to 10 seconds at 34 wPMA.

By 36 wPMA, 2 different EEG patterns of REM sleep are seen. Both are continuous, but the EEG pattern before a period of NREM sleep contains generous amounts of intermixed delta activity (high-amplitude slow [0.1–4 Hz] waves), whereas REM sleep after a period of NREM sleep is characterized by a predominance of theta (low-amplitude, 4–7 Hz) activity.[26]

At 27 to 34 wPMA, 40% to 45% of sleep is spent in active/REM sleep, 25% to 30% in quiet/NREM, and 30% in indeterminate sleep. After 35 wPMA, infants spend 55% to 65% of sleep in active/REM sleep, 20% in quiet/NREM sleep, and 10% to 15% in indeterminate sleep. Term neonates spend 50% to 60% of sleep in active/REM sleep, 30% to 40% in quiet/NREM sleep, and 10% to 15% in transitional sleep. The duration of a sleep cycle is 30 minutes for infants less than 35 wPMA, increasing to 50 to 65 minutes for infants 35 wPMA or more.

Sleep/Wake Patterns in Infants 0 to 2 Months of Age

By 37 to 38 wPMA (beginning maturational age for term infants), the EEG in wake and REM sleep is characterized by a continuous mixture of different frequencies *(activité moyene).* Because the EEG activity in wakefulness and REM sleep are so similar in appearance, behavioral correlates are needed to differentiate them (**Table 32-1**).

The EEG background most often observed at this maturational age is trace alternant, characterized by synchronous symmetrical bursts of 1 to 3 Hz delta on a continuous background of lower-amplitude activity (**Figure 32-1**). The more mature EEG pattern in term infants is high-voltage slow (HVS) characterized by 50 to 150 μV 1-3 Hz activity (**Figure 32-2**) generally first seen at 38 to 39wPMA. **Figure 32-3** shows a 30-second epoch of REM sleep recorded in an infant 46 wPMA.

Trace alternant usually disappears by 44 weeks' to as late as 46 weeks' chronological age (wCA), replaced by HVS. By 46 wCA, NREM sleep is characterized by HVS, no eye movements, regular respiration and heart rates, and periodic chin electromyogram activation related to sucking. REM sleep is best identified by reduced chin electromyogram, rapid eye movements, irregular respiration and heart rate, and continuous mixed frequencies especially near 3 Hz. **Table 32-1** summarizes the polysomnographic characteristics and their behavioral correlates of wakefulness, NREM sleep, and REM sleep in babies 0 to 2 months of age.

Table 32-1. Polysomnographic Sleep/Wake Characteristics in Infants 0 to 2 Months of Age

State	Behavior	Respiration	EEG	EOG	Chin EMG
REM	Eyes closed, REMs, sucking, grimacing, squirming, facial grimaces, fine limb muscle twitches, chin, body and limb tremors, intermittent stretching, large athetoid body movements	Irregular, some central apneas or periodic breathing may be seen	LVI or M (rarely HVS)	Eyes closed with (and without) REMs	Low with or without transient motor activity
NREM	Eyes closed, few or no movements, periodic sucking can occur	Regular	TA, HVS, M, or sleep spindles	Eyes closed with no eye movements	Present, could be lower than wakefulness
Wakefulness	Calm or active with eyes open, crying, feeding	Irregular, rapid and shallow	LVI or M	Eye blinks, conjugate 0.5–1 Hz vertical eye movements, conjugate, irregular, sharply peaked REMs, scanning lambda waves (sharply contoured 250–350 ms waveforms occipital regions), transient eye closure, crying	Present, movement artifact

Abbreviations: EEG, electroencephalogram; EMG, electromyogram; EOG, electro-oculogram; LVI, low-voltage intermixed; M, mixed; HVS, high-voltage slow waves; NREM, non–rapid eye movement; REM, rapid eye movement; TA, trace alternant; W, wakefulness.

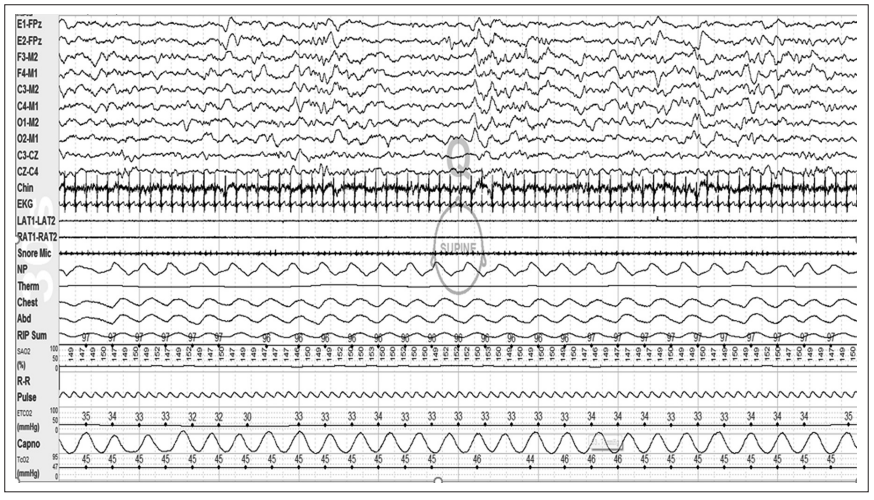


Figure 32-1. A 30-second polysomnographic epoch showing trace alternant in an infant 40 weeks' postmenstrual age.

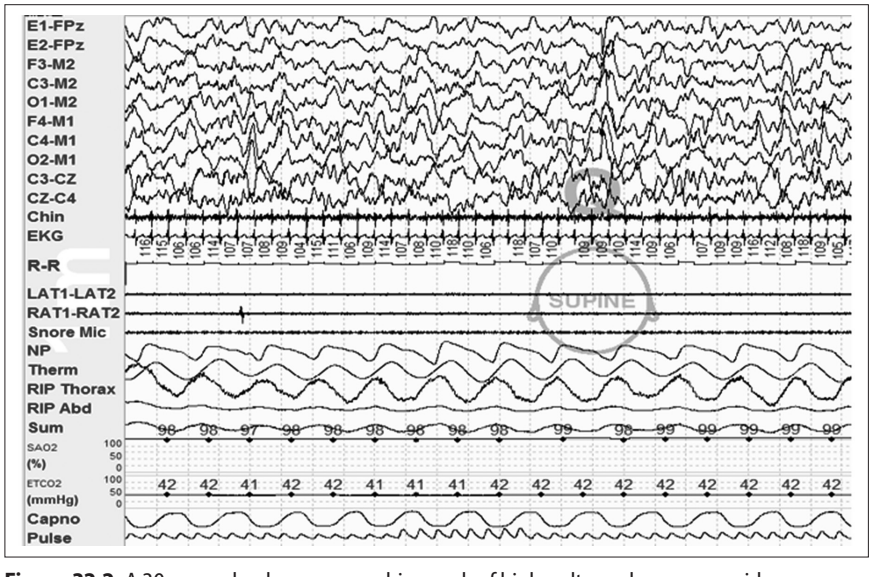


Figure 32-2. A 30-second polysomnographic epoch of high-voltage slow non–rapid eye movement sleep in an infant 48 weeks' post-menstrual age.

Indeterminate Sleep in Babies Aged 0 to 2 Months

Many epochs of sleep until 3 months post-term are best scored as indeterminate or transitional sleep (stage T) even though the percentage of stage T rapidly falls beginning after 36 wPMA. Parmelee et al[7] reported that 67% of total sleep time was best scored as indeterminate in an infant 30 wCA, 38% at 40 wCA, 29% at 3 months post term.[7]

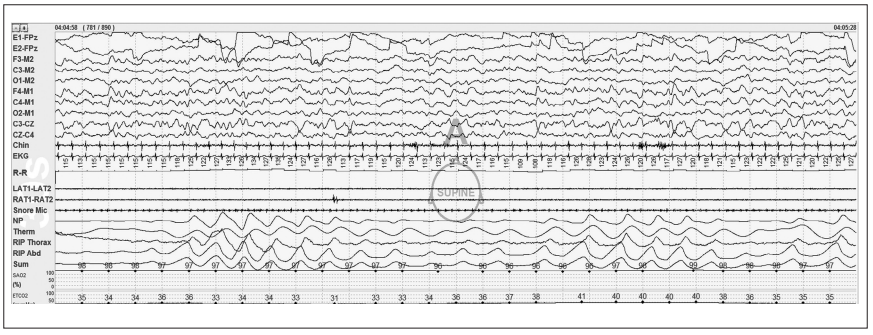


Figure 32-3. A 30-second polysomnographic epoch of rapid eye movement sleep recorded in an infant 46 weeks' postmenstrual age. Note the irregular breathing and rapid eye movements.

Polyphasic Sleep in Babies Aged 0 to 2 Months

Sleep in term newborns is characterized by 5 to 6 periods of sleep across 24 hours, which can last 50 to 300 minutes; these alternate with wake periods lasting 90 to 180 minutes. Hunger and satiety drive when a newborn sleeps and wakes. Until approximately 44 wCA, sleep cycles repeat in a polyphasic pattern across the 24-hour day, interrupted approximately every 3 to 4 hours by an awakening for care and feeding.[28,29] Non-rapid eye movement and REM sleep are typically evenly distributed during the night, although sleep is often more restless in the first half of the night.[28] Bottle-fed babies sleep longer (3–5 hours) than breastfed babies (2–3 hours): breast milk contains more whey, which is easier to digest; whereas formula milk contains more casein, which babies digest more slowly.

REM-NREM-REM sleep cycles typically last an average of 50 to 60 minutes (range 30–70 minutes). Within a given sleep cycle, REM sleep lasts 10 to 45 (mean 25) minutes, NREM sleep near to 20 minutes, and indeterminate/transitional sleep about 10 minutes.[29,30] Wakefulness represents only 8% to 10% of a 24-hour day in infants up to 48 wPMA.[29] Stage N after the first period of stage R often begins with HVS for 3% to 5% of the cycle, then a longer period of trace alternant for 25%. Transitional/indeterminate sleep most often occurs at sleep onset, especially when sleep transitions from REM to NREM sleep, or following arousals. The percentage of indeterminate sleep lessens with increasing maturational age: 38% of sleep at 40 wPMA, 24% of sleep at 3 months of age (largely disappearing by 6 months of age).[31]

Development of EEG Biomarkers of Mature NREM and REM Sleep

The major polysomnographic biomarkers of drowsiness and sleep are hypersynchrony, saw-tooth waves, sleep spindles, vertex sharp waves, K-complexes, and slow-wave activity (SWA) of NREM 3 sleep.[32]

Hypnagogic hypersynchrony is a distinctive EEG pattern of drowsiness and NREM 1 sleep characterized by paroxysmal runs or bursts of diffuse synchronous 75 to 350 μV 3–4.5 Hz waves often maximal over the central, frontal, or fronto-central EEG derivations. Hypnagogic hypersynchrony often disappears with deeper stages of NREM sleep. It is seen in 30% of infants at 3 months post term birth, and 95% between 6 months and 4 years. Hypnagogic hypersynchrony gradually disappears (seen in 10% of children aged 11 years; it is rare after ages 12 or 13 years).

Sawtooth waves are brief bursts of often notched 4- to 6-per-second waves lasting 2 to 3 seconds, which are seen during phasic REM sleep when rapid eye movements are present. They are usually maximal over the midline central region.

Table 32-2 summarizes the age when distinctive polysomnographic features of sleep and wake first appear.

Table 32-2. Age When Distinctive PSG Features of Sleep and Wake First Appear

Distinctive Polysomnographic Electroencephalographic Feature	Characteristics	Age at First Appearance
Sleep spindles	Brief (usually 0.5–1.5 sec) bursts with a frequency range of 11–16 Hz. These are generated in the thalamus and play an important role in sensory processing and long-term memory.	**6 weeks to 3 months post-term;** first appear maximal over midline central (Cz) and shift from side to side (C3, C4).
Sawtooth waves of rapid eye movement sleep	Brief bursts of often-notched 4- to 6-per-second waves lasting 2–3 seconds, which are seen during phasic rapid eye movement sleep when rapid eye movements are present. They are usually maximal over the Cz.	**As early as age 7 weeks post-term:** prominent over the frontal (F3, F4, FZ) and central (Cz, C3, C4) regions. Typically 2–6 Hz.
Dominant posterior rhythm	An EEG rhythm over the occipital regions during wakefulness, which is (1) best seen with eyes closed during periods of physical relaxation and relative mental inactivity and (2) "reactive" (ie, attenuated/blocked by attention).	Dominant posterior rhythm first appears at a slower frequency of 3.5–4.5 Hz by **3–4 months post-term;** increases to 5–6 Hz by 5–6 months; 7.5–9.5 Hz by 3 years; mean 9 Hz by 9 years and 10 Hz by 15 years; maximal over occipital electrodes.

Table 32-2. Age When Distinctive PSG Features of Sleep and Wake First Appear (*continued*)

Distinctive Polysomnographic Electroencephalographic Feature	Characteristics	Age at First Appearance
K-complexes	A 50–100 μV surface electronegative wave lasting 200 msec, followed by a surface-positive 30–50 μV 300–500 msec wave maximal over the prefrontal and frontal scalp EEG derivations.	First appear **3–6 months post-term** maximal over frontal regions. Usually present by age 5–6 months. Between ages 3 and 5 years, K-complexes are striking: very high amplitude, primarily surface-electro-negative, sharply contoured, occurring in runs of 3–8 in 1–3 seconds. By adolescence, K-complexes resemble those seen in adults and repeat at rates of one every 1–3 seconds.
Slow-wave activity of non-rapid eye movement (NREM) 3 sleep	High amplitude (> 75, usually 100–400 μV) 0.5–2 Hz activity maximal frontal regions slow-wave activity.	First appears **2–5 months post-term** maximal over frontal regions.
Hypnagogic hypersynchrony	Paroxysmal runs or bursts of diffuse bisynchronous 75 to 350 μV 3–4.5 Hz waves maximal central, frontal, or fronto-central regions observed in NREM 1 sleep. Usually disappears with deeper NREM sleep.	First appears **3–6 months post-term.** Seen in 30% of infants at 3 months post-term, 95% between 6 months and 4 years of age. Gradually disappears (seen in 10% of children 11 years of age; rare after ages 12 or 13 years).
Vertex sharp waves (V-waves)	Monophasic EEG surface-negative sharp waves maximal central regions; last < 0.5 second (usually < 200 msec); occur in bursts or runs. Most often seen in the transition to NREM 1 sleep but can occur in either NREM 1 or NREM 2 sleep.	Broad vertex waves over central region first appear by **6 months post-term.** Vertex sharp waves, which resemble those seen in older children and adults, typically first appear 16 months post term.

Sleep Spindles

The first major EEG feature of mature sleep to appear after birth is sleep spindles,[3] which are sometimes seen as early as 3 to 4 weeks in neonates following birth.[32–34] Sleep spindles are usually present by 6 to 8 weeks' postnatal age, reflecting development of the thalamocortical structures,[3,35–37] and may develop earlier in babies born prematurely.[38] Initially, sleep spindles occur asynchronously, shifting from side to side but, by 2 years of age, sleep spindles, when

seen, are bisynchronous. Across an entire recording of sleep, 50% of sleep spindles will occur synchronously (bilaterally) at 6 and 9 months of age; increases to 70% by 12 months, and, by 18 months to 2 years, sleep spindles are typically synchronous.

Sleep spindles in children can occur independently at 2 different EEG frequencies and maximal over 2 different scalp locations: frontally predominant 11–12.75 Hz spindles, and centroparietal 12–14.75 Hz spindles (**Figure 32-4**). Frontal spindles decrease in prevalence around age 13 years, although they are seen in some young adults, especially early in a night of sleep.

Sleep spindles play an important role in memory processing, which occurs preferentially during NREM 3 sleep.[3,39–41] Sleep spindles are also thought to facilitate thalamocortical sensory gating, synaptic plasticity, and somatosensory development.[42] Higher spindle density is associated with better cognition, memory, and social behavior in children.[43,44] Delayed appearance or abnormal-appearing sleep spindles are an early biomarker of metabolic and/or brain abnormalities.[45,46]

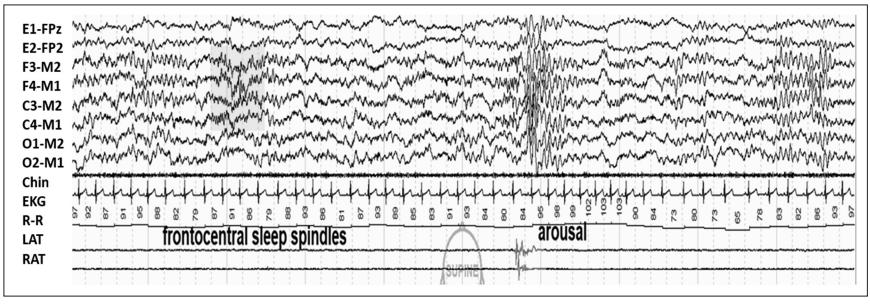


Figure 32-4. Until age 13 years, sleep spindles in children often occur independently at 2 different electroencephalographic frequencies and maximal over 2 different scalp locations: 11–12.75 Hz maximal over the frontal and 12–14.75 Hz over the centroparietal regions.

Vertex Waves

Vertex waves are seen in later NREM 1 and NREM 2 sleep, maximal over the central EEG derivations, and predominantly surface electronegative.

Vertex waves are thought to either be a direct response to an external stimulus or a mechanism to maintain sleep after a stimulus.[47] Functional magnetic resonance imaging studies show spontaneous vertex waves localize to the primary sensorimotor cortices.[48] Vertex waves may serve a role in modulating awareness of the external work during NREM sleep by gating neocortical sensory function.[48] Studies suggest NREM sleep transients (vertex sharp waves, hypnagogic hypersynchrony, K-complexes, and sleep spindles) are usually coupled with hippocampal ripples.[49] Hippocampal ripples are 80 to 200 Hz neocortical rhythms, which are particularly important in sleep-related memory processing.

Infrequent, broad, immature vertex waves over the central derivations have been observed as early as 6 months term. Vertex waves resembling those seen in older children and adults first appear later at 16 months term.[50] Beginning around 30 months of age, vertex waves in young children often occur in repetitive runs. Around 36 months of age, vertex waves are more often high amplitude (>250 μV) and sharply peaked, occasionally misidentified as epileptiform (**Figure 32-5**). Between ages 3 and 13 years, vertex waves evolve to sharply peaked, primarily surface waveforms similar to those seen in adults.[51,52]

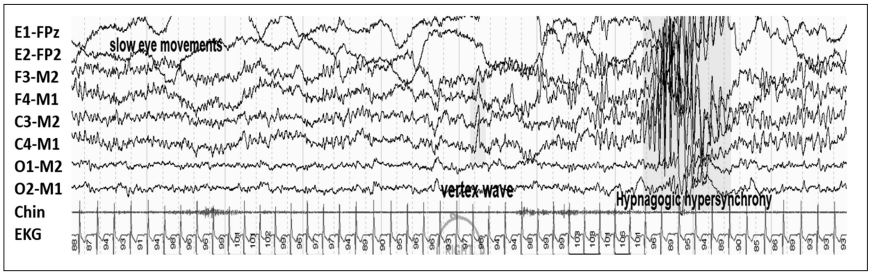


Figure 32-5. Around 36 months of age, vertex waves are more often high amplitude (>250 μV) and sharply peaked, occasionally misidentified as epileptiform.

K-complexes

K-complexes appear to play an important role in maintaining sleep but also promoting arousal. K-complexes are thought to reflect the brain judging whether a particular stimulus is harmless (keep sleeping) or potentially dangerous (worthy of waking).[53,54] K-complexes also appear to play roles in memory consolidation and synaptic homeostasis.[55]

K-complexes, an EEG biomarker of NREM 2 sleep, are usually present by age 5 to 6 months and, at this age, are characterized by a 50- to 100-μV surface-electronegative wave lasting 200 msec, followed by a surface-positive 30- to 50-μV wave lasting 300 to 500 msec, which is maximal in amplitude over the prefrontal and frontal scalp. K-complexes usually follow sleep spindles. K-complexes are most easily provoked by auditory stimulus (eg, loud clap). They may or may not result in an arousal (less likely, awakening).

Between ages 3 and 5 years, K-complexes are striking: very high amplitude, primarily surface-electronegative, sharply contoured, occurring in runs of 3 to 8 in 1 to 3 seconds. By adolescence, K-complexes resemble those seen in adults and repeat at rates of 1 every 1 to 3 seconds.[52,56,57]

Slow-Wave Activity of NREM 3 Sleep

Slow-wave activity as seen in NREM 3 sleep may be seen as early as 4 to 4.5 months and is usually present by 5 to 6 months.[2,36,58,59] Slow-wave activity is often 300 μV or greater in amplitude in young children.[4] A study recording

24-hour polysomnogram in 31 normal infants younger than 6 months found that sleep spindles first appeared at approximately 8 to 12 weeks term and "true slow wave with delta waves" of slow-wave sleep first appeared between 3 and 6 months term.[60] NREM 1, 2, and 3 sleep can usually be distinguished between 4 and 6 months term.[2,28,58,60–63]

Non-rapid eye movement 3 serves an important role for storage of long-term memories into the neocortex. Sleep spindles, slow oscillations, and hippocampal ripples during NREM sleep provide the neurobiological scaffold for reactivating memory traces learned while awake, processing them, and channeling them for integration in neocortical sites for long-term storage. Memory processing during NREM 3 sleep works best if sleep spindles are coupled to slow oscillations, and spindle-slow oscillation coupling improves from childhood to adolescence.[64,65] In a 2020 study, Hahn et al[65] tested the ability of children to store memories, retesting them later as adolescents. The ability to recall a set of words was better after a full night's sleep. Memory recall was best when sleep spindles were coupled with slow oscillations (called phase coupling). Children with better spindle-slow oscillation coupling had improved memory formation once they became teenagers. Hahn et al[65] demonstrated that increases in spindle-slow oscillation coupling strength occur across childhood and adolescence and better coupling is associated with enhanced memory formation.

Developmental Changes in Sleep Architecture

The most conspicuous changes in sleep architecture during infancy and early childhood are (1) decrease in total sleep time; (2) gradual consolidation of periods of sleep at night and wakefulness in the day; (3) decrease in the intensity (EEG power) of NREM 3 SWA; and (4) a steady decline in the percentage of sleep time spent in REM sleep.[66]

Development of Circadian Rhythm and Sleep/Wake Patterns in Babies and Young Children

In the last 10 weeks of gestation, the circadian rhythm of the fetus is synchronized with the mother's maternal rest-activity cycle, heart rate, cortisol, melatonin, and body temperature rhythms.[4] Newborns exhibit no rest-activity circadian rhythm independent of their mother before about 1 month of age (because it has not yet developed).

Neonates are born with low levels of maternally transferred melatonin, which dissipates in a week, and endogenous rises in melatonin to detectable levels are not observed until approximately 6 weeks following birth.[67] The rise in the core body temperature correlating with morning waking first occurs around 6 weeks following birth. Circadian regulation of cortisol secretion

(which is lowest from midnight to 4:00 am, peaking early morning) develops by age 6 months.

Development of circadian rhythms in the newborn is influenced by length and timing of light exposure, feeding, and rest/activity cycles. By 5 to 6 weeks following birth, sleep becomes more concentrated during the night and wakefulness more prevalent during the day.[68] By 12 to 14 weeks, a diurnal pattern is established with a long nocturnal sleep period, shorter daytime naps, and 1 to 3 hours of wakefulness preceding the nocturnal sleep period.

Using sleep questionnaires and actigraphy, a large study[5] of 1,427 infants found that the average percentage of daytime sleep decreased from 36 ± 9% at 3 months of age to 26 ± 7% at 8 months of age. Infants who developed a 24-hour rhythm later than others (1) slept more hours per day; (2) had a later sleep-wake rhythm; (3) experienced more difficulties in settling to sleep; (4) had longer sleep-onset latency; and (5) were awake longer during the night. Still, by 6 months of age, most typically developing infants display a circadian pattern with period, amplitude, and phase activity similar to those of an adult. The researchers found the photoperiod (hours of daylight per 24 hours) during the first 3 months was related to the slower development of sleep/wake rhythm at age 3 months.

Providing cycles of dark and light in neonatal intensive care units may foster development of the rest-activity circadian rhythm.[69,70] Neonates born extremely preterm when exposed to timed light in the neonatal intensive care unit show an earlier emergence of the 24-hour sleep/wake rhythm compared to neonates born term.[71]

Infants aged 2 to 12 months typically sleep 9 to 12 hours per night and nap 2 to 4.5 hours per day. In infants aged 6 to 12 months, the longest continuous sleep period is about 7 hours. Sleep consolidation is observed in 70% to 80% of infants by age 9 months. Infants between 2 and 12 months of age normally arouse 2 to 4 times a night. In some infants, arousals are brief and they are able to return to sleep without parental intervention ("self-soothers"); others alert their parent(s) by crying ("signalers").

Between 25% and 50% of infants aged 6 to 12 months have what parents regard as problematic night awakenings. Nocturnal awakenings often *increase* during the second 6 months after birth. This "relapse" is thought to be triggered by separation anxiety, a normal developmental stage, which often peaks between ages 6 and 18 months, and can make it difficult for children to separate at bedtime or self-soothe when they wake at night.[67]

Developmental issues have an impact on sleep in toddlers. Between 10% and 20% of children exhibit bedtime refusal/resistance, and 15% to 20% have problematic night awakenings. The child's transition from crib to bed usually

occurs at about age 2 to 3 years, often prompting them to visit the parents' bed. A child's drive for autonomy and independence may also lead to increased bedtime resistance. Transitional objects are useful at this developmental age, fostering independence and self-soothing. Regression to more immature patterns of sleep is a common response to stress. Children aged 3 to 5 years often need 11 to 12 hours of sleep per 24 hours. Nighttime sleep becomes consolidated into long periods of approximately 10 hours.

Daytime Napping

A longitudinal study[72] found that 84% of infants were napping twice a day at age 6 months and 16% of infants were napping 3 times a day. Most children aged 15 to 24 months take only one afternoon nap, typically for 2 hours. A 2020 meta-analysis found that <2.5% of children cease napping prior to age 2 years and 94% of children cease napping by age 5 years.[73] By ages 3 to 5 years, naps often decrease from one to none. As sleep consolidates during the night, the need for daytime sleep gradually disappears. Napping often reappears in adolescence as a compensation for late bedtimes, insufficient sleep, and sleep debt. (See Chapter 36, Insomnia.) Declarative, motor, and emotional memory are better if a nap follows learning.[74]

Ultradian Distribution of NREM-REM Sleep Cycles

Ultradian biological rhythms are recurrent periods or cycles repeated throughout a 24-hour day; circadian rhythms are one cycle completed daily; and infradian rhythms are biorhythms that recur in periods longer than a day (eg, human menstrual cycle). Until approximately 44 wCA, ultradian cycles of REM-NREM-REM sleep last a mean of 50 to 60 minutes (range 30–70 minutes) and are interrupted approximately every 3 to 4 hours by an awakening for care and feeding.[29] Cycles of NREM and REM sleep are typically evenly distributed across day and night, and 7 to 13 cycles may occur during nocturnal sleep.[28,75] Wakefulness represents only 8% to 10% of a 24-hour day in babies up to 8 weeks post-term.[29]

By age 6 months, NREM 3 sleep is preferentially present toward the beginning of the night, and REM sleep in the later portion. Sleep cycle length varies with age: an average of 55 minutes in babies at term; 58 minutes at 9 months; 71 minutes at age 2 years; 79 minutes at age 5 years; 85 to 115 minutes at ages 8 to 12 years, and 90 minutes in adults.[36,76] The mean ultradian cycle length in schoolchildren is approximately 85 to 90 minutes with 4 to 6 cycles of NREM-REM sleep occurring across a night.[77] Sleep efficiency (percentage of time in bed spent sleeping) remains constant across infancy to adolescence.[76,78] The longest sleep period by age 1 year is 8 to 9 hours, supplemented by naps. By age 5 years, it is 10 hours, and this remains stable until puberty, when it begins to decline.[76,78]

The percentage of sleep time spent in REM sleep falls to 30% by 12 months of age and reaches adult percentages of 20% to 25% by age 5 years. The proportion of sleep spent in NREM sleep increases while REM sleep decreases such that NREM 3 sleep occupies a greater proportion of sleep time than REM sleep at age 12 months. From ages 5 to 19 years, the percentage of REM sleep remains relatively stable while the percentage of NREM 2 sleep increases with a concomitant decrease in NREM 3 sleep.[76,78]

Decrease in NREM 3 Slow Wave Activity

The massive decline in SWA with growth and maturation reflects extensive elimination of unnecessary cortical synapses occurring during adolescence, the final step in brain neurodevelopment. Parallel declines in synaptic density, delta wave amplitude, and cortical metabolic rate during adolescence would suggest this. The delta power of NREM 3 sleep activity decreases by more than 60% between ages 10 and 20 years.[79] The density of SWA also declines across recurring periods of NREM sleep within a night. A longitudinal study showed delta power of the sleep EEG begins to decrease around age 11.5 years, reduced by 60% by age 16 years.[79] The amplitude of SWA shows an inverted U-shape development: initially increasing in childhood, peaking just before puberty, and then decreasing in puberty and adolescence.[79] The fall in delta power begins earlier in girls than in boys (consistent with observed age-related changes in gray matter volume) but then slows so that the overall rate of decline is similar between girls and boys at age 16.[79]

Shift From REM to NREM Sleep Onsets

Until 50 to 52 wPMA, infants generally enter sleep through REM.[80] Several studies[79,81,82] found two-thirds of sleep onsets were REM sleep in babies 3 weeks post term, but only 18% at age 6 months. REM latencies of 20 to 40 minutes are typical in infants aged 3 to 12 months.[80] REM latencies increase from 15 ± 20 minutes at age 3 months to 70 ± 29 minutes at age 24 months. REM latencies average 116 minutes in children aged 1 year, and 136 minutes in children aged 11 to 18 years. At least some of this may be due to the longer sleep cycles in older children since, after infancy, REM usually begins at the end of the second sleep cycle. The percentage of sleep spent in REM sleep declines from 50% at birth to 40% at ages 3 to 5 months, and to 30% at ages 1 to 2 years, reaching adult percentages of 20% to 25% by ages 3 to 5 years.

Decrease of Total Sleep Time

Total sleep time decreases across infancy, early childhood, and adolescence. A seminal longitudinal study by Iglowstein et al[37] followed 493 children from birth to age 16 years and found total sleep duration decreased from an average of 14.2 ± 1.9 hours at 6 months to 8.1 ± 0.8 hours at age 16 years. Also, the

variance (greater variability in sleep duration) was noted, showing a similar declining trend: the interquartile range at age 6 months was 2.5 hours, and 1 hour at age 16 years. For example, 96% of all children slept 10.8 to 15.6 hours at age 2 years compared to 8 to 10.7 hours at age 12 years.[37]

A 2012 meta-analysis by Galland et al[66] found mean sleep durations were 12.8 hours (range 9.7–15.9) in infants; 11.9 hours (9.9–13.8) in toddlers/preschool-aged children; and 9.2 (7.6–10.8) in schoolchildren.

Socioeconomic Differences in Sleep Patterns in Infants and Children

Although sleep is biologically driven, socioeconomic differences significantly modulate sleep behavior in infants and children. A study[83] that recorded actigraphy at approximately 1 month and 6 months of age in 306 infants[83] found racial and ethnic differences in sleep emerge in early infancy. Nighttime and 24-hour sleep durations increased less in Hispanic and Black infants compared to white infants, with differences largely explained by socioeconomic and environmental factors. Adjustment for maternal education and household income attenuated all observed daytime and nighttime sleep duration differences other than in Asian infants and children, where persistently reduced nighttime sleep at age 6 months was observed.

Other cross-sectional studies have found that boys, children from under-resourced areas, and children of color had shorter sleep times than girls, children from high-resource areas, and white children, respectively[84]; and that children of racial or ethnic minority were more likely than white children to have a bedtime of 11:00 pm or later.[85]

A 2021 study[86] examined the impact of daily experiences of racial and ethnic discrimination on sleep in 95 adolescents. They found that daily discrimination was a low-frequency but high-impact event that, when it occurred, was associated with short sleep duration. Social support from friends was associated with a negative impact on sleep duration; parental support promoted sleep quality. Support from teachers protected adolescents from the negative effects of discrimination on sleep duration.

Ontogeny of Dreaming in Children

Even though it has been established that REM sleep appears in utero and infancy, there is no evidence regarding whether or not infants dream. A recent review analyzing findings of different studies of the ontogeny of dreaming found that different methods for collecting dreams in children often result in highly variable and sometimes contradictory assessments and outcomes.[87] Fairly consistent observations include (1) dream narratives in younger children are often shorter and simpler than those reported by older children and

adults; (2) preschoolers, when reporting their dreams, often verbalize only one relevant aspect of the dream and may have difficulty distinguishing between internal and external events; and (3) the highest prevalence of nightmares is between ages 6 and 10 years.[88] Schoolchildren in whom nightmares are reported to occur often are more likely to have emotional problems or anxiety.

key points

- Sleep, especially REM sleep in the fetus, neonate, and infant, fosters early brain development and connects the body with the brain (embodiment) by facilitating mapping of the somatosensory, visual, auditory, pain, and tactile regions of the cerebral cortex.[12]
- The EEG and polysomnographic features of sleep and wakefulness evolve across infancy and early childhood as the brain develops.
- Insufficient or fragmented sleep, especially during infancy, can disrupt the normal development of the brain, but also has an impact in later childhood and adolescence.

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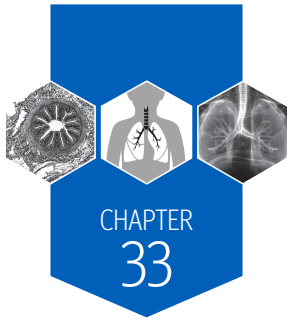
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Obstructive Sleep Apnea Syndrome

Courtney M. Quinlan, DO, MS
Suzanne E. Beck, MD

Introduction

Obstructive sleep apnea syndrome (OSAS) in children is a sleep-related breathing disorder characterized by partial and/or complete upper airway obstruction that disrupts sleep architecture and normal ventilation during sleep.[1] It is a relatively common condition that, if left untreated, increases morbidity and decreases quality of life in affected children.[2]

Guidelines published in 2012 by the American Academy of Pediatrics (AAP) provide a structured outline of how primary care providers and pediatric specialists may best screen, diagnose, manage, and treat pediatric patients with OSAS.[2] Although the knowledge surrounding pediatric OSAS has expanded since the publication of these guidelines, many unanswered questions remain, allowing for significant research opportunities.

Epidemiology of OSAS in Children

The prevalence of pediatric OSAS is estimated to be between 1% and 5% of school-aged children.[3] Risk factors include obesity, tobacco exposure, and low family income.[4,5]

Although OSAS affects children of all ages, peak prevalence occurs between the ages of 2 and 8 years, correlating with the peak of adenotonsillar size in relation to the airway.[6] In children younger than 2 years, an increased incidence of OSAS is associated with male sex, trisomy 21, preterm birth, and child care attendance.[7] Other processes, such as craniofacial abnormalities, neuromuscular disorders, and genetic and inflammatory conditions, also predispose children to OSAS.

Pathophysiology

The pathophysiology of childhood OSAS is best conceptualized as the classic triad depicting the interrelationship of upper airway narrowing, reduced upper airway tone, and other factors such as obesity, genetics, and

metabolism (**Box 33-1**). Adenotonsillar hypertrophy is the most common cause of OSAS in children, but other causes of upper airway narrowing may also predispose a child to OSA, including craniofacial abnormalities such as retrognathia, micrognathia, midface hypoplasia, and macroglossia. Children with a more collapsible upper airway are also at a higher risk for OSAS. Specific factors such as upper airway hypotonia, neuromotor weakness, and inflammation increase the collapsibility of a child's upper airway. The combination of upper airway narrowing and increased collapsibility may be present in a variety of disease processes, as discussed later in this chapter.[6,8]

Box 33-1

Factors Contributing to Obstructive Sleep Apnea Syndrome

- Upper airway narrowing
  - Adenotonsillar hypertrophy
  - Craniofacial structure
  - Obesity
- Abnormal upper airway neuromotor tone
- Genetic factors
- Hormonal factors
- Obesity

Clinical Presentation

The 2012 AAP guidelines on the diagnosis and management of childhood obstructive sleep apnea syndrome recommend that all children should be screened for snoring by their general health care provider.[2] Children who habitually snore should undergo a focused evaluation for further signs and symptoms associated with OSAS. Although snoring does not reliably predict whether a child has OSAS, almost all children with OSAS do snore.[9,10] It should be noted that children and infants with cleft palate or muscle weakness may not snore or may not be heard and, therefore, snoring may be underreported. Although a physical examination may be helpful in evaluating children who would benefit from a polysomnographic study, such as children with tonsillar hypertrophy, it is important to note that there are not always significant physical examination findings in children with OSAS. If the focused examination raises concern regarding OSAS, particularly inattention or behavioral problems, providers should obtain a polysomnogram or refer the patient to a sleep specialist for a more comprehensive evaluation. Nonspecific examination findings include adenoidal facies, high arched palate, micrognathia, retrognathia, large tongue, adenotonsillar hypertrophy, nasal obstruction, abnormal muscle tone, and signs of right-sided heart failure. If a child or parent does not report snoring, it is important to continue to screen the child at each well visit since snoring may develop.

In addition to screening otherwise healthy appearing children for snoring and other sleep-related symptoms, the pediatrician should ask about the child's daytime functioning. Younger children with OSAS may exhibit daytime

hyperactivity or behavioral problems,[11] which often result in poor school performance and difficulty paying attention. In teenagers, poor sleep quality due to OSAS may result in daytime hyperactivity, but it also may resemble the daytime sleepiness seen more frequently in adult populations.[12]

Children with obesity are particularly susceptible to OSAS. In 2011–2012, 16.9% of children aged 2 to 19 years had obesity.[13] Children with obesity who have OSAS have a higher risk of developing metabolic syndrome and cardiovascular complications than do children with either condition individually. Though the cause of OSAS in children with obesity is multifactorial, adenotonsillectomy should be considered in conjunction with weight loss when adenotonsillar hypertrophy is present.

If a child is at high risk for OSAS and has a significant comorbidity (genetic syndrome, neuromuscular disease, preterm infant, craniofacial abnormality), the child should be referred to a pediatric sleep medicine specialist for further evaluation.

OSAS in Special Populations

OSAS in Infants and Young Children

Obstructive sleep apnea syndrome in the infant population is distinct from OSAS in older children. The infant airway structure and chest wall mechanics predispose the infant to paradoxical breathing and intermittent hypoxemia, which may mimic or intensify OSAS. Further, an increased amount of REM sleep normally found in infants places them at heightened risk to develop OSAS. Obstructive sleep apnea syndrome in infants is often associated with comorbidities, such as genetic syndromes, failure to thrive, and prematurity.[14] Unlike older children who often have obesity, infants and young children with OSAS may have failure to thrive. This may be due to increased metabolic demands secondary to untreated OSA.

Polysomnographic scoring in infants is problematic. In adults, an apnea or a hypopnea is scored if its duration is 10 seconds or longer. Because of the faster respiratory rate in children, an apnea in a child is scored if the child misses 2 breaths.[15] However, with the even faster respiratory rate of infants, 2 missed breaths represents only 2 to 3 seconds and may have no physiological consequences. The increased compliance of the infant's chest wall may lead to paradoxical respirations, particularly in REM sleep, which is completely normal. Thus, the physician must review the polysomnographic study findings in infants with even greater care. Infants with mild OSAS, without hypercapnia or hypoventilation, may be managed with supplemental oxygen or simply observation, while those with moderate to severe OSAS may benefit from positive airway pressure (PAP) therapy or surgical intervention.[16]

Preterm infants are at higher risk of developing sleep-disordered breathing and OSAS compared to those born at term because of risk factors such as immature control of breathing, decreased upper airway muscle tone, and small upper airway caliber.[17] In addition, infants with lung disease, such as bronchopulmonary dysplasia, are at higher risk for OSAS because of increased work of breathing and a propensity for oxyhemoglobin desaturation as a result of their position on the oxyhemoglobin desaturation curve.[18] Some preterm infants with severe OSAS may need tracheostomy and/or noninvasive positive pressure ventilation to overcome their upper airway obstruction.

OSAS in Genetic Conditions

Numerous genetic conditions, particularly those that affect upper airway anatomy and/or compliance, may increase the risk of developing OSAS. Some examples include trisomy 21, craniofacial abnormalities, sickle cell disease, and neuromuscular disease.

The prevalence of OSAS in children with trisomy 21 is high, with some estimates reaching 50% to 100%.[19,20] Individuals with trisomy 21 have numerous risk factors for OSAS, including hypotonia, midface hypoplasia, mandibular hypoplasia, a small upper airway with superficially positioned tonsils, and obesity. Most children with trisomy 21 benefit from adenotonsillectomy as a first line of treatment despite other risk factors.[21,22] Given the high prevalence of OSAS in children with trisomy 21 and presentation with atypical symptoms, the AAP recommends full overnight polysomnography by the age of 4 years.[23]

Patients with craniofacial abnormalities are also at a higher risk of developing OSAS, though they may not exhibit typical sleep-disordered breathing symptoms such as snoring, daytime fatigue, or hyperactivity.[24]

Anatomic abnormalities may include mandibular hypoplasia, cleft palate, retrognathia, micrognathia, midface hypoplasia, craniosynostosis, and head and neck tumors, among others. The first line of treatment in patients with craniofacial abnormalities is surgical correction of the underlying defect. If this is not possible because of the patient's age, the need for multistaged surgery, or other reasons, the patient may respond to medical management, noninvasive ventilation, and, rarely, tracheostomy. These children benefit from referral to a multidisciplinary subspecialty team including speech therapists, otolaryngologists, audiologists, plastic surgeons, pediatric sleep or pediatric pulmonary physicians, and orthodontists.

Children with neuromuscular disease may have both upper airway obstruction and nocturnal hypoventilation due to coexisting decreased respiratory drive,[25] diffuse muscular weakness, and associated pharyngeal muscle weakness. There is a bimodal presentation of sleep-related breathing disorders in patients with Duchenne muscular dystrophy (DMD), with OSA found in the first decade of life and hypoventilation more commonly seen at the beginning of

the second decade.[26] Almost all children with DMD will develop nocturnal hypoventilation and go on to require nocturnal positive pressure ventilation, though this may soon change given new targeted biologics. Often, these children experience nonobstructive nocturnal hypoventilation prior to demonstrating any daytime symptoms. For patients with neuromuscular weakness, polysomnography for sleep-disordered breathing should be considered when the partial pressure of carbon dioxide ($PaCO_2$) is 45 mm Hg or higher on arterial blood gas.[27] The 2004 American Thoracic Society consensus statement regarding respiratory care of patients with DMD recommends a review of sleep quality and symptoms of sleep-disordered breathing at every patient encounter, as well as annual polysomnography with continuous carbon dioxide (CO_2) monitoring from the time the patient is using a wheelchair or when clinically indicated.[28]

Diagnosis

Polysomnography

Obstructive sleep apnea syndrome should be distinguished from primary snoring, central apnea, fixed upper airway obstruction, nonobstructive alveolar hypoventilation, and sleep-related epilepsy.[29] Polysomnography is the gold standard for diagnosing OSAS in the pediatric population.[2]

It is important to keep in mind that OSAS is the clinical syndrome associated with repeated upper airway obstruction with interrupted sleep, and thus the polysomnographic findings should always be put into clinical context. The *International Classification of Sleep Disorders, 3rd Edition*,[29] defines pediatric OSAS as requiring all of the following:

A. Caregiver reports snoring, labored and/or obstructive breathing;

B. Caregiver reports observing at least one of the following: paradoxical inward ribcage motion during inspiration, movement arousals, diaphoresis, neck hyperextension, excessive sleepiness, hyperactivity or aggressive behavior, slow rate of growth, morning headaches, secondary enuresis;

C. Polysomnographic recording demonstrating one or more scoreable obstructive hypopnea or obstructive apnea per hour with at least one of the following: frequent arousals from sleep associated with increased respiratory effort, arterial oxygen desaturations associated with apneas, hypercapnia during sleep, or markedly abnormal esophageal pressure swings; or periods of hypercapnia, desaturation, or both associated with snoring, paradoxical inward ribcage motion during inspiration with frequent arousals or esophageal pressure swings; and

D. The disorder is not better explained by another disorder, medications, or substance.

Note that clinical signs and symptoms as well as polysomnographic findings are required to establish the diagnosis. There are limited data to support the apnea-hypopnea index (AHI, the number of respiratory events per hour of sleep) with 1 as a cutoff. A total AHI less than 1.5 is often used to define a statistical norm, and complications of OSA such as elevated blood pressure are usually not seen at an AHI less than 5.[30,31]

In comparison to adult polysomnography, pediatric polysomnography also measures carbon dioxide, uses video monitoring, and scores arousals with respiratory events. Carbon dioxide is monitored using end-tidal CO_2, transcutaneous CO_2, or both to identify hypoventilation since prolonged partial upper airway obstruction with hypoventilation is not uncommon in children. For the purposes of polysomnography, hypoventilation is defined as $PaCO_2$ 50 mm Hg or greater for at least 25% of sleep time.[30] Short central pauses in breathing can be physiologically normal in children. Central apneas are not scored unless they are greater than 20 seconds or at least the duration of 2 missed breaths followed by arousal, desaturation, or bradycardia. The pulse oximeter used in a sleep laboratory is typically more sensitive, with shorter averaging times compared to those with blood oxygen saturation (SpO_2) monitors used on the hospital floors or at home. **Figure 33-1** depicts a typical 2-minute polysomnographic epoch of rapid eye movement (REM) sleep, with obstructive apnea resulting in oxyhemoglobin desaturations, hypercapnia, and arousals.

Although it is the gold standard, in-laboratory polysomnography is expensive and requires experienced technicians. In addition, access to polysomnography is often limited because of the scarcity of pediatric tertiary care centers. Interpretation of polysomnographic findings in children must be done by a sleep professional using pediatric scoring criteria, as adult criteria miss 80% of

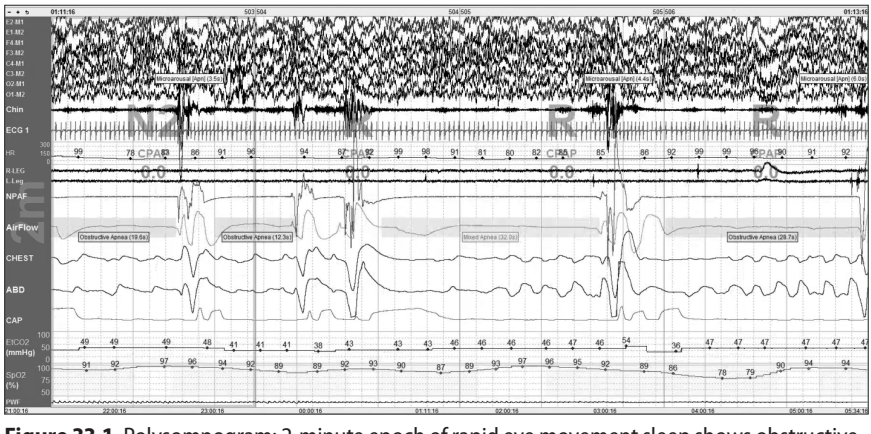


Figure 33-1. Polysomnogram: 2-minute epoch of rapid eye movement sleep shows obstructive apnea with intermittent oxyhemoglobin desaturation, hypercapnia, and arousal in a 3-year-old girl with adenotonsillar hypertrophy.

pediatric OSAS.[32] The American Academy of Sleep Medicine requires that pediatric criteria be used at least until the age of 13 years.[33]

Upper Airway Imaging

Upper airway imaging may be helpful to assess patients with complicated upper airway anatomy and residual OSA. It is important to note that no upper airway imaging modality can replace polysomnography in the diagnosis of OSA; it can, however, be useful to direct treatment.

Lateral neck radiographs are useful to visualize the upper airway from the nasopharynx to the upper thoracic trachea. They allow the evaluation of the adenoids, tonsils, and prevertebral soft tissue's effect on the airway. Radiographs are easily obtained and relatively inexpensive, with low radiation exposure, but they are not usually needed in routine evaluation of pediatric OSAS. However, they can be helpful to assess adenoid regrowth.

Axial computed tomography (CT) is a quick, easily available mode of assessing the 3-dimensional structure of the upper airway. This modality is ideal for identifying soft tissue and bony abnormalities. Cone-beam CT is a technique within CT that is much faster and uses less radiation than a conventional CT scan. Dynamic 3-dimensional CT is another type of CT that creates a dynamic, 3-dimensional image of the upper airway. However, young patients may require sedation.

Magnetic resonance imaging (MRI) creates a 3-dimensional image of the patient's upper airway without exposing the child to ionizing radiation. It allows precise measurement of the bony structures and soft tissues of the upper airway. Unfortunately, MRI often requires sedation, which may alter the collapsibility of a child's upper airway.

Drug-Induced Sleep Endoscopy

Drug-induced sleep endoscopy (DISE) is a technique used to evaluate collapsibility of the upper airway during periods of simulated sleep, allowing the physician to directly visualize the area of upper airway obstruction and therefore allowing individualization of surgical management.[34] DISE is typically indicated for children who have persistent OSA after adenotonsillectomy, those with OSA but without tonsillar hypertrophy, children with risk factors predisposing to multiple sites of obstruction, or when sleep-state–dependent laryngomalacia is suspected.[35] Like MRI, DISE requires sedation, which may alter the upper airway anatomy and collapsibility.

Home Sleep Apnea Tests

The home sleep apnea test (HSAT) is a widely used resource among the adult population to diagnose OSAS. The HSAT is a simplified monitoring system that tracks parameters such as nasal air flow, oxyhemoglobin saturation, and

breathing effort overnight. It allows patients to complete a sleep study from their home. Unfortunately, since the HSAT measures fewer variables than in-lab polysomnography, there may be an underestimation of the severity or presence of OSA. The American Academy of Sleep Medicine guidelines released in 2017 stated that the use of an HSAT is not recommended for diagnosis of OSAS in children.[36] Previous studies have demonstrated that use of the HSAT is technically feasible when trained clinicians are placing the electrodes; however, the probability of these tests being successful is less likely when the patient's caregivers place the electrodes.[37] The HSAT is discussed more fully in Chapter 34, Sleep Testing in the Laboratory or Home.

Pediatric polysomnography not only confirms the diagnosis of OSA but also establishes the severity of the disease. Children with severe OSA are less likely to be cured with adenotonsillectomy[38] and are at higher risk for perioperative respiratory complications.[39] Therefore, children with severe OSA should be treated and observed in a facility where pediatric intensive care is available if needed.

Genetics

There is evidence of specific genetic markers among adults with OSAS.[40] Research is emerging on the genetic landscape of pediatric OSAS.[41] The biologic relevance of specific genes may suggest the utility of novel therapies to treat the underlying cause of OSAS.

Management and Treatment

Adenotonsillectomy

Adenotonsillectomy is generally considered the first line of treatment for pediatric OSAS[2] and usually results in remission of symptoms and normalization of the AHI in mild to moderate cases.[38] A large, randomized, single-blind study showed that adenotonsillectomy resulted in improved behavior, quality of life, and polysomnographic findings compared to "watchful waiting" but did not significantly improve objective scores of attention and executive function on neuropsychological testing.[42]

As in all surgeries, notable postoperative complications may arise from adenotonsillectomy. Postoperative respiratory complications occur in 1.4% to 5% of adenotonsillectomies.[39] Early complications may include pulmonary edema, laryngospasm, bronchospasm, hypoxemia, and hypercapnia. Late complications include dehydration and tonsillar bleeding. A prospective study of consecutive children undergoing adenotonsillectomy for OSAS within 12 months of preoperative polysomnography showed that age younger than 3 years, SpO_2 nadir less than 80%, SpO_2 less than 90% for more than 1.1% of total sleep time, and peak CO_2 60 mm Hg or greater predicted early respiratory complications in a high-risk population.[39]

Because of the complex pathophysiology of OSA, residual OSA may exist after surgical intervention or it may recur later in adolescence.[8] Therefore, it is best to view the underlying cause of OSAS in children as a dynamic process resulting from a combination of structural and neuromotor abnormalities, rather than from structural abnormalities alone.[6] Follow-up for patients with severe OSA or persistent symptoms is essential.

Positive Airway Pressure Therapy

If adenotonsillectomy is not effective or is not desired by the family or the physician, PAP therapy may be effective. PAP is delivered through a mask interface, which provides a "pneumatic splint" to maintain a patent upper airway at the site of the obstruction by increasing the intraluminal pressure to exceed the pressure at which there is pharyngeal collapse.[1]

Multiple types of PAP devices are available, including continuous positive airway pressure, automatic positive airway pressure, bilevel positive airway pressure, and average volume-assured pressure support. Continuous positive airway pressure delivers a constant pressure from the machine to the patient's upper airway. This pressure usually ranges from 4 cm H_20 to 20 cm H_20 in the pediatric population.

Automatic positive airway pressure, which is widely used in adults, may be effective in a wide range of age groups, including infants.[16,43] However, the algorithms are proprietary and were developed for adults. The physician may set a range of expiratory PAP settings, and the machine auto-titrates (based on these proprietary algorithms) to the patient's needs, maintaining a patent airway while asleep. These devices seem to deliver pressures similar to those derived from titration polysomnography, but because the algorithms were derived for adults, there remains some concern about using them for small children.

Average volume-assured pressure support works by delivering a range of pressures (inspiratory PAP range and expiratory PAP range) with a set backup rate to hit a specific target tidal volume with each breath; it should be reserved for pediatric patients with difficult-to-treat OSAS and other lung pathologies.

If a decision is made to initiate PAP therapy in a child, the patient should undergo a comprehensive evaluation, including interface fitting and demonstration of placing mask and headgear, education regarding the home machine, detailed assessment of bedtime routine and sleep habits, rationale for PAP therapy, expectations for use, and available support. Parental understanding and cooperation are essential. Techniques to enhance adherence include modeling and/or desensitization. This evaluation can be done on an outpatient basis unless the child is very young, is medically fragile, or has severe gas exchange abnormalities, in which case inpatient initiation should be considered. Close follow-up should occur to ensure that the patient is using and

benefiting from the PAP and to assess for side effects. Once the patient is accustomed to the PAP therapy, they should undergo a PAP titration study to ensure that therapeutic pressures have been reached.

Medications and Oral Appliance

Other methods of treatment include intranasal corticosteroids, oral antileukotrienes, and oral appliances. For children with moderate to severe adenoidal hypertrophy, intranasal corticosteroids may be beneficial in reducing the size of adenoidal tissue and improving OSAS.[44] Oral antileukotriene modifiers are also associated with improved breathing during sleep in patients with mild OSAS.[45] Though the benefits of oral leukotrienes and intranasal steroids are widely accepted, there are conflicting reports as to the long-term effects of anti-inflammatory medications with respect to efficacy and safety.

Oral appliances are another management option for children with OSA. Though data are limited in children, oral appliances are effective in adults with mild-to-moderate OSA.[46] Because maxillary transverse deficiency (crossbite) is often seen in children with OSAS, pediatric oral appliances usually focus on rapid maxillary expansion. Rapid maxillary expansion increases the transverse dimension of the upper arch as well as buccal movement of the posterior teeth and alveolar processes. Multiple small studies have demonstrated a reduction in OSAS severity after patients underwent this intervention; it may be a good option for children with this orthodontic pathology, particularly if they are nonadherent with PAP. The orthodontist must be experienced with the procedure and be comfortable dealing with children.[47,48]

Sequelae of Untreated OSAS

Consequences of untreated or unrecognized OSAS include neurocognitive deficits, behavioral problems, and cardiovascular and metabolic risks. Children with untreated OSAS have a higher prevalence of daytime hyperactivity,[11] poor school performance, and nocturnal enuresis.[31,49,50] Up to one-third of children with OSAS or loud frequent snoring may demonstrate characteristics associated with hyperactivity and inattentiveness.[51] Children who underwent adenotonsillectomy have demonstrated improved attention and reduced hyperactivity postoperatively.[52]

Children with OSAS are at increased risk for hypertension.[31,53] Right heart failure and pulmonary hypertension are well-documented outcomes of OSAS.[54] In addition to cardiovascular comorbidities, children with OSAS have a higher incidence of metabolic syndrome. Specifically, they are at greater risk of developing insulin resistance and dyslipidemias. These associations not only increase morbidity and mortality in children with OSAS, but they also increase their health care utilization.[55]

key points

- Obstructive sleep apnea syndrome is characterized by partial and/or complete upper airway obstruction that disrupts sleep architecture and normal ventilation during sleep.
- The prevalence of OSAS is approximately 1% to 5%, with peak prevalence between 2 and 8 years of age.
- The gold standard for diagnosis of OSAS is polysomnography.
- AAP guidelines from 2012 recommend that all children should be screened for snoring by their pediatrician at every well visit.
- Adenotonsillectomy is the most common initial treatment for children with OSAS.
- Children with severe OSAS should undergo close perioperative monitoring.
- Medical treatments for OSAS include positive airway pressure, anti-inflammatory medications, and oral appliances.
- Consequences of untreated or unrecognized OSAS include neurocognitive deficits, behavioral problems, and cardiovascular and metabolic risks.
- Special attention should be given to specific populations such as infants, preterm infants, and patients with trisomy 21, craniofacial abnormalities, and neuromuscular disease.

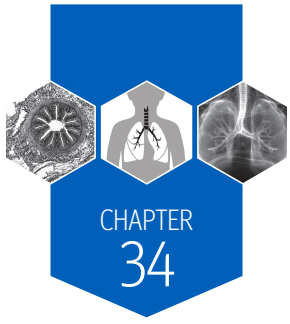
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CHAPTER
34

Sleep Testing in the Laboratory and Home

Deborah M. Brooks, MD
Lee J. Brooks, MD, FAAP

Introduction

Obstructive sleep apnea (OSA) is a disorder in which breathing starts and stops repeatedly during sleep. Apneas, the cessation of breathing, can be classified as either obstructive or central, depending on where the breathing dysregulation originates. This chapter will briefly mention central sleep apnea but will primarily focus on OSA in children.

Obstructive respiratory sleep disorders represent a continuum, ranging from habitual, primary snoring (regular, non-pathologic) to OSA.[1] Primary snoring, as distinguished from OSA, is defined as snoring without significant obstructive apneas, frequent arousals from sleep, or gas exchange abnormalities. In contrast, OSA is sleep characterized by recurrent episodes of complete or partial airway obstruction associated with arousals, awakenings, and/or oxyhemoglobin desaturation.[2–5]

Obstructive sleep apnea is the most common respiratory sleep abnormality in children during the first 2 years after birth and is usually worse during rapid eye movement (REM) sleep.[6,7] Obstructive sleep apnea affects 1% to 4% of children, and the main risk factors include adenotonsillar hypertrophy, obesity, craniofacial abnormalities, and neuromuscular diseases.[8,9] While OSA occurs in children of all ages, it is thought to be most common in preschool-aged children because the tonsils and adenoids are the largest in comparison to the size of their airway. Primary snoring, in contrast, is even more common and occurs in 3% to 12% of preschool-aged children.[10]

Children are typically brought to the pediatrician's office when their parents or siblings notice noisy breathing, snoring, cessation of breathing, increased body movements during sleep, or increased nocturnal awakenings.[3] Daytime sleepiness and neurobehavioral problems can also be present.[9–11]

Obstructive sleep apnea is classified according to its severity, typically denoted by the Apnea-Hypopnea Index (AHI), which measures the number of respiratory events per hour of sleep. *The International Classification of Sleep*

Disorders, Third Edition (ICSD-3), defines pediatric OSA as having an AHI 1 or greater or a pattern of obstructive hypoventilation defined as at least 25% of total sleep time with elevated carbon dioxide (CO_2) ($PaCO_2 > 50$ mm Hg) in association with snoring, flattening of the nasal pressure waveform, or paradoxical respiratory efforts.[6] However, there are few data to support this cutoff, and a total AHI less than 1.5 is often used as a cutoff. Complications of OSA, such as elevated blood pressure, are usually not seen at an AHI less than 5.[12] Other factors, notably the depth of hypoxemia, should also be taken into account.

Obstructive sleep apnea in children is associated with significant morbidity (**Box 34-1**), which is why it is important to recognize and diagnose the condition in a timely fashion.[1,4,10,11,13] According to the American Academy of Pediatrics Subcommittee on Obstructive Sleep Apnea, the goals of diagnosis (**Box 34-2**) are to identify children at risk for adverse outcomes, avoid unnecessary interventions in patients not at risk for adverse outcomes, and evaluate which children are at risk for complications so that appropriate precautions can be taken. In children, upper airway obstruction is usually caused by hypertrophy of the tonsils and adenoids, and treatment with an adenotonsillectomy is typically effective.[11,14] Severe OSA is associated with increased perioperative complications and even residual OSA after surgery, so accurate preoperative assessment of the presence and severity of the OSA is imperative.[5,15,16] For children who are not surgical candidates or who do not respond to surgery, continuous positive airway pressure is an option.[10] It is also important, especially in young children, to know if central sleep apnea is present, as this can change management.[13] Appropriate treatment of OSA can result in improvements in behavior and cognitive abilities.[16] (See Chapter 33, Obstructive Sleep Apnea Syndrome.)

Box 34-1

Morbidities Associated With Pediatric Obstructive Sleep Apnea

- Periodic hypoxemia
- Hypercarbia
- Increased respiratory effort
- Intrathoracic pressure changes
- Neurocognitive impairment
- Behavioral problems
- Failure to thrive
- Cor pulmonale

Box 34-2

Goals of Diagnosis for Obstructive Sleep Apnea

- Identify patients at risk for adverse outcomes.
- Avoid unnecessary intervention.
- Evaluate which patients are at risk for complications.
- Determine if central sleep apneas are present.

Diagnosing and monitoring OSA is different in children than it is in adults. There is a plethora of monitoring devices (some of which will be discussed later in this chapter) that work very well in adults, but not in children. In general, home testing has been shown to be no less accurate than in-laboratory polysomnography

(PSG) in adults, but this is not the case in children.[11] Children are fundamentally different from adults, and they experience a different kind of OSA. In children with OSA, partial airway obstruction is more common, and oxygen desaturation less common, as compared to adults with OSA.[2] These episodes may be missed completely by oximetry-based monitoring.[5] Additionally, the cutoff for clinically significant OSA is higher in adults, thereby eliminating the need for discrimination between low and very low AHI values.[6] Scoring is also different, as the pediatric scoring criteria allow the option to score an hypopnea if the event is associated with an arousal, rather than just a 3% oxygen desaturation, thereby making electroencephalogram (EEG) monitoring essential.[5] The lack of EEG or CO_2 monitoring on some home testing options may significantly underestimate the presence and severity of OSA in children.[5] Children also sleep differently and are notably more restless during sleep, and children with OSA have more movement arousals than age-matched controls, increasing artifact signal.[2] Monitors with leads can pose a risk of strangulation and entrapment with young children.[17] Children are also generally less tolerant of the machines, and their body habitus, as well as cognitive and emotional maturity, can vary widely, making it more difficult to predict who will be able to tolerate the sensors.[5] In addition, the first-line treatment for adults with OSA is continuous positive airway pressure, which is generally noninvasive, while the treatment in children is usually surgery (See **Box 34-3**.) The base-line AHI predicts the child's response to surgery and perioperative complications, so it is important to know the severity, not just the presence, of OSA in children.[15] Home sleep apnea testing has made a significant impact in adult sleep medicine, but as will be explained in this chapter, these results cannot be extrapolated to children.

Box 34-3

Treatment Options for Pediatric Obstructive Sleep Apnea

- Adenotonsillectomy
- Continuous positive airway pressure
- Craniofacial surgery
- Hypoglossal nerve stimulation
- Tracheostomy

Steps in Diagnosis

The first step in evaluating OSA in children is a thorough sleep history and physical examination. The sleep history should include any report of snoring, labored breathing, observed apneas, restless sleep, diaphoresis, enuresis, cyanosis, excessive daytime sleepiness, and behavioral or learning problems. The best historian is the person who observes the child sleeping on a regular basis, which may be a sibling who shares a room with the patient. Physical examination should pay special attention to the anatomy of the pharynx, including tonsillar size, and a thorough cardiovascular examination. Oftentimes, findings on physical examination during wakefulness are normal or nonspecific related to adenotonsillar hypertrophy. While adenotonsillar

hypertrophy is a major risk factor for OSA in children, numerous studies have shown that there is no relation between the size of the tonsils on inspection and the presence of OSA; it is the combination of the size and the neuromuscular tone of the upper airway that leads to OSA.[18] While they add important information, history and physical examination alone have a poor sensitivity and specificity in diagnosing sleep apnea. A patient with any of the complications noted in this text is considered to have obstructive sleep apnea syndrome.[10,15,16]

In addition to the standard history and physical examination, several questionnaires have been developed to screen for OSA, although they generally exhibit low sensitivity and specificity.[8] The Clinical Sleep Score is a composite score derived from the physical examination, subjective symptoms, and clinical history. This combination has been shown to correlate relatively well with AHI on PSG.[4] The overall performance of questionnaires supports their use more as a screening tool than as a diagnostic agent, such that a negative score would be unlikely to mislabel a child with OSA as being healthy, but a positive score would be unlikely to accurately diagnose a particular child with certainty.[16]

In-Laboratory PSG

An overnight in-laboratory polysomnogram is the gold standard for diagnosing OSA in children.[1,4,5,7–10] In-laboratory polysomnograms are preferred for children because the test provides an objective measure of disturbances in respiratory parameters and sleep architecture, can differentiate habitual snoring from sleep apneas while determining the severity of the apneas, and can differentiate OSA from other sleep disorders, including movement disorders and parasomnias.[4] (See Chapter 35, Sleep-Related Movement Disorders, and Chapter 37, Parasomnias.) Polysomnography includes simultaneous recordings of EEG, electro-oculogram, electrocardiogram, submental and leg electromyogram, oronasal thermistor, nasal pressure, thoracic and abdominal wall movement sensors, end-tidal and/or transcutaneous CO_2, and pulse oximetry, all under the continuous observation of a trained technician (**Table 34-1**).[6] These channels are used to measure the presence and severity of obstructive, mixed, and central respiratory pauses, which are especially important in children in whom hypoventilation is possible (particularly patients with neuromuscular or central nervous system disorders).[4,7,19] The sensors can also determine partial airway obstruction, oxyhemoglobin desaturations, and sleep architecture.[7]

Table 34-1. Polysomnography Components and Their Importance

Polysomnography Component	Measurement	Importance
Electroencephalogram	Sleep vs wakefulness; sleep architecture	Can identify seizure activity; determines total sleep time (which is denominator for Apnea-Hypopnea Index); determines if events happen during sleep or wake (eg, baby crying may mimic apneas)
Electro-occulogram	Eye movements	Differentiates rapid eye movement (REM), non-REM, and wakefulness
Submental electro-myogram	Pharyngeal muscles (genioglossus)	Determines atony, which indicates REM sleep
Leg electromyogram	Leg movements	Measures periodic limb movements during sleep
Oronasal thermistor	Exhaled air temperature	Exhaled air has a higher temperature than inhaled air, shows presence of airflow
Thoracic and abdominal movement sensor	Chest and abdominal movement	Differentiates between obstructive and central events
Pulse oximeter	Oxyhemoglobin saturation	Measures extent and duration of hypoxemia; identifies hypopneas
Electrocardiogram	Heart rate and rhythm	Identifies bradycardia and more severe arrhythmias
Video recording	Body movements, extraneous events causing arousal	Helps identify wakefulness from sleep, especially in infants; helps identify body movements including tonic-clonic seizures and periodic limb movements
Nasal carbon dioxide (CO_2) capnograph or transcutaneous CO_2 monitor	CO_2	Identifies hypoventilation
Laryngeal microphone	Snoring sounds	Identifies presence of snoring

Despite their gold-standard designation, in-lab polysomnograms are expensive, time-consuming, inconvenient, and limited in their availability, which can lead to long wait times.[1,2,4,5,9,13] To alleviate some of that burden, nap polysomnograms are occasionally used, particularly in infants. Nap polysomnograms are commonly performed during the day. Even though they are more convenient, nap polysomnograms generally underestimate sleep-disordered breathing in children.[3] Nap polysomnograms are useful if the result is strongly positive, but an overnight polysomnogram is still required if the nap study is negative or inconclusive. Nap polysomnograms have lower predictive value as compared to the overnight polysomnogram because of decreased total sleep time and particularly decreased REM sleep, when respiratory events are most prevalent.[6]

If a full overnight in-laboratory polysomnogram is not available, and the patient's clinical presentation shows a high likelihood of OSA as opposed to other sleep disorders, the clinician may order alternative diagnostic tests and consider proceeding to a full polysomnogram if the results are inconclusive. The 2017 American Academy of Sleep Medicine (AASM) guidelines do not support the use of home sleep apnea testing for the diagnosis of OSA in children, although they do permit the use of portable monitors as an alternative to PSG in certain situations based on the physician's clinical judgment (taking into account access to available diagnostic tools, individual patient circumstances, and available treatment options).[5,19,20] The European Respiratory Society is somewhat more liberal and allows video PSG, nap PSG, respiratory polygraphy, and nocturnal pulse oximetry as tools to diagnose OSA, although it still lists in-laboratory PSG as the more preferable modality.[1] Generally, portable apnea monitoring tends to be helpful if the results are strongly positive, but it has a poor predictive value if the results are negative; thus, children with a negative portable study should still undergo a more thorough evaluation, including full in-laboratory PSG. Portable studies have limited ability to evaluate the severity of OSA, which limits their ability to predict perioperative morbidity.[10,16]

Despite their low sensitivity and specificity, portable apnea monitoring devices do have some advantages.[16] These studies are feasible and reproducible, but not as accurate as full polysomnograms. Home studies are also less expensive, more convenient, and more accessible, with theoretically less "first night effect" (decreased sleep and sleep efficiency on the first night of testing).[4] However, these benefits might be mitigated by the need to repeat a full polysomnogram because of inconclusive results or a technically inadequate study.

Monitoring Classifications

In 1994, the AASM Portable Monitoring Task force classified portable monitoring into 4 categories (**Table 34-2, Table 34-3**), of which types 2 through 4 are applicable to home testing.[4]

Type 1 Monitoring

Type 1 monitoring is a fully attended polysomnogram with 7 or more channels, completed in a laboratory setting under the continuous observation of a trained technologist.[4] As discussed previously, this is considered the gold standard for diagnosing OSA in children because it provides an objective quantitative evaluation of sleep and respiratory disturbances.[16] Type 1 polysomnograms also allow patients to be stratified according to their severity, which helps determine which children are at risk for perioperative complications.

Table 34-2. Comparison of Obstructive Sleep Apnea Monitoring Device Classifications

Components	Type 1 (In-Laboratory Polysomnography)	Type 2 (Unattended Polysomnography)	Type 3 (Respiratory Polygraphy)	Type 4 (1–2 Parameters)
Electroencephalogram	X	X		
Electro-occulogram	X	X		
Submental electromyogram	X	X		
Leg electromyogram	X	X		
Oronasal thermistor	X	X	X	
Thoracic and abdominal movement sensor	X	X	X	
Pulse oximetry	X	X	X	X
Electrocardiogram	X	X		
Video	X	Can be included but usually not	Can be included but usually not	
Carbon dioxide: nasal or transcutaneous capnograph	X	Can be included but usually not	Can be included but usually not	
Laryngeal microphone	X	X		

Table 34-3. Advantages and Limitations of Portable Monitoring Devices

Monitoring Type	Advantages	Limitations	Guidance on Use
Type 1 (fully attended in-laboratory polysomnography [PSG])	"Gold standard"; can identify hypopneas, hypoventilation, movement disorders	Expensive; labor-intensive	"Gold standard" for a reason; best test, if available
Type 2 (unattended PSG with ≥7 channels, or "PSG in the home")	More convenient for families; theoretically less "first night effect"because child is sleeping at home	Expensive; labor-intensive; less useful in young children; signals can be lost overnight	May be useful in older children and adults when there is high clinical suspicion for straightforward, uncomplicated obstructive sleep apnea (OSA), but, if negative, may still need an in-laboratory polysomnogram. Works best when a trained professional goes to the house and places the sensors.
Type 3 (respiratory polygraphy)	More convenient for families; theoretically less "first night effect"because child is sleeping at home	Less sensitive and specific; does not typically measure carbon dioxide so cannot determine hypoventilation	May be useful in older children with strong history and physical examination findings suggestive of severe OSA. Should not be used in children younger than 3 years, and should be used sparingly in children younger than 12 years because of high failure rate in these populations. It should not be used in patients in whom hypoventilation is likely or suspected, including those with Down syndrome or neuromuscular, craniofacial, or skeletal syndromes. If inconclusive, a conventional polysomnogram should be performed. Results are improved if a trained professional sets up the sensors at the beginning of the night.
Type 4 (1–2 signal channels)	Inexpensive, small, convenient	Poor sensitivity overall; poor negative predictive value; cannot differentiate obstructive from central apneas	May be useful in prioritization of treatment. Cannot replace full PSG because of its poor sensitivity and is not sufficient for identification of OSA in otherwise healthy children. If negative, a full polysomnogram is necessary.

Type 2 Portable Monitoring

Type 2 monitoring consists of an unattended polysomnogram with 7 or more channels.[4] This is essentially a "polysomnogram in the home" and typically includes EEG as well as respiratory monitoring. These ambulatory polysomnograms are appropriate and reliable in some adults, but they should not be used for the exclusive evaluation of severe OSA in children, especially preschool-aged children, because these monitoring systems rarely include capnography.[13,16] In adults and older children, there is no significant difference in respiratory parameters compared to in-laboratory polysomnogram, but the type 2 monitors had a high error rate in children younger than 5 years.[4,6,16] Under research conditions, when trained staff go to the child's home and apply the sensors, there is a high degree of technically acceptable recording, particularly in children older than 5 years.[4,19]

Type 2 studies are still quite labor intensive and expensive because a technologist must travel to the home to set up and take down the equipment. The scoring is no different from in-laboratory polysomnograms.[4] Video recordings are not always included, nor is CO_2 monitoring, which is especially important in children in whom there is a concern for hypoventilation, such as those with neuromuscular disease, underlying lung disease, or obesity hypoventilation. Other limitations for in-home polysomnograms include potential interference from siblings, lack of electrical outlets near the bed, signal artifact from home technology, and insufficient battery life if the unit is unplugged (eg, for a bathroom trip) and not replugged.[4] In many cases, even if the caregivers noted that sensors came off overnight, few attempted to replace them. Nasal cannula flow signals are often suboptimal with no technologist continuously monitoring the patient.[4,21] Any cost advantage of type 2 monitoring may be mitigated by the need for a technologist to set up the devices in the home and the not infrequent need to conduct a full polysomnogram in the lab because of an inconclusive home study. There is currently one US Food & Drug Administration-approved device for type 2 monitoring in adults, but the AHI is not comparable to PSG in children.[11]

Type 3 Portable Monitoring

Type 3 studies, also known as respiratory polygraphy (RP), are more limited than types 1 and 2 and typically consist of only 4 to 7 monitoring channels, generally without EEG monitoring of sleep stages.[4,16] The AASM recommends that an RP study include, at a minimum, airflow, respiratory efforts, and oxyhemoglobin saturation.[20] Home RP is accepted and used effectively in adults and is, in many cases, the preferred option for adult sleep medicine.[8] The research in children is more limited, although type 3 portable monitoring may offer a viable alternative for the diagnosis of otherwise healthy children with moderate to severe obstructive sleep apnea syndrome, particularly where

access to a full polysomnogram is limited.[4] Respiratory polygraphy, especially when set up by a sleep technologist at the home in a research setting, can identify an AHI that highly correlates to a type 1 polysomnogram in older children, aged 12 through 17.[21] The correlation is likely to be lower in the clinical setting. These devices also demonstrate relatively high sensitivity and specificity to diagnose OSA when the AHI is greater than 10, but RP is inferior to PSG in more mild or moderate cases of OSA. Similar to the other portable monitors, the percentage of successful recordings is higher if the RP is set up by trained staff. However, even under ideal conditions, these studies tend to underestimate the AHI because hypopneas causing arousals are missed (with no EEG) and the total sleep time is only an estimate without EEG confirmation.[4]

Respiratory polygraphy is not helpful in certain special populations, including children with Down syndrome, Prader-Willi syndrome, and neuromuscular diseases, because hypoventilation is not detected using these monitors, which lack capnography.[6,19] Younger children often have difficulty tolerating the sensors, and, even with detailed oral and written instructions, caregivers are frequently unable to place the sensors adequately.[14] Additionally, if a child is sleeping poorly, a type 3 monitor, which cannot stage sleep, may miss obstructive events because those tend to cluster during REM sleep.[4] As with type 2 monitoring, because of the high specificity but low sensitivity, a negative test necessitates an in-laboratory polysomnogram.[8] Other limitations of RP include that total recording time, rather than total sleep time, is used for the denominator for AHI.[13]

Research evaluations of RP devices have used the same equipment as the polysomnogram (minus certain signals). Home RPs are designed to be portable, and, while similar, they are not the same as in-laboratory equipment and may yield poorer results than even these studies suggest.[4] Any cost advantage of type 3 portable monitoring may be mitigated by the need for a technologist to set up the devices in the home, and the not infrequent need to perform a full polysomnogram because of an inconclusive home study.

Type 4 Portable Monitoring

Type 4 monitoring consists of only 1 or 2 signal channels, traditionally, but not exclusively, with pulse oximetry as one of the measurements.[4] The second channel may be electrocardiogram/heart rate, peripheral arterial tonometry, or chest wall movement. As with other portable monitoring systems, type 4 monitors have a good positive predictive value in patients where there is a high suspicion for OSA, but the monitors also have a poor negative predictive value, indicating that oximetry is useful when results are positive but if the test is negative, the patient still requires a full in-laboratory polysomnogram.[10,11] Overall, single-channel recording has not been shown to correlate well with

in-laboratory PSG for the diagnosis of OSA.[2,11] Oximetry alone is generally insufficient for the diagnosis of OSA because of the higher rate of inconclusive test results, especially considering that children with OSA can experience arousals and sleep fragmentation and not develop desaturations. Children also tend to move around in their sleep, which can result in motion artifacts.[16] Pulse oximetry alone cannot differentiate between obstructive and central apneas.[11] Type 4 monitoring can, however, be useful in the prioritization of treatment and can play a more central role in places where polysomnograms are not available.[4] These monitors are most useful in children being treated with home oxygen to determine the feasibility of stopping the oxygen therapy.

Other Monitoring Options

Since 1994 when the American Academy of Sleep Medicine developed these classifications for portable monitoring, several newer technologies have been developed. While some of these methods will be described briefly, it is important to note that none can fully replace a full in-laboratory polysomnogram for the diagnosis of OSA in children.

Radiologic Studies

Certain radiologic studies have been used to help diagnose OSA, such as the presence of airway narrowing on a lateral neck radiograph, which increases the probability of predicting OSA on PSG.[16]

Acoustic Pharyngometry

Acoustic pharyngometry uses reflected sound waves administered through the mouth to assess the size of the pharynx; however, the accuracy is still being studied. When sound waves are administered through the nose (acoustic rhinometry), nasal resistance can be assessed. A high nasal resistance suggests an increased risk for OSA.[22,23]

Snoring Evaluations

Snoring evaluations, independent from a history and physical examination, generally do not correlate well with the severity of OSA because the loudness of the snoring does not necessarily correlate with the degree of obstructive apnea.[16] Snoring may disappear following surgery such as adenotonsillectomy, yet OSA may persist if the baseline OSA was severe.

Peripheral Arterial Tonometry

Studies have found changes in cardiovascular parameters, such as heart rate variability, pulse transit time, and peripheral arterial tonometry, in children with OSA, but the sensitivities and specificities of these assessments are variable and generally are not used as a single measurement.[16] Peripheral arterial tonometry assesses changes in peripheral arterial volume as a measure

of transient elevations of sympathetic tone associated with nighttime arousals. Peripheral arterial tonometry, combined with pulse oximetry and actigraphy, provides a relatively high degree of correlation of sleep variables in adults, and in children with severe OSA, as compared to PSG.[4,24]

Pulmonary Function Tests

Using pulmonary function tests, a "sawtoothed" pattern of the maximal expiratory flow-volume loop (**Figure 34-1**) has been suggested to screen for OSA in adults, but younger children may have difficulty performing the maneuver.[16]

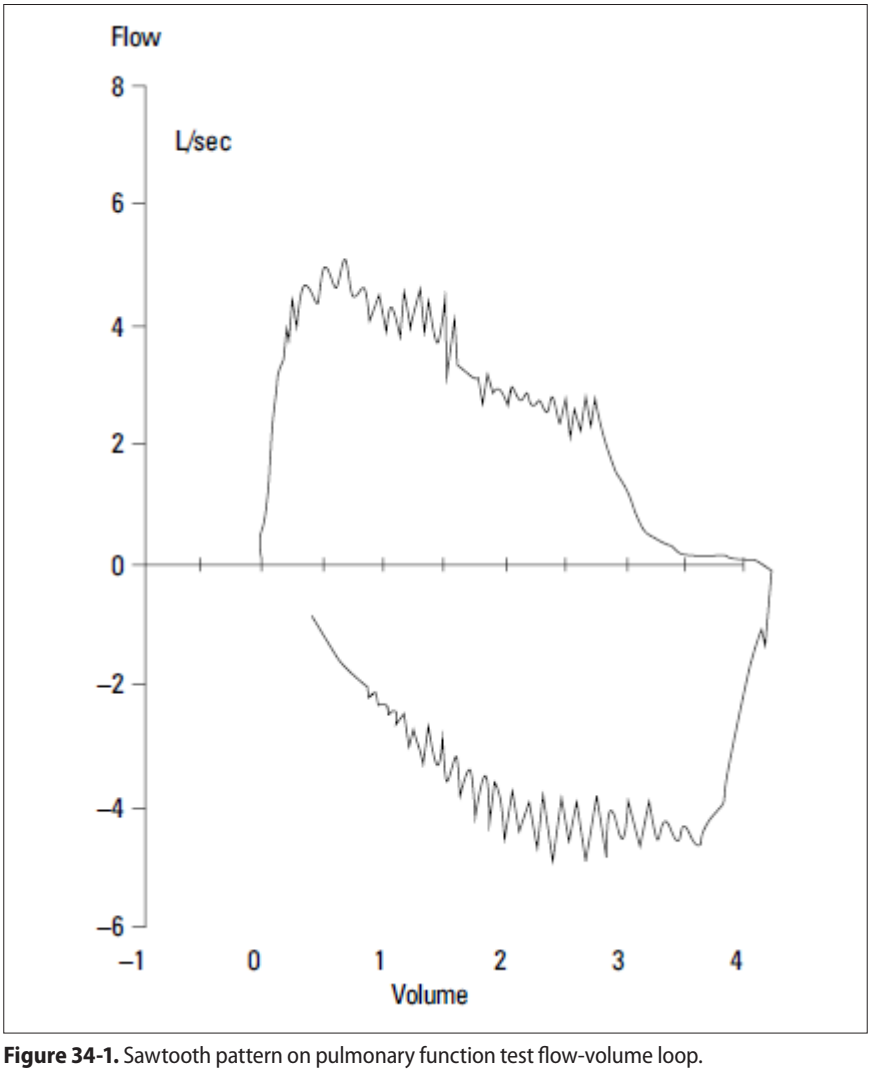


Figure 34-1. Sawtooth pattern on pulmonary function test flow-volume loop.

From Sahni S, Blood A, Paulus S, Talwar A. "Saw-Tooth Sign" in upper airway disorders—a case report. *Pneumonol Alergol Pol.* 2015; 83: 140-143.

Proteomics Studies

Some studies have tried to use urinary or serum proteomics analysis for screening for OSA; in a highly selected patient population, urinary proteins did have a high sensitivity and specificity, although more studies are needed.[16,25]

Audio and Video Recording

Audio and video recording, facilitated by the near-universal presence of cell phones, shows a lot of discrepancies in screening for and diagnosing OSA in children.[10] Home video may be a useful first step in the clinical evaluation of children suspected of having OSA as it has a generally high sensitivity and medium specificity. The most useful information gleaned from a recording is differentiating snoring from other respiratory noises. Limitations of video recordings include that neither the sleep state nor any other parameters are monitored.[3] Audio recording alone is inferior to video recording because it notes only one variable: the presence of noisy breathing.

Investigators have attempted to use video game modalities to assess sleep in the home, similar to, but more comprehensive than, traditional video recording. The Microsoft Kinect video game system has been the subject of some studies. The Kinect system has 3 optical sensors to provide body tracking, 3D body reconstruction, skeletal tracking, and joint tracking to detect respiratory activity, particularly visualizing paradoxical movements of the thorax and abdomen and monitoring of limb movements. The system alone cannot detect oxygen saturation levels, arousals, or changes in heart rate. One study showed that the Kinect system can accurately measure respiratory movements under low light conditions and, therefore, detect apneas even in young children, although more studies are necessary.[17]

Radar

Radar has also been examined as a noncontact monitoring device for OSA; however, to make use of the Doppler effect in sleep requires that the recording system be within 1 meter of the patient. If radio frequency identification technology is used, sensors are still required on the patient's body, which may be uncomfortable and prone to distortion by the patient's movements and signal interference.[17]

Thermal Cameras

Thermal video cameras have been used to detect CO_2 emissions or to determine skin temperature differences between inhalation and exhalation. However, these measurements can be affected by head position, movement artifact, and anything that might cover the face, such as a blanket.[17]

Image Sequence Analysis

Image sequence analysis uses the optical flow of the chest surface captured by video camera, but lighting conditions are a major drawback and the data has to be interpreted after the video is analyzed, so abnormal events cannot be captured in real time. Three-dimensional surface information of the patient's chest, captured by time-of-flight cameras for detecting respiratory motion, is also severely affected by noise and motion artifact, and the technique is quite expensive.[17]

Capacitor-based Systems

Capacitor-based systems detect static charge contained within bedding material and can discern breathing movements, but studies with children so far have had limited success.[4]

Sheets and Mats

Sheets and mats with pressure, vibration, and sound sensors also exist, although so far the vibration-sensing mat underestimates AHI in adults and the pressure-sensing sheets can detect central apneas but not obstructive ones.[4] A newer device, the Sonomat, a mattress pad with both sound and movement sensors, is showing some promise in identifying both obstructive and central apneas in children.[26]

Biomotion Sensors

Noncontact biomotion sensors can use radio waves to measure movement and respiration from the bedside table and have been useful in adults with an AHI greater than 15.[4] As yet, good studies in children are lacking.

Conclusion

While portable home monitoring of OSA is accepted and validated in adults, it has significant deficiencies and is not regularly used in children. However, the ultimate judgment regarding this, and any specific care, must be made by the treating physician considering the individual circumstances of the patient.[5] This is not to say that home monitoring will never be appropriate in children, but given the few validated studies in youngsters and the conflicting results, in-laboratory PSG remains the gold standard for diagnosing and evaluating OSA in children.

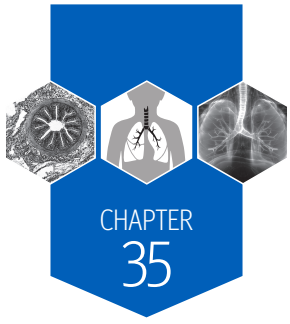
key points

- Obstructive sleep apnea affects 1% to 4% of children and, undiagnosed and untreated, can cause behavioral problems, poor school performance, and daytime sleepiness. Obstructive sleep apnea in children is typically caused by enlarged tonsils or adenoids and is corrected surgically.
- The gold standard for diagnosing OSA in children is with an in-laboratory polysomnogram.
- Simpler and less expensive testing options are available, but they only incorporate a fraction of the measurements that are recorded using a polysomnogram.

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Sleep-Related Movement Disorders

Jennifer Accardo, MD, MSCE

Introduction

Pediatric pulmonologists have led the way in identification and treatment of obstructive sleep apnea in children. However, pediatric sleep practice requires knowledge of non-respiratory sleep disorders as well as respiratory ones. Parents often voice concerns about children's movements during sleep and restless sleep. While these are often related to sleep-related breathing disorders (see Chapter 33, Obstructive Sleep Apnea Syndrome), movements may represent sleep disorders in their own right, sometimes but not always comorbid with sleep-related breathing disorders.

Sleep-related movement disorders in children typically disrupt sleep at its initiation, with stereotyped, simple movements. The *International Classification of Sleep Disorders, 3rd Edition (ICSD-3)* catalogs restless legs syndrome (RLS; also known as Willis-Ekbom disease), periodic limb movement disorder (PLMD), sleep-related leg cramps, sleep-related bruxism, sleep-related rhythmic movement disorder, benign sleep myoclonus of infancy, and propriospinal myoclonus at sleep onset; as well as sleep-related movement disorders due to medical disorder, medication or substance, or unspecified; and isolated symptoms and normal variants such as excessive fragmentary myoclonus, hypnagogic foot tremor and alternating leg muscle activation, and sleep starts (also known as hypnic jerks).[1] In addition, restless sleep disorder is a newly defined sleep disorder not yet added to the classification.[2] The most frequently discussed of these entities, on which this chapter will focus, are RLS and PLMD.

Epidemiology

The American Academy of Sleep Medicine (AASM) defines a periodic limb movement index (PLMI) of more than 5 periodic limb movements of sleep (PLMS) per hour as abnormal.[1] A large cross-sectional study of more than 10,000 subjects based on National Institutes of Health criteria for RLS revealed a prevalence of 1.9% in children aged 8 to 11 years, and 2% in children aged 12 to 17 years. In these groups, 0.5% and 1% respectively reported moderate to severe symptoms at least twice a week.[3] A cross-sectional study of community-recruited

children aged 5 to 17 years who had polysomnography (PSG) performed for research purposes noted 7.7% with PLMI more than 5 per hour, and 1.5% more than 15 per hour.[4]

In terms of other sleep-related movement disorders, bruxism may affect 15% to 49% of typically developing children.[5] Up to 3% of infants and toddlers identified through well child checks had sleep-related rhythmic movement disorders, confirmed by videosomnography.[6] Researchers estimate the prevalence of restless sleep disorder at 7.7% of children clinically referred to a sleep center.[7]

Pathophysiology

Research implicates iron, a key mediator of the dopaminergic system, in the pathophysiology of RLS and PLMD. A detailed description of these proposed mechanisms is beyond the scope of this chapter but is available in several published original research studies and reviews.[8] Iron deficiency due to any cause can lower the threshold for RLS/PLMD symptoms, even without clinical anemia as measured by hemoglobin, and iron levels may not measure its availability to the central nervous system specifically. Serum ferritin acts as a marker for bioavailability of iron in the cerebrospinal fluid. It should be drawn on first morning fasting. Because serum ferritin acts as an acute phase reactant and can remain elevated more than 5 weeks post-infection, consider delaying laboratory work in the immediate aftermath of illness and ordering an erythrocyte sedimentation rate or C-reactive protein to assess for residual inflammation.[8]

Diagnosis

Clinical Features

Surface electrodes on the tibialis anterior muscle monitor the occurrence of limb movements (LMs) during PSG, placed and filtered as per the most recent version of *The AASM Manual for the Scoring of Sleep and Associated Events*.[9] Rhythmic sequences of LMs constitute PLMS. Limb movements last 0.5 to 10 seconds, with a minimum 8 microvolt increase in voltage over resting electromyography.[9] Periodic limb movements of sleep consist of at least 4 LMs, each separated by 5 to 90 seconds, not scored if occurring within 0.5 seconds of the onset or offset of a respiratory event (see **Figure 35-1**).[9]

Periodic limb movement disorder manifests during sleep. Family members may observe the patient to be kicking during sleep, but they may or may not wake up. It is diagnosed when the following criteria are met: polysomnographic documentation of PLMS occurringmore than 5 times per hour; associated with disturbed sleep or impaired function; and not better explained by another disorder, sleep or otherwise.[1] Other movement variations include alternating leg muscle activation and hypnogogic foot tremor.

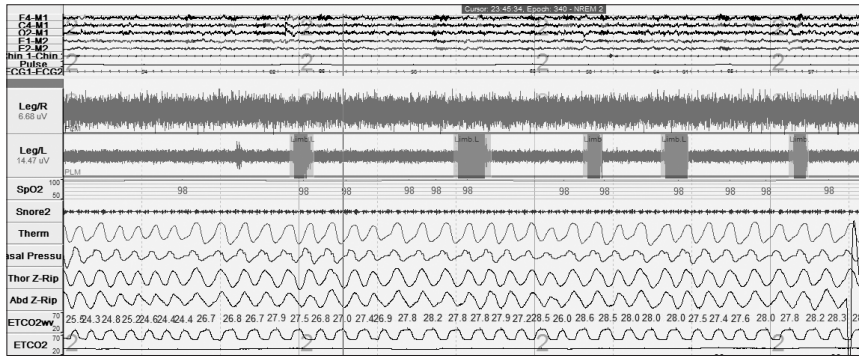


Figure 35-1. Periodic limb movements of sleep on polysomnography during non-REM sleep in a 16-year-old girl with 4 limb movements over the course of three 30-second epochs. Note that these particular leg movements are not associated with arousals or alteration of cardiopulmonary function.

Restless legs syndrome, in contrast, is a clinical diagnosis, not the result of laboratory testing. Its symptoms occur during wakefulness and may interfere with sleep onset. Successful diagnosis depends on history, which presents a challenge in young children and children with communication disorders. Restless legs syndrome and PLMD overlap and share pathophysiology, such that their diagnosis is often entwined. In addition, diagnosis of PLMD may precede that of RLS.[10]

The International Restless Legs Syndrome Study Group (IRLSSG)[11] published the following essential diagnostic criteria for RLS:

- An urge to move the legs usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs. For children, the description of these symptoms should be in the child's own words.
- The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.
- The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
- The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day.
- The occurrence of the above features is not solely accounted for as symptoms primary to another medical or a behavioral condition.

In a retrospective study of children with RLS, subjects presented with sensory complaints in their legs and the urge to move, occurring at rest, worse during evenings and nights, and alleviated by movement. They often felt tired during the day, sometimes demonstrating excessive daytime sleepiness. More than half reported insomnia, and most had an elevated PLMI on PSG.[12]

Diagnosis of pediatric RLS presents some unique challenges. Because children must describe symptoms in their own words, clinicians should take into consideration their developmental levels and language abilities in thinking about how they are likely to describe their sensations. Children sometimes respond better to requests to draw how their legs feel (see **Figure 35-2**).[13] Effects of RLS in children often manifest more in their academics and behavior than in other domains reported by adults.[10]

Clinical features supporting the diagnosis of pediatric RLS include[10]

- Periodic limb movements of sleep > 5 per hour
- Family history of RLS among first-degree relatives
- Family history of PLMS > 5 per hour
- Family history of PLMD among first-degree relatives

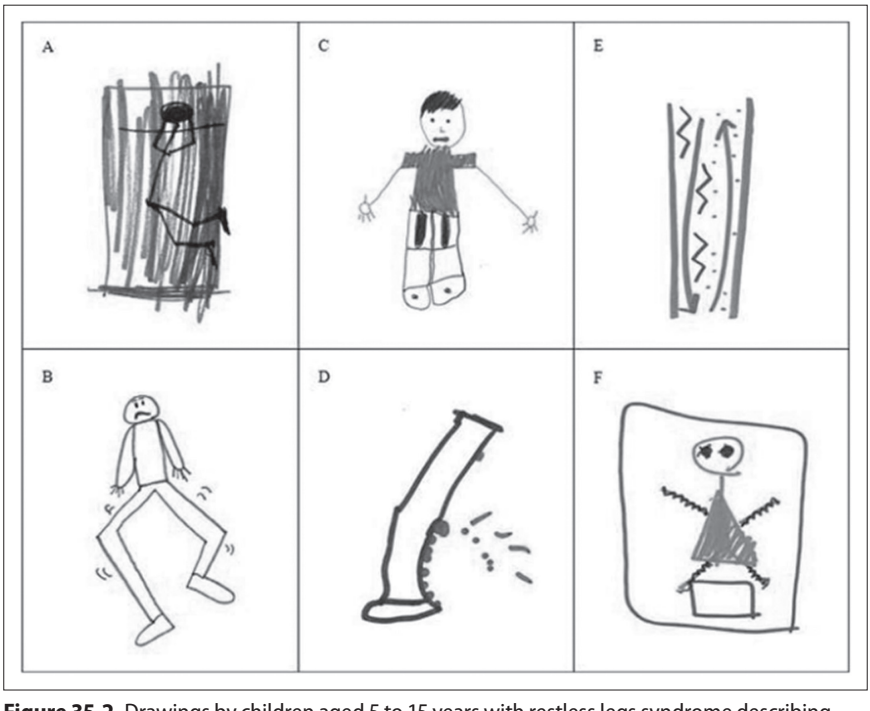


Figure 35-2. Drawings by children aged 5 to 15 years with restless legs syndrome describing their symptoms. Samples of the accompanying descriptions included the following: "I'm trying to stretch my legs out"; "like it's ant bites"; "these represent my tingles."

From Picchietti DL, Arbuckle R A, Abetz L, et al. Pediatric restless legs syndrome. *J Child Neurol*. 2011;26(11):1365-1376. https://doi.org/10.1177/0883073811405852. © 2011 by SAGE Publications. Reprinted by permission of SAGE Publications.

Sleep-related bruxism requires evidence of teeth grinding, via grinding sounds heard during sleep, and either evidence of unexpected tooth wear for age or symptoms such as jaw muscle pain, temporal headache in the morning, or jaw locking on waking (see also **Figure 35-3**).[1]

Rhythmic movement disorders, too, consist of movements of specific ranges of frequency (0.5–2 Hz) and amplitude (2× background electromyography activity), occurring in clusters of at least 4 events.[9] Such movements can include repetitive body rocking, headbanging, or rolling at sleep onset.[6] These may be described by the family or seen on the video during PSG.

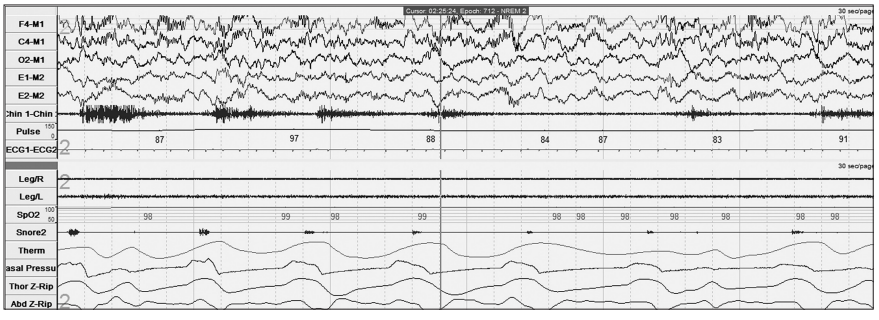


Figure 35-3. A 30-second polysomnographic epoch demonstrating sleep bruxism in a 6-year-old girl consisting of sustained (tonic) chin muscle activity.

Role of PSG

The AASM practice parameter[14] recommends PSG in children as a standard of care to clarify whether children have PLMD (this diagnosis requires an objective correlate.) Polysomnography can also be used to evaluate children with disorders triggered by sleep disruption such as epilepsy, frequent non-rapid eye movement (non-REM) parasomnias, nocturnal enuresis, or PLMD if suspected, at the level of guideline. Polysomnography can provide supportive data for diagnosis of RLS, as an option. Sleep-related bruxism alone, however, does not provide sufficient indication for PSG.[14] Clinicians should bear in mind that PLMS can vary significantly from night to night in children as well as in adults.[15]

Common Contributing Conditions

While genetic variants play an important role in RLS/PLMD, other medical conditions place children at increased risk of these disorders as well.[16] As alluded to previously, iron deficiency and anemia figure prominently. Conditions such as kidney disease and sickle cell disease logically follow as risk factors due to the anemia involved. Spinal pathologies may also provoke symptoms.

Epilepsy remains part of the differential diagnosis for many sleep-related movement disorders, especially when markedly stereotyped movements occur and are not consistent with classic sleep disorder presentations (the "triple flexion"

of PLMS). However, epilepsy, although associated with increased problems with sleep, does not in and of itself carry a higher risk of RLS/PLMD.

Children with attention-deficit/hyperactivity disorder more frequently have RLS/PLMD than typically developing peers; likewise with Tourette syndrome and tic disorders.

Separation anxiety, as well as generalized anxiety disorder, carries a higher risk for development of sleep bruxism, which should prompt additional screening and mental health referral if appropriate.[5] Children with autism and intellectual disabilities more frequently engage in sleep-related rhythmic movement disorders, but such movements are not exclusive to them. Typically developing children with rhythmic movements may present earlier in life than children with disabilities.[17] In the absence of other symptoms, sleep-related rhythmic movements should not prompt suspicion for autism. These children often have attention-deficit/hyperactivity disorder.[18]

Sequelae

The effects of disrupted sleep on children and families in general have been extensively documented elsewhere. Subjects with PLMI more than 5 per hour have higher arousal indices compared with peers.[4] A case control study looking specifically at children diagnosed with RLS and a matched comparison group documented significantly lower quality of life in children with RLS symptoms at least twice a week.[19]

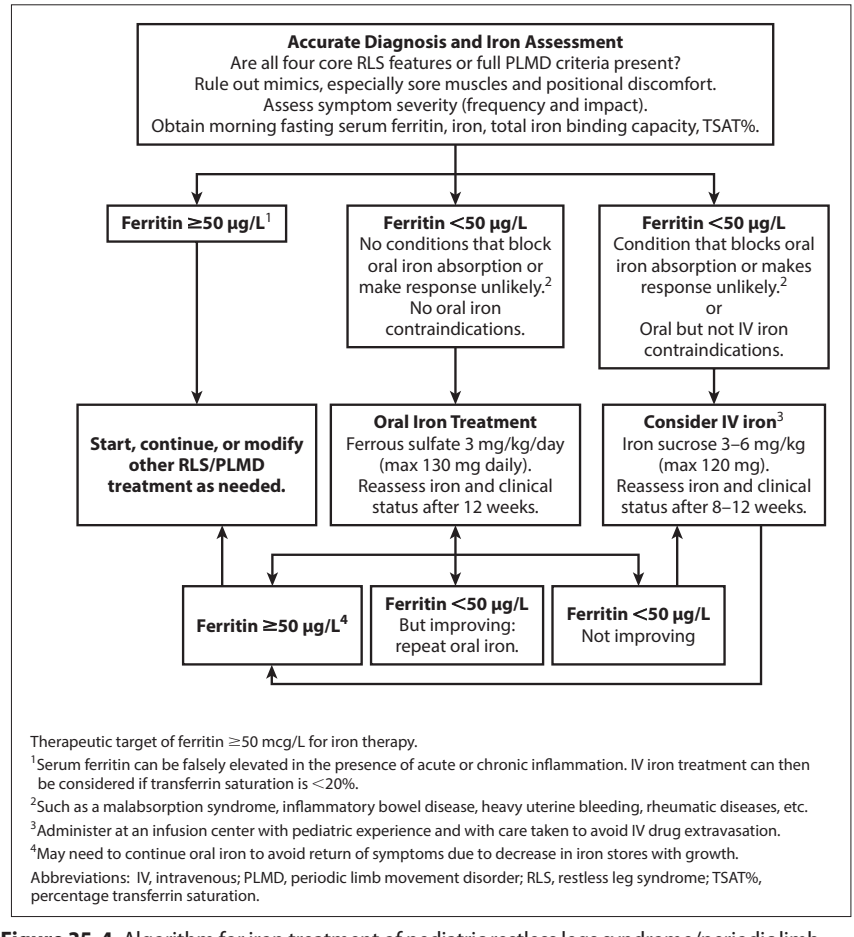
Sleep bruxism not only causes wear and tear on teeth, but can also lead to broken teeth, temporomandibular joint disorders, and headaches.[5] Sleep-related rhythmic movement disorders that are persistent and vigorous can lead to damage to self and property, resulting in bruising, injury, and broken furniture (eg, energetic body rocking gradually loosening screws to bed frames). Further, these rhythmic movements can be both quite persistent and treatment resistant.[17]

Management

Treatment Options

Clinicians should consider iron supplementation as treatment for RLS/PLMD before proceeding to other medication options. The IRLSSG reviewed studies of oral iron supplementation and intravenous iron infusion for treatment of children with RLS. They found inadequate evidence to draw conclusions about the safety or efficacy of either.[8] Nevertheless, they reported a consensus recommendation that oral iron treatment probably decreases symptoms of RLS and helps sleep quality in children with RLS and PLMD.[8] Limiting factors for oral iron can include gastrointestinal effects, particularly constipation, as well as aversion to the distinctive taste of the supplements. However, increased dietary iron alone may not be sufficient to effect change.

The 50th percentile for serum ferritin is the most commonly used marker of body iron stores. 50 mcg/L (50 ng/mL) is typically used as the cutoff below which iron supplementation is recommended in children with RLS, though some have proposed 75 mcg/L (75 ng/mL). A cohort of children with serum ferritin less than 50 mcg/L (<50 ng/mL) showed a significant increase in ferritin following 8 weeks of oral iron supplementation. However, changes in RLS scores did not meet statistical significance.[20] Adherence to supplementation naturally influenced response, defined as increase of of more than 10 mcg/L (>10 ng/mL). Subjects who responded reported more frequent change in symptoms and less frequent constipation.[21] While intravenous iron infusion has been studied in children, and it appears on the IRLSSG flowchart for iron supplementation in children with RLS (**Figure 35-4**), only a few



Therapeutic target of ferritin ≥50 mcg/L for iron therapy.

[1]Serum ferritin can be falsely elevated in the presence of acute or chronic inflammation. IV iron treatment can then be considered if transferrin saturation is <20%.

[2]Such as a malabsorption syndrome, inflammatory bowel disease, heavy uterine bleeding, rheumatic diseases, etc.

[3]Administer at an infusion center with pediatric experience and with care taken to avoid IV drug extravasation.

[4]May need to continue oral iron to avoid return of symptoms due to decrease in iron stores with growth.

Abbreviations: IV, intravenous; PLMD, periodic limb movement disorder; RLS, restless leg syndrome; TSAT%, percentage transferrin saturation.

Figure 35-4. Algorithm for iron treatment of pediatric restless legs syndrome/periodic limb movement disorder.

From Allen RP, Picchietti DL, Auerbach M, et al; International Restless Legs Syndrome Study Group (IRLSSG). Evidence-based and consensus clinical practice guidelines for the iron treatment of restless legs syndrome/Willis-Ekbom disease in adults and children: an IRLSSG task force report. *Sleep Med.* 2018;41:27–44 PMID: 29425576.

centers actually have experience with infusion for pediatric sleep disorder indications.

Parents often ask about magnesium supplementation as an option, apparently due to its reputation in treating leg cramps. However, systematic review of its effects on RLS/PLMD was inconclusive.[22]

Medication

Medications can both treat and provoke sleep-related movement disorders. As is common in pediatrics, there are currently no US Food & Drug Administration-approved medications for RLS/PLMD. Dopaminergic agonists (ie, carbidopa/levodopa, pramipexole, ropinirole, and rotigotine) remain popular among adults for treatment of these conditions. Knowledge of side effects in children is limited; the potential for augmentation (worsening symptoms as treatment continues) and dopaminergic effects such as behavioral disinhibition (classically, impulsive behaviors such as gambling and compulsive sexual behaviors in adults) tend to concern prescribers, as does the potential for nausea and vomiting.[16] Hypnotic supplements and medications used in pediatrics can blunt symptoms of RLS, possibly due to hastening sleep onset. Melatonin, clonidine, gabapentin, and pregabalin are generally well tolerated.[16] Non-benzodiazepine hypnotics such as zolpidem, zaleplon, and eszopiclone, should be used with caution in the pediatric population due to their tendency to provoke parasomnias and concerns about difficulty weaning off them. Clinicians typically reserve opioids such as methadone for refractory cases, and there is little guidance for their off-label use in pediatric RLS/PLMD. Most selective serotonin reuptake inhibitors, except for bupropion, exacerbate RLS and PLMD.

Lifestyle

Regular physical exercise, consistent sleep schedule with age-appropriate opportunity for adequate sleep duration, and moderation in caffeine intake also alleviate symptoms of RLS.[16]

key points

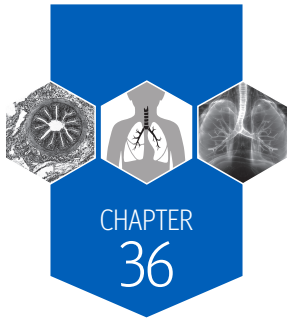
- Diagnosis of RLS depends on history, not on polysomnographic data.
- Polysomnographic evidence of periodic LMs can support RLS but should not be the sole basis for diagnosis.
- Signs and symptoms of PLMD occur during sleep; RLS symptoms occur during wake but can interfere with sleep onset.
- Expert consensus recommends iron supplementation as first-line treatment in pediatric RLS/PLMD. Serum ferritin levels should be maintained at 50 to 75 mcg/L (50–75 ng/mL).

Addressing anxiety via behavioral strategies or outpatient therapy may lessen sleep bruxism. Some evidence supports mandibular advancement in adolescents as treatment for sleep bruxism as well, and dental evaluation is advisable in any case.[23]

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Insomnia

Priya Prashad, MD, MSCE, DABSM

Insomnia is the inability to fall asleep or to stay asleep. It is often quite stressful to both affected children and youth and their parents. In young children, insomnia is defined as difficulty initiating and maintaining sleep, waking up earlier than desired, resistance going to bed on appropriate schedule, or difficulty sleeping without parent or caregiver intervention.

A number of classification systems have been proposed for insomnia. The *International Classification of Sleep Disorders, 3rd Edition (ICSD-3)* defines insomnia as "a repeated difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity and circumstances for sleep, and results in some form of daytime impairment." Short-term, chronic, and other types of insomnia are the three major categories according to the *ICSD-3*.[1]

The most detailed classification system is the older *International Classification of Sleep Disorders, 2nd Edition (ICSD-2).* The *ICSD-2* classification system categorizes 11 subtypes of insomnia.[2] This chapter will focus only on those subtypes that primarily affect children.

Major Categories of Insomnia

Short-term insomnia may last for several weeks or up to 3 months. It is usually caused by severe trauma such as moving, death, divorce, substance use or withdrawal, or other temporary stressors.[1]

Chronic insomnia is long-term insomnia that lasts more than 3 months and can be years or even decades.[1] It may be caused by medical or mental illness, long-term stress and anxiety, sleep-onset association disorders, bedtime refusal or fears, circadian rhythm disorders, or poor sleep hygiene.

Other Ways of Describing Insomnia

While the sleep disorder of insomnia is principally classified as either short-term or chronic, there are other terms that may be used to describe when the insomnia occurs during the night.

Sleep-onset insomnia, difficulty falling asleep at the beginning of the night, is commonly caused in pediatric patients by a sleep-onset association disorder, delayed sleep phase syndrome, or anxiety.[2] In adults, stress, anxiety, "not being able to turn one's mind off," going to bed too early when not sleepy, restless legs syndrome, sleeping in an uncomfortable bed, and a suboptimal sleep environment (eg, with noise or light) are typical underlying etiologies.[2]

Sleep maintenance insomnia is defined as repeated awakenings during the night with difficulty returning to sleep. The underlying causes are similar to those for sleep-onset insomnia, along with pain or illness.[2]

Terminal insomnia is awakening early in the morning and not being able to fall back to sleep when desired. This can be caused by poor sleep quality, an increased amount of light sleep, sleep-onset association disorder, or, commonly, anxiety or depression.[2] Older adults are most likely to experience this pattern of insomnia due to advanced sleep phase syndrome, but young children can be affected as well, especially if, when awakening early in the morning, they are allowed to return to sleep in their parents' bed.

Subtypes of Insomnia

The *ICSD-2* classifies insomnia into 11 categories, as follows[2]:

- Adjustment insomnia (acute insomnia)
- Psychophysiological insomnia (primary insomnia)
- Paradoxical insomnia
- Insomnia due to medical condition
- Insomnia due to mental disorder
- Insomnia due to drug or substance abuse
- Insomnia not due to substance or known physiologic condition, unspecified
- Inadequate sleep hygiene
- Idiopathic insomnia
- Behavioral insomnia of childhood (BIC)
- Primary sleep disorders causing insomnia

The main subtypes affecting children are (1) adjustment insomnia, (2) psychophysiological insomnia, (3) paradoxical insomnia, (4) insomnia due to medical condition, (5) insomnia due to mental disorder, (6) inadequate sleep hygiene, (7) idiopathic insomnia, and (8) behavioral insomnia of childhood.

Adjustment Insomnia

Adjustment insomnia is temporally associated with an identifiable stressor and expected to resolve.[2] Examples of common stressors affecting children are moving, death, divorce, illness, and disruption in learning due to the COVID-19 pandemic.

Psychophysiological Insomnia

For older children and adolescents, problems with initiating and maintaining sleep are typically described using the term *psychophysiological insomnia*.[2] This form of insomnia involves an excessive amount of anxiety and worry regarding sleep and sleeplessness. The individual's heightened anxiety about sleeping for a less-than-adequate amount of time makes falling asleep more challenging, which, in turn, makes sleep a more negative experience and may lead to a vicious cycle.[3]

Paradoxical Insomnia

Paradoxical insomnia is most often attributed to patients with behavioral or psychological aspects to their insomnia that have negative conditioning/associations with their usual sleeping locations. The complaint of severe insomnia occurs without evidence of objective sleep disturbance and without daytime impairment to the extent that would be suggested by the amount of sleep disturbance reported. The patient often reports little or no sleep on most nights.[2] These patients sleep better in the sleep laboratory or in a hotel than they usually do at home.[3]

Insomnia Due to Medical Condition

Common examples affecting children include obstructive sleep apnea, restless legs syndrome, eczema, asthma, allergies, gastroesophageal reflux, fibromyalgia, and medications.[2]

Insomnia Due to Mental Disorder

Insomnia due to mental disorder is characterized by the onset of the mental disorder and improves and worsens with the severity of the mental disorder.[2] Anxiety, depression, and stress are common examples that can sometimes affect even young children. Neurodevelopmental disorders such as autism spectrum disorder or attention-deficit/hyperactivity disorder may also play a role.

Inadequate Sleep Hygiene

Inadequate sleep hygiene for pediatric patients is characterized by irregular sleep and wake times, stimulating activities or caffeine near bedtime, or use of the bed for activities other than sleep.[2] For adolescents, this can include the use of electronic devices prior to sleep, doing homework or watching TV in bed, and going to bed and waking up much later on weekends than weekdays.

Idiopathic Insomnia

Idiopathic insomnia is insomnia present since infancy or childhood, which has no identifiable precipitant (insidious onset) and no period of sustained remission.[2]

Behavioral Insomnia of Childhood

By 3 to 6 months after birth, a term infant's circadian rhythms have matured to the point where they may begin to sleep through the night.[3] During the first 6 months of infancy, parents should begin to establish healthy sleep habits to prevent later sleep problems, such as exposing newborns to light and noise during the daytime but keeping the room dark and quiet at night, particularly when the baby wakes at night to feed.

One of the main sleep problems arising during the developmental period of 6 months to 2 years is difficulty with self-soothing. Bedtime problems and frequent night awakenings are highly prevalent in young children, occurring in 20% to 30% of infants, toddlers, and preschoolers.[4]

The classical description of BIC includes 3 subtypes.[4]

Sleep-onset association disorder occurs when children become dependent on specific associations (eg, rocking, feeding, parental presence, cuddling) to fall asleep. For example, if the child is used to being rocked to sleep, when they have a normal night waking on the conclusion of a sleep cycle, they are unable to fall back to sleep until the nighttime ritual is repeated (in this case, rocking and the presence of a parent). For older children, sleep-onset may be associated with watching television or using phones, tablets, or other electronics.

Limit-setting sleep disorder involves the refusal to go to bed or repeated requests used as attempts to delay bedtime (eg, asking to use the bathroom, one more story), and is common in young children. In these cases, parents demonstrate difficulties in adequately enforcing bedtime limits. Parents often have difficulties enforcing limits at other times of day as well.

Combined type involves a child having a negative association with sleep coupled with resistance or refusal to go to bed due to a lack of limit setting by caregivers. This can be particularly challenging for parents of children with developmental delay and of children with autism spectrum disorder.[5]

Differential Diagnosis

A referral to a sleep laboratory for a polysomnography study is not necessary to diagnose behavioral or psychophysiological insomnia, but may be needed if other primary sleep disorders such as sleep-related breathing disorders, narcolepsy, or periodic limb movement disorder are being considered. These

disorders may present similarly to insomnia as night awakenings or daytime sleepiness, especially in adults.[3]

Diagnostic Considerations

Health care providers should routinely ask parents and the child about sleep: regularity and duration of sleep, sleep-onset delay, night awakenings, symptoms of sleep-disordered breathing, and signs of increased daytime sleepiness or poor sleep quality. Actigraphy uses a wristwatch-like device to measure movement, from which sleep can be inferred, allowing for assessment of sleep-onset latency, wake after sleep onset, total sleep time, and sleep efficiency. It can be useful to guide the individualized diagnosis and treatment of insomnia. If actigraphy is unavailable, a 2-week sleep diary can provide similar information if the family is careful in filling it out. Consumer-oriented products are less reliable.

Management

Behavioral treatments and cognitive restructuring are the most appropriate first line of treatment for behavioral insomnia and psychophysiological insomnia. These interventions are based on principles of learning and behavior, including reinforcement. Primary goals typically involve some combination of developing positive sleep-related associations, establishing routines, and implementing relaxation skills.[5]

For behavioral insomnia, these interventions frequently rely on parent training to effect changes in the parent's behavior, which facilitate changes in the child's behavior.

For the treatment of sleep-onset association disorders, the associations are weaned slowly and gradually until the child is falling asleep and sleeping independently. Graduated extinction involves parents ignoring bedtime crying and tantrums for predetermined periods (5–15 minutes) before briefly checking on the child to facilitate self-soothing.[5] Limit setting with young children, 2 to 6 years of age, may involve limiting the number of times the child can make a request, whereas limit setting for school-aged children, 6 to 11 years of age, often revolves around how late the child can watch television, snack, do homework, or use the internet. A consistent bedtime routine and addressing nighttime fears can help reduce negative associations with sleep.

Interventions for the adolescent with inadequate sleep hygiene include education, incorporating relaxation strategies into a bedtime routine, sleep restriction (ie, limiting time in bed based on how long one actually sleeps), and using the bed only for sleep to create more positive associations with sleeping and a greater physiologic pressure for sleep. Avoiding light exposure when waking at night will prevent suppression of melatonin.

Cognitive behavioral therapy for insomnia is a highly effective and evidence-based approach consisting of cognitive restructuring (reshaping negative thought patterns), stimulus control (weakening association of being awake in bed), sleep restriction (gradually decreasing the amount of time spent in bed awake), and sleep hygiene (incorporating a bedtime routine and good sleep habits) therapies for psychophysiological insomnia in adolescents and adults.[3]

Hypnotic medications may provide rapid, short-term improvements to sleep problems in adults, but medications typically do not have long-term positive effects on sleep and patients often develop physiologic and psychologic dependence and tolerance.

There are no medications approved by the US Food & Drug administration for treatment of insomnia in children, and there are concerns about the safety and side effects of using these medications off-label. Children may develop physiologic and psychologic dependence and tolerance to over-the-counter sleep aids as well.[4]

Expected Outcomes/Prognosis

A growing body of literature suggests that behavioral interventions for childhood insomnia are effective. Behavioral interventions lead not only to improvements in children's sleep, but also to improvements in child behavior and parental well-being. Similarly, cognitive restructuring and behavior changes in childhood can lead to long-lasting improvements in the sleep of adolescents and adults.

A referral to a sleep medicine specialist may be needed for any persistent and complex cases, especially those that require pharmacotherapy or involve concerns for underlying sleep-breathing disorders. Behavioral insomnia in children with autism spectrum disorder, attention-deficit/hyperactivity disorder, and anxiety and mood disorders might warrant a referral to developmental pediatrics or neurology.[4] Referral to psychology or psychiatry may be needed if there is underlying anxiety or depression contributing to the insomnia in a child of any age.

Insomnia is most effectively treated on an outpatient basis with a customized treatment plan including parent training, cognitive behavioral therapy, and frequent follow-up.

Prevention

The best strategy for reducing sleep problems in infants and children is to educate parents to prevent sleep issues from starting. Newborns have a physiologic need to wake during the night to feed.[4] By 2 to 3 months, parents can start being aware of trying not to create adverse sleep associations (eg, putting the child to sleep when drowsy but without rocking or feeding). Sleep-onset

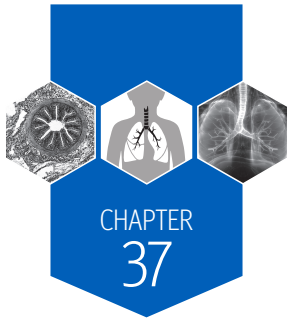
associations can be modified at any age, but it becomes more difficult and requires more time as the child grows older. Sleep hygiene plays an important role in virtually all sleep interventions and typically involves a combination of creating an environment that is conducive to sleep and engaging in healthy sleep habits in all ages. Educating adolescents, particularly on keeping regular schedules, limiting use of electronics at night, and not sleeping in excessively on weekends (more than 1 hour later than on weekdays), allows them an opportunity to consciously make informed choices about their sleep habits. Parents should be aware of the recommended amounts of sleep per age.[6]

key points

- Medication should rarely be the first option for the treatment of insomnia. If used, medication should always be combined with behavioral interventions and cognitive behavioral therapy.
- Behavioral strategies that are customized to the individual family situation have a higher chance of success than a "one model fits all" approach.

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Parasomnias

Priya Prashad, MD, MSCE, DABSM

Introduction

Parasomnias are undesirable physical events or experiences that occur during entry into sleep, within sleep, or during arousal from sleep. They may occur during non-rapid eye movement (NREM) sleep, rapid eye movement (REM) sleep, or transitions to and from sleep.[1]

Many parasomnias emerge and peak during the childhood years, the most common being the *arousal parasomnias:* confusional arousals, sleep terrors, nightmares, and somnambulism or sleepwalking.[1] Confusional arousals occur in 17.3% of children aged 3 to 13 years. Sleepwalking has an 18.3% lifetime prevalence, and sleep terrors are experienced by 1% to 6.5% of children and 2.2% of adults. Rarely, these continue to adulthood, but another group of rare parasomnias is only experienced by adults: REM behavior disorder, sleep-related eating disorder, and sexsomnia.[2]

Pathophysiology

The arousal parasomnias have similar predisposing characteristics and triggers, suggesting common pathophysiology. Parasomnias tend to be common in families, so there may be a genetic factor. A history of sleep-walking or sleep talking in other family members of a child experiencing parasomnias is common. Parasomnias may be triggered by increased arousals from sleep, including from underlying obstructive sleep apnea, restless legs syndrome, periodic limb movement disorder, or gastroesophageal reflux.[2] Other triggers can be any disruption to the person's normal sleep pattern, including sleep deprivation, fever and illness, travel, and sleeping in a new or unfamiliar environment. These disorders are most common in childhood, particularly the preschool age, and usually resolve by adolescence except for a rare few.

Clinical Features

Non-Rapid Eye Movement Sleep Disorders of Arousal

Disorders of arousal in NREM sleep result from an incomplete arousal and occur at the transition from deep NREM (stage N3) sleep into the lighter stages of NREM sleep or from stage N3 into the awake state. They are most prevalent during the first third of nocturnal sleep because N3 sleep is most prominent early in the night.[2] Since the events occur during deep N3 sleep, the child is oblivious to surroundings, is difficult to awaken, and has no memory of the event in the morning.

Confusional Arousals

Confusional arousals occur mainly in infants and toddlers and begin with whimpering or moaning, then evolve to calling out or crying. The child cries out words like "no" or "go away," appears distressed, and remains inconsolable. They may appear confused, with eyes open or closed, very agitated or even combative. Episodes may last 5 to 15 minutes before the child calms and returns to sleep. Reassuring comments in a soothing voice may help calm the child, but often parental presence or trying to wake the patient may prolong the episodes.

Sleep Terrors

Sleep terrors are more intense than confusional arousals. Episodes begin with a loud scream and an intense look of fear, mydriasis, sweating, and tachycardia; episodes can last several minutes.[2] The child is unaware of the caregiver's presence and will be confused and disoriented if awakened. As with confusional arousals, attempts to console the child may prolong or intensify the episode. Thrashing or other bodily movement is common, and the child tends not to remember the episode in the morning. Recording events with a video can be helpful for diagnosis. Sleep terrors usually self-resolve as the child grows older.

Somnambulism

Mild episodes of somnambulism, in which a toddler sits up and crawls around the bed or an older child walks to the bathroom, may initially go unnoticed. Some patients exhibit a combination of sleep terrors and sleepwalking, though one type usually predominates. Patients may be found walking into a parent's room, bathroom, or different parts of the house. They can negotiate obstacles and seem to be awake. A video can be helpful for diagnosis. Some patients have injured themselves by attempting to walk downstairs or climb through windows, or by leaving the house. As with other arousal disorders, sleepwalkers are unaware of the presence of other people. They are difficult to awaken and may be confused on arousal, but no harm will result from awakening them. The house should be made safe, with dangerous objects such as knives

locked away, and doors and windows secured. Tying a bell to the door of their room can alert the parents, who can gently guide the child back to bed.[2]

Increasing total sleep time by as little as half an hour a night and maintaining a regular sleep-wake schedule may decrease or prevent episodes. Anticipatory awakening about 15 to 20 minutes prior to the usual time of occurrence may modify the sleep state and prevent the event in some cases. A low dose of a benzodiazepine (eg, clonazepam) may be used to treat persistent, severe, and frequent episodes, but most cases do not require treatment with medication.[2]

Patients should be informed about the usually benign and self-limiting nature of parasomnias. Sleep quality and daytime function generally remain unaffected; the events do not lead to brain damage or cognitive problems. Similar to sleep terrors, symptoms usually will resolve as children grow older or reach puberty.[2,3]

Disorders of Rapid Eye Movement Sleep

Since REM sleep predominates during the final third of the night, these disorders generally occur in the early hours of the morning. Because muscle tone is inhibited during REM sleep, bodily movement is rare.[2]

Nightmares

Nightmares may be from an identifiable source such as a frightening movie or video game, but, more commonly, they come from unspecific fears. They tend to be more common in patients with a history of post-traumatic stress disorder and anxiety. There is little confusion or disorientation involved; the person is often able to recall clear details upon awakening. Management includes reassurance/comforting, treatment of underlying anxiety disorder if one exists, writing down the content or drawing pictures of the nightmare, and changing the ending to a more pleasant conclusion for recurring nightmares (imagery rehearsal).[2]

Rapid Eye Movement Behavior Disorder

REM behavior disorder is characterized by aggressive motor behavior as part of dream enactment that results from a loss of muscle atonia during REM sleep and may lead to injury.

REM behavior disorder occurs in less than 1 percent of adults (usually in men older than 50 years) and is even less common in children. Treatments include melatonin and benzodiazepines (such as clonazepam) and discontinuing medications known to exacerbate RBD (including selective serotonin reuptake inhibitors).[2]

Sleep Groaning/Catathrenia

Sleep groaning, or catathrenia, occurs during the exhalation phase in REM sleep. It is different from, but may be confused with, snoring, which occurs during inspiration.[4] A video of the events can be helpful, and a

polysomnogram may be supportive of a diagnosis of catathrenia. It is not typically noticed by the person producing the sound but can be disruptive to the family. In the few published cases, most patients, whether adult or pediatric, complained of daytime fatigue. In adult patients with catathrenia, decreased airflow, oxygen desaturation, arousals, and hypoventilation have been seen on polysomnograms. Nocturnal groaning/moaning, fatigue, disrupted and poor family sleep, morning grogginess, and behavioral problems were also associated with catathrenia.[4] Due to the rarity of this disorder, long-term effects and prognosis are largely unknown. There are no known anatomical underlying causes, including otolaryngologic or vocal cord abnormalities. Continuous positive airway pressure may be an effective treatment even if obstructive sleep apnea is not present.[5]

Sleep-Related Hallucinations

Patients see, hear, feel, or smell something that does not exist during sleep. Hallucinations that occur while falling asleep are called hypnagogic; those upon waking from REM sleep are called hypnopompic. They have a close association with sleep paralysis, somnambulism, and somniloquy. Narcolepsy, anxiety, and sleep deprivation can be underlying causes.[6]

NREM Parasomnias

Non-rapid eye movement parasomnias occur during partial arousals in slow-wave sleep.

Bruxism

Bruxism is an involuntary and forceful clenching, grinding, or rubbing of teeth during NREM sleep that can be associated with anxiety and some neurodevelopmental disorders. A dental evaluation can be helpful, especially if there is associated jaw pain. The patient, especially if older, can be fitted with a mouth guard to prevent grinding down of the teeth.[6]

Rhythmic Movement Disorder

Rhythmic movement disorders may manifest as headbanging, body rocking, or other movements. In some infants and toddlers, this starts at sleep onset and when attempting to fall back to sleep. These movement disorders are thought to be a form of self-soothing, and parents can be reassured that they generally resolve spontaneously by the age of 3 to 4 years.[7]

Nocturnal Enuresis

The possibility of obstructive sleep apnea should be considered in children presenting with nocturnal enuresis, particularly if they have one or more of the following: habitual snoring or observed apneas, obesity, adenotonsillar hypertrophy and/or mouth breathing, or secondary enuresis.[8] This improves with age, although about 3% of army recruits have been known to wet the

bed. Bell and pad devices can alert the child that enuresis is beginning. Medications such as imipramine have also been used.[8]

Sleep Paralysis

In sleep paralysis, atonia that normally occurs during REM sleep intrudes into wakefulness at sleep onset or when waking up. It may last for several seconds to minutes and may be terrifying. Consciousness is preserved as well as awareness of surroundings, but the person is unable to move and may feel pressure on the chest or experience hallucinations. Sleep paralysis is often associated with narcolepsy (see Chapter 38, Narcolepsy and Other Disorders of Excessive Somnolence), but a form known as *recurrent isolated sleep paralysis* can occur with anxiety and sleep deprivation.[8]

Sleep-Related Eating Disorder

Sleep-related eating disorder is characterized by recurrent episodes of involuntary binge eating after partial awakening from sleep in the absence of hunger or thirst. There is a partial or complete amnesia for eating episodes, a strong association with other parasomnias, and a high frequency of arousals from slow-wave sleep. Ingesting inedible materials is common, and sleep-related eating disorder may result in injuries from food preparation, weight gain, abnormal lipid levels, diabetes, and dental caries.[9] Sleep-related eating disorder is similar to somnambulism in that the patient is not really awake and has no recollection of the episodes. It is important to distinguish from night-eating syndrome, in which there is a period of insomnia prior to food intake and the patient is actually awake.

Sexsomnia

Sexsomnia encompasses behaviors that occur during sleep, including sexual intercourse, sexual assault, masturbation, sexual vocalizations, and fondling. These events can be increased with shift work, with use of selective serotonin reuptake inhibitors, and in patients with Parkinson disease.[10] Very rarely has a sexsomnia defense been successfully used in a case of sexual assault or abuse. Some studies have shown improvement with clonazepam or effectively treating underlying obstructive sleep apnea. Though sexsomnia is generally seen in adults, there have been a few reported cases of teenagers with this condition.

Kleine-Levin Syndrome

While both disorders are rare and intermittent, Kleine-Levin syndrome (KLS) is also characterized by cyclic episodes of hypersomnia, hyperphagia, hypersexuality, and cognitive or mood changes. The hypersexuality of KLS differs from sexsomnia because the former occurs during wakefulness.[11] When present, symptoms of KLS may persist for days, weeks, or even months, during which everyday activities cease.

Exploding Head Syndrome

A benign disorder that is characterized by the sensation of a sudden loud noise or explosive crashing sound that occurs during the transition from sleep onset or awakening, occurring daily to weekly. The episodes can wake the person up abruptly just as they are starting to fall asleep or begin to wake up.[12] They can be terrifying and accompanied by flashes of light or myoclonic jerks. Usually, treatment is not needed, other than reassurance.

Differential Diagnosis

Nocturnal seizures can mimic sleep terrors. Sleep terrors can be easily confused with nightmares. **Table 37-1** breaks down the differences between these 3 parasomnias.

Table 37-1. Differential Diagnosis of Parasomnias

Feature	Sleep Terrors	Nightmares	Nocturnal Seizures
Age of onset	Childhood	Childhood	Any age
Family history of similar events	Often present	Nonfamilial	May or may not be present
Time of occurrence	First one-third of night sleep	Final one-third of the night	Sleep onset
Frequency of events	Can be separated by weeks or months	Nightly or separated by weeks/months	Nightly
Most common sleep stage at occurrence	Slow-wave sleep	Rapid eye movement (REM) sleep	Stages I or II of non-rapid eye movement sleep
Duration of event	5–30 minutes	Less than 5 minutes	0.5 to 5 minutes
Description of events	Non-stereotypical movements	Little movement	Stereotypical movements
Post-event symptoms	None; no recollection of episode	Full alertness generally returns immediately upon awakening	Postictal symptoms: headache, extreme grogginess, hard to arouse, as well as incontinence of urine or stool
Electroencephalogram abnormalities	No	No	Yes
Structural central nervous system lesion	No	No	Possibly

Derived from Boursoulian LJ, Schenck CH, Mahowald MW, Lagrange AH. Differentiating parasomnias from nocturnal seizures. *J Clin Sleep Med.* 2012;8(1):108–112.

Indications for Polysomnography

Nocturnal polysomnography (PSG) is usually not needed in patients with arousal parasomnias. Indications for PSG include habitual snoring, observed apneas, daytime somnolence, behavioral problems, and mood disturbance, suggesting sleep fragmentation from underlying obstructive sleep apnea. Leg discomfort or involuntary jerking movements during sleep are suggestive of restless legs syndrome or periodic limb movements during sleep.[13] While restless legs syndrome usually occurs during wakefulness (see Chapter 35, Sleep-Related Movement Disorders), PSG may be useful to quantitate sleep fragmentation from periodic limb movements of sleep. Atypical features that raise concern for nocturnal seizures include daytime neurologic symptoms, highly stereotyped behaviors, older age group, multiple occurrences on a single night, and very frequent occurrences (eg, several nights each week). (See **Table 37-1**.) In this case, the polysomnogram should include extra electroencephalogram leads to better detect and qualify any seizures.[2]

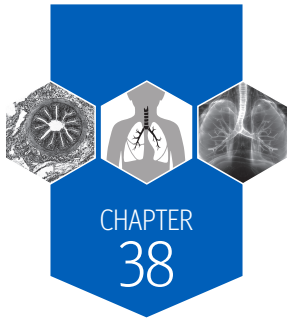
key points

- Asking the parent to video record the suspected parasomnia can be helpful in determining the diagnosis because patients may have no memory of the episodes or have difficulty articulating what they felt.
- Often, there is a history of sleepwalking or sleep talking in other family members of a child experiencing parasomnias.
- Medication can be helpful in severe or very frequent cases, but generally all that is needed is reassurance and/or regulation of the patient's sleep-wake schedule. Most parasomnias tend to improve by puberty.

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CHAPTER
38

Narcolepsy and Other Disorders of Excessive Somnolence

Nadav Traeger, MD, DABSM, FCCP, FAAP

Introduction

Excessive daytime somnolence (EDS) is the inability to stay awake or adequately alert during the time of the day when the person should not be asleep. Adequate alertness is important for good health, optimal academic and physical performance, and avoiding accidental injuries and motor vehicle crashes. Excessive daytime somnolence may manifest in various ways as reported by the patient or the parent/guardian: increased tendency to fall asleep, low energy or motivation, crankiness, moodiness, irritability, crying, hyperactivity, inattention, memory impairment, decreased school perfomance, behavioral problems, increased tendency for errors/accidents, excessively long night sleep, or persistence of naps past the age they should have been outgrown or recurrence of previously discontinued daytime napping.[1]

Etiology

The most common etiologies for EDS are

- Inadequate amount of sleep relative to the person's needs. This may be voluntary/purposeful (eg, to have more time for homework, sports, reading, socializing, watching TV) or because of an innate inability to fall asleep or stay asleep (insomnia).
- Disruption of sleep. This may be due to extrinsic/environmental factors (eg, light, noise) or intrinsic causes (eg, obstructive sleep apnea syndrome [OSAS] or other sleep disorders).
- Inappropriate timing of sleep, as may occur with jet lag or in teens whose internal clock is out of synch with conventional time.

Less common, but often underdiagnosed, are central disorders of hypersomnolence. This group of disorders encompasses clinical situations in which the primary manifestation of EDS is not due to disrupted nocturnal sleep (eg, from OSAS) or circadian rhythm misalignment. These include insufficient sleep syndrome and narcolepsy (discussed in the following text), as well as idiopathic hypersomnia, Kleine-Levin Syndrome, hypersomnia due to a medical disorder, hypersomnia due to a medication or substance, and hypersomnia associated with a psychiatric disorder. In as much as it is possible, it is important to reach an accurate diagnosis of the etiology of the EDS to be able to choose the most appropriate therapy. Many conditions produce sleepiness and can mimic, and often coexist with, a hypersomnia of central origin. These include OSAS, periodic limb movements, insufficient sleep, psychiatric disorders, sedating medications, and circadian rhythm disorders. Once properly identified, such a primary or concomitant disorder should be treated with specific interventions, including the use of central nervous system (CNS) stimulants, if needed.

The overall prevalence of EDS in the pediatric population is not accurately known, with one study reporting that it was a complaint in 14% of the children at 2 general pediatric clinics.[2]

Diagnostic Tests

The evaluation of a child presenting with EDS centers on a thorough sleep history. This should include the child's sleep habits: the typical time the child gets into bed, falls asleep, and wakes up. From this information, the clinician can estimate the typical amount of sleep obtained by the patient and then compare that to what is typical for age (see **Box 38-1**).

Box 38-1

Recommended Amounts of Sleep for Pediatric Populations

The American Academy of Sleep Medicine Consensus Statement on Recommended Amount of Sleep for Pediatric Populations (endorsed by the American Academy of Pediatrics) states the following amounts of sleep should be obtained per 24 hours on a regular basis to promote optimal health:

- **Infants aged 4 months to 12 months: 12 to 16 hours (including naps)**
- **Children aged 1 to 2 years: 11 to 14 hours (including naps)**
- **Children aged 3 to 5 years: 10 to 13 hours (including naps)**
- **Children aged 6 to 12 years: 9 to 12 hours**
- **Teenagers aged 13 to 18 years: 8 to 10 hours**

Derived from Paruthi S, Brooks LJ, D'Ambrosio C, et al. Recommended amount of sleep for pediatric populations: a Consensus Statement of the American Academy of Sleep Medicine. *J Clin Sleep Med.* 2016;12(6):785–786.

A more accurate assessment can be obtained with sleep diaries and with actigraphy devices. Consumer sleep technologies, including wearable devices, may allow for meaningful conversations with patients and increase active participation in their health care, but data regarding the validity and accuracy of such devices are currently lacking.[3,4] The bedtime routine should be evaluated for behaviors or activities, on the part of both the patient and the parent/guardian, that may be contributing to difficulty with initiation or maintenance of sleep. Questions regarding the sleep environment should be targeted toward factors that would make it less conducive to sleep (ideally the bedroom should be dark, quiet, and comfortably cool [23.8˚C (<75˚F)]). Inquire if there are alerting activities that are performed in bed (eg, using electronics, reading, homework, eating) during any part of the day. Ask about symptoms that are specific for sleep disorders (eg, snoring, difficulty falling asleep or staying asleep, narcolepsy symptoms). If there are such symptoms, then further investigation should be directed towards them, such as performing an overnight polysomnogram (sleep study) or referral to a pediatric sleep medicine specialist as clinically indicated. The medical history should be explored for conditions and medications that may interfere with sleep or directly cause excessive somnolence. Screening for psychiatric disorders, as well as substance use, is also indicated because many of these involve sleep disturbances. The severity of daytime sleepiness can be quantified subjectively using tools such as the modified (pediatric) Epworth Sleepiness Scale (**Box 38-2**), which can be completed by the patient or the caregiver.

A diagnostic polysomnogram is indicated if there is clinical suspicion that the daytime sleepiness is due to OSAS or narcolepsy. The former would be the case if the daytime sleepiness is accompanied by habitual snoring, observed apneas, or labored breathing during sleep. The determination of whether an individual has isolated (benign) snoring or OSAS cannot reliably be made clinically but should be based on a polysomnogram.[1] A polysomnogram may also be indicated in the absence of these respiratory symptoms if the patient has a medical condition such as obesity, craniofacial anomalies, certain genetic syndromes, or neuromuscular disease, since these would place the patient at a particularly high risk for having OSAS and/or obesity hypoventilation. If narcolepsy is suspected, a multiple sleep latency test (MSLT) should be performed in the daytime following the polysomnogram.

While restless legs syndrome is a clinical diagnosis, at times an overnight polysomnogram is performed to obtain supportive evidence in the form of an elevated Periodic Limb Movement Index.[1,5]

A MSLT is indicated if there is clinical suspicion for the diagnosis of narcolepsy or idiopathic hypersomnia, or if there is a specific clinical need to objectively measure the severity of the daytime sleepiness.[1,6] Clinicians should keep in mind that these various measures of daytime sleepiness (history, questionnaires, MSLT) do not always correlate with each other and must be used with appropriate clinical judgment.[1]

Box 38-2

The Epworth Sleepiness Scale (for ages 4 years and up).

How likely is your child to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times. Even if your child has not done some of these things recently, try to work out how the situation would have affected them. Use the following scale to choose the most appropriate number for each situation:

0 = No chance of dozing

1 = Slight chance of dozing

2 = Moderate chance of dozing

3 = High chance of dozing

Situation Chance of Dozing:

Sitting and reading (or during storytelling): _____

Watching TV: _____

Sitting inactive in a public place (eg, a movie theater): _____

As a passenger in a car for an hour without a break: _____

Lying down to rest in the afternoon: _____

Sitting and talking to someone: _____

Sitting quietly after lunch (eg, in class): _____

In a car, while stopped for a few minutes in traffic: _____

Total: _____

A total score of ≥ 10 is considered to be abnormal.

From Melendres MC, Lutz JM, Rubin ED, Marcus CL. Daytime sleepiness and hyperactivity in children with suspected sleep-disordered breathing. *Pediatrics.* 2004;114(3):768–775.

Treatment

Treatment strategies should be directed at the underlying etiology. For those who have insufficient sleep, increase the amount of sleep. This may be as simple as increasing the time in bed (more opportunity for sleep) or may involve treatment of underlying insomnia. (See Chapter 36, Insomnia.) Habits or environmental factors that may be interfering with getting a good night's sleep should be corrected. OSAS, if present, should be treated. (See Chapter 33, Obstructive Sleep Apnea Syndrome) If the EDS seems to be caused by a medication, then it should be stopped or switched to a nonsedating alternative, if permitted by clinical circumstances. Psychiatric disorders and substance use should be addressed.

Insufficient Sleep Syndrome

Insufficient sleep syndrome is the most common entity among central disorders of hypersomnolence[7] and is basically chronic volitional sleep restriction. Individuals with this syndrome show excessive daytime sleepiness, fatigue, and reduced sleep at night as a result of electing overly demanding daytime schedules or by volitionally delaying sleep to engage in desired workplace, recreational, or social activities.[8] However, when allowing themselves sufficient time to sleep, these individuals are able to initiate and maintain sleep easily and for a normal duration.[9] This is in contrast to those with chronic insomnia disorder, who tend to have excessive wake time and reduced sleep time despite routinely allotting sufficient time to sleep.[10] Moreover, chronic insomnia disorder is not typically associated with excessive daytime sleepiness and unintentional daytime sleep episodes, which are often observed in those with patterns of volitional sleep restriction.[8] Insufficient sleep syndrome is usually apparent on viewing a sleep diary or on actigraphy, and a polysomnogram is rarely needed.

Narcolepsy

Clinical Manifestations

Narcolepsy in childhood is under-recognized and underdiagnosed, often mistaken for behavioral or mood disorders. Narcolepsy is characterized by excessive daytime sleepiness and symptoms of rapid eye movement (REM, stage R) sleep dissociation, meaning that there is intrusion of REM sleep into wakefulness. There are 2 diagnostic subtypes: narcolepsy type 1 (with cataplexy) and type 2 (without cataplexy).[1]

The main symptoms of narcolepsy are cataplexy, excessive daytime sleepiness, hypnogogic or hypnopompic hallucinations, sleep paralysis, and sleep disruption. The presence of cataplexy is specific and diagnostic for narcolepsy type 1, while the other symptoms can also occur with other sleep disorders,

or even in normal healthy people. The body is relatively atonic during stage R sleep, which is when dreams occur. Cataplexy is the intrusion of this aspect of stage R sleep into wakefulness, resulting in recurrent episodes of loss of muscle tone without loss of consciousness. These are generally sudden, brief (< 2 minutes), and bilaterally symmetrical. The paralysis usually evolves gradually, first affecting the face and neck and then progressing to the trunk and limbs. Respiratory muscles are not involved, but some patients may feel a sensation of dyspnea. Positive motor events (eg, muscle twitching or small jerks, especially of facial muscles) are not uncommon. There is great interpersonal variation in severity and triggers. While some patients with narcolepsy have multiple attacks per day, some have them less than once a month. The degree of muscle weakness can range from very subtle (unsteady gait or drooping of eyelids, jaw, or shoulders that may not even be noticeable to others) to dramatic (generalized muscle atonia with collapsing to the ground). The typical trigger is a strong positive emotion (eg, laughter, surprise), but negative emotions (eg, anger) can also induce an episode. Cataplexy is triggered only by laughter for some patients, while others may have multiple emotional triggers, and sometimes there is no clear relation to emotions.[1,11]

Excessive daytime somnolence is the most common and often the most debilitating symptom that occurs in individuals with narcolepsy. It is also the least specific symptom, as evidenced by the long list of potential etiologies detailed in the previous text. Patients with narcolepsy typically experience repeated daily episodes of unintentional lapses into sleep. Unlike patients with other sleep disorders (eg, OSAS), patients with narcolepsy typically wake up feeling relatively refreshed after a full night's sleep or a brief nap but then begin to feel sleepy again after variable times (perhaps 1–2 hours), especially when sedentary. Be mindful that, as detailed above, sleepy children can have seemingly paradoxical symptoms that appear more typical of mood or behavioral disorders.[1,11]

The other 2 symptoms, hallucinations and sleep paralysis, are also not specific for narcolepsy. In both of these situations, stage R sleep phenomena (dreaming and muscle atonia) intrude into wakefulness. The hallucinations are vivid, dreamlike experiences (visual, auditory, and/or tactile) that occur during transition between wake and sleep. They may be frightening and involve the perception that there is someone or something in the room. They may occur upon falling asleep (hypnagogic hallucinations) or upon waking (hypnopompic hallucinations). Unlike psychotic episodes, these rarely involve complex auditory hallucinations or fixed delusions. Such hallucinations are estimated to occur in about 20% of the general population.

Sleep paralysis is the temporary inability to move the body's voluntary muscles occurring during the transition between wake and sleep. During these episodes, the person is awake and conscious but is unable to move at all (including limbs or sometimes even opening the eyes). Episodes may last for a couple of minutes, can be very frightening, and may also include a sensation of dyspnea because the accessory respiratory muscles can be affected (yet breathing will continue because the diaphragm, an involuntary muscle, remains unaffected).[1] The reported prevalence of sleep paralysis among people with narcolepsy varies from about a quarter[12,13] to about two-thirds.[14,15] In comparison, the lifetime prevalence of at least one episode of sleep paralysis is 7.6% of the general population, 28.3% of college students, and 31.9% of psychiatric patients.[16]

Etiology

Narcolepsy type 1 is caused by a deficiency in CNS hypocretin (also known as orexin), most likely caused by a selective loss of hypothalamic hypocretin-producing neurons.[11] A strong association with certain human leukocyte antigen (HLA) subtypes (DR2/DRB1*1501, DQB1*0602) suggests the involvement of an autoimmune process in the destruction of these hypocretin-releasing brain regions.[17] The specific triggering event is unknown, with varying lines of evidence implicating various environmental factors such as trauma or infections (including β-hemolytic streptococcus and viruses such as influenza) and, in rare instances, also physical damage resulting from strokes, trauma, tumors, and neurologic disease.[11] The genetic and environmental factors associated with narcolepsy type 2 are unknown.[11,18]

Epidemiology

Narcolepsy type 1 occurs in 0.02% to 0.18% of people in the United States.[19] The prevalence of narcolepsy type 2 is more uncertain but is thought to represent a minority (about 15% to 25%) of the total population of patients with narcolepsy.[1] Both sexes are affected, with a slight preponderance of males.[1] Typically, the age of onset is between 10 and 20 years[11] (only rarely prior to age 4 years[20]), but the diagnosis may not be made for decades after symptom onset.

Diagnostic Tests

Multiple Sleep Latency Test

An overnight polysomnogram followed the next morning by an MSLT test is indicated if there is clinical suspicion for the diagnosis of narcolepsy.[1,21] The MSLT is a validated tool used to obtain an objective measure of sleepiness and evaluate for the emergence of REM sleep during even brief periods of sleep. It is based on the premise that the sleepier the patient, the faster they will fall asleep. During the MSLT, a patient in the sleep laboratory is given 5 nap

opportunities at 2-hour intervals starting 1.5 to 3 hours after the end of the nocturnal polysomnogram.[6] The patient is given 20 minutes to fall asleep, and 20 minutes after sleep onset to achieve REM sleep. An MSLT with a mean sleep latency of 8 minutes or less and 2 or more sleep-onset REM periods is needed for the diagnosis of narcolepsy.

Cerebrospinal Fluid Hypocretin-1

The diagnosis of narcolepsy type 1 can also be established if cerebrospinal fluid (CSF) hypocretin-1 concentrations, as measured by immunoreactivity, are either at or below 110 pg/mL or less than one-third of normal for that specific assay. The measurement of CSF hypocretin-1 is not needed for the diagnosis of narcolepsy type 2, but, if performed, it needs to be either greater than 110 pg/mL or greater than one-third of normal for that specific assay.

Genetic Analysis

Genetic analysis has some limited utility in the diagnosis of narcolepsy. Approximately 12% to 38% of the general population carries the DQB1*0602 genotype. This subset of the population includes virtually all individuals with narcolepsy type 1; thus, a negative HLA test would make the diagnosis of narcolepsy type 1 exceedingly unlikely. Negative HLA testing would also be predictive of normal CSF hypocretin-1 concentrations. Human leukocyte antigen testing is not generally helpful in the evaluation of narcolepsy type 2, since about 45% of affected individuals are positive for the DQB1*0602 genotype.

Treatment of Narcolepsy

Narcolepsy is treated with medication as well as lifestyle/behavioral approaches. Addressing the excessive daytime sleepiness is important because it can negatively impact quality of life, socializing, performance at school or work, and patient safety (in everyday situations as well as vocational activities where drowsiness/inattention may cause injuries to self or others). The other narcolepsy symptoms (cataplexy, hypnagogic hallucinations, sleep paralysis, and disrupted nocturnal sleep) are likewise treated if bothersome to the patient. There is some inherent trial and error in the process of picking the appropriate medication and dose for any given patient. Furthermore, due to fluctuations in symptom severity, it is quite common to have a need to change medications and dosing over time.

Medications

Medications for the treatment of narcolepsy have traditionally fallen into one of 2 categories: CNS stimulants (which are used to treat the EDS) and CNS neuromodulator agents (which are used to treat cataplexy and other symptoms[22]), but there have been recent additions that can address both of these symptom categories. Factors to contemplate when considering these medications include efficacy, adverse effects, convenience of administration,

abuse potential, comorbid conditions, and coverage by individual health insurance plans. Patients may require a combination of medications to adequately control their symptoms.

Stimulants/Wake-Promoting Medications

Stimulants can be used to counteract EDS.[22] These medications are taken during the daytime and are used to promote wakefulness and alertness. These include amphetamine, methamphetamine, dextroamphetamine, methylphenidate, and solriamfetol.[23,24] The exact mechanism of action of modafinil and armodafinil is unknown, while the others work by increasing/stimulating CNS dopamine and norepinephrine.[23,24] Modafinil and armodafinil have less abuse potential as compared to the stimulants. Modafinil and armodafinil can lower the efficacy of hormonal birth control, so patients should be advised to take a higher dose and consider adding an alternate form of contraceptive (eg, barrier method).

Other Neuromodulator Agents

Medications taken to treat the non-EDS symptoms, especially cataplexy, include tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, and dopamine and norepinephrine reuptake inhibitors.[22–24] These medications are taken during the daytime.

Oxybates

The 2 medications in the oxybate class are sodium oxybate and a newer, lower sodium version of a mixture of calcium, magnesium, potassium, and sodium oxybates. Both are approved by the FDA for the treatment of EDS as well as cataplexy in patients 7 years and older. These medications are taken at night in 2 divided doses: the first is taken at bedtime and the second is taken 2.5 to 4 hours later (during a naturally occurring awakening or via alarm). The exact mechanism of action is unknown but seems to be via stimulation of CNS $GABA_B$ receptors.[23,24] The active ingredient of these is a form of γ-hydroxybutyrate, which raises concerns regarding misuse; thus, in the United States, it is only dispensed from a single centralized certified pharmacy.

Histamine Agonist

Pitolisant is currently the only medication in this class. It is a histamine-3 (H3) receptor antagonist/inverse agonist,[23,24] and it is assumed that it works by increasing CNS levels of histamine, as well as other wake-promoting neurotransmitters (acetylcholine, dopamine, norepinephrine),[24] although the exact mechanism of action is unknown. It is currently approved by the FDA for the treatment of both EDS and cataplexy in adults. This medication is taken as a once-daily dose in the morning. Like modafinil and armodafinil, pitolisant does not seem to have misuse potential and carries the same warning regarding hormonal contraceptives.

Non-pharmacologic Remedies for Narcolepsy

Good sleep habits are important for everyone, and especially those with hypersomnia, to improve sleep quantity and quality. Patients should be encouraged to go to sleep and wake up at the same time every day, including weekends. Regular exercise at least 4 hours prior to bedtime can improve daytime alertness and improve sleep at night. Caffeine, alcohol, and nicotine should be avoided since these substances interfere with nocturnal sleep. There is specific concern about use of alcohol (and other CNS depressants) in conjunction with taking oxybates.

Two to 3 short (15–20 minutes), planned daily naps at strategic times during the day may be refreshing, reduce sleepiness for a few hours, and prevent unplanned lapses into sleep.[23] The combination of regular bedtimes and two 15-minute regularly scheduled naps reduced unscheduled daytime sleep episodes and sleepiness when compared to stimulant therapy alone.[22] Naps that exceed 30 minutes may be unrefreshing and result in increased drowsiness. Schools are usually cooperative in scheduling later start times and a study hall for nap purposes once the diagnosis is explained to them.

All patients with narcolepsy and other etiologies of severe EDS are at increased risk of accidental injury and death related to occupational and recreational activities, especially driving. They should be counseled about avoiding or taking precautions when performing activities (eg, driving, operating machinery) that would be dangerous if a sleep attack was to occur.

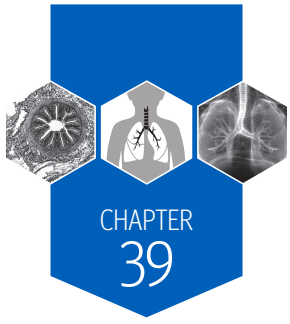
Other options to consider on an individualized basis are cognitive behavioral therapy, support in planning school/work, peer support, and psychological counseling.

key points

- Excessive daytime somnolence can cause a variety of symptoms and can have a profound effect on a person's health and quality of life.
- There are several causes of EDS, and the etiology can usually be identified with a good clinical history, a physical examination, and sometimes testing.
- Identifying the etiology of the EDS will direct the clinician to the appropriate treatment.

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Sudden Infant Death Syndrome and Brief, Resolved, Unexplained Events

Zarmina Ehsan, MD, FAAP

Introduction

Brief, resolved, unexplained events (BRUEs) are relatively common occurrences among newborns and infants. They encompass a broad range of presentations that may be attributable to a variety of underlying medical diagnoses with variable prognoses. Most infants and young children with BRUEs present in urgent care settings (emergency department and hospital), but primary care providers and pulmonologists will often be involved in both acute evaluation and long-term management. As such, the role of these providers is to (1) determine whether and what testing is needed and (2) observe the infant/child long-term.

The term *apparent life-threatening event (ALTE)* was introduced in 1986 to replace the term *near-miss SIDS* since there was no good evidence that these events were, in fact, precursors to sudden infant death syndrome (SIDS). A National Institutes of Health Consensus Conference on Infantile Apnea defined ALTE as an episode frightening to an observer that involved a combination of apnea (central or obstructive), color change (cyanosis, pallor, or plethora), marked change in muscle tone (usually limpness), and choking or gagging.[1] The American Academy of Pediatrics (AAP) suggested in 2016 that the term ALTE be replaced by BRUE when certain criteria are met.[2] BRUE is the preferred term referring to an event involving infants less than 1 year of age, when the event is characterized by the observer as sudden, brief (lasting <1 minute, although typically 20–30 seconds), and resolved (infant has returned to baseline state of health after the event) and "with a reassuring history, physical examination, and vital signs at the time of clinical evaluation by trained medical providers."[2] Events are typically characterized by (1) cyanosis or pallor, (2) absent, decreased, or irregular breathing, (3) marked change in tone (hypertonia or hypotonia), and/or (4) altered responsiveness. BRUE should not be diagnosed unless the event is unexplained (ie, there is no etiology determined for a qualifying event following a history and physical

examination). Infants who present with a BRUE are further categorized as lower vs higher risk based on risk of recurrence and/or presence of a serious underlying medical condition (**Figure 39-1**). These criteria have been shown to have an excellent negative predictive value for a high-risk BRUE of 90% but a poor positive predictive value of only 23%.[3] Because BRUE may be caused by a wide variety of unrelated underlying disease states, the comprehensive evaluation and subsequent management of high-risk infants can be challenging.

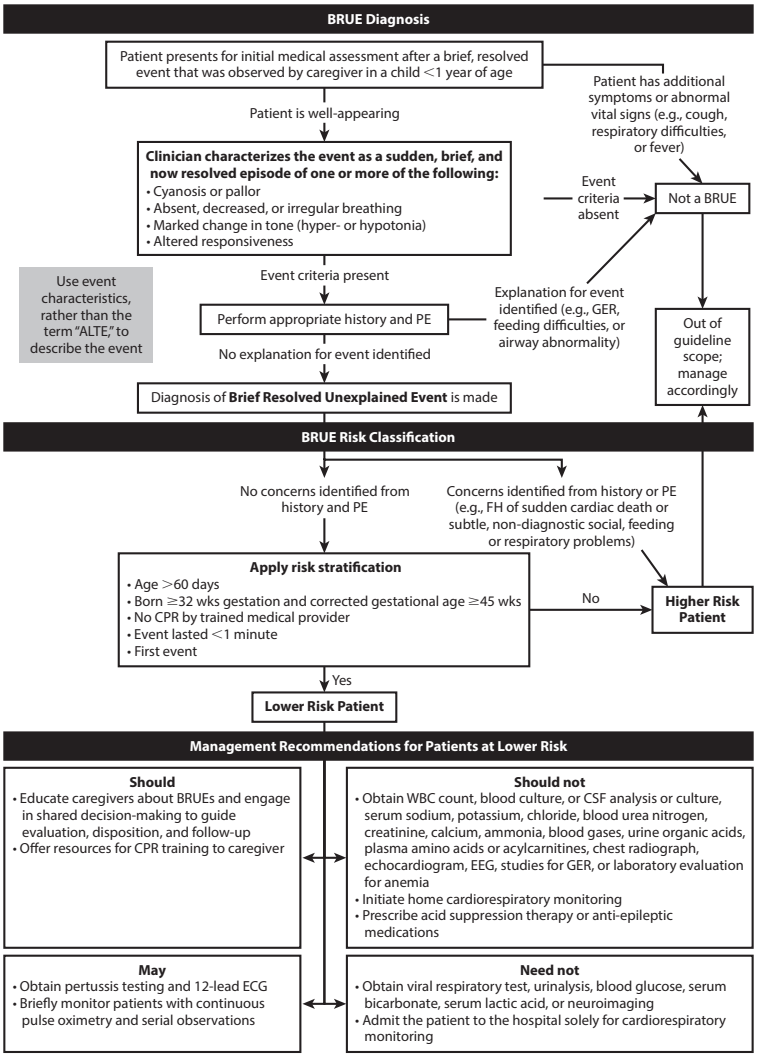


Figure 39–1. Diagnosis, risk classification, and recommended management of a brief, resolved, unexplained event. CSF, cerebrospinal fluid; FH, family history; PE, physical examination; WBC, white blood cell.

From Tieder JS, Bonkowski JL, Etzel RA, et al. Brief resolved unexplained events (formerly apparent life-threatening events) and evaluation of lower-risk infants. *Pediatrics*. 2016;137(5):e20160590.

Sudden infant death syndrome (SIDS) is the sudden death of an infant younger than 1 year of age that cannot be explained even after a full investigation that includes a complete autopsy, examination of the death scene, and review of the clinical history.[4] Currently, SIDS is classified under the umbrella term *sudden unexpected infant death (SUID),* which includes SIDS, accidental suffocation in a sleeping environment, and other deaths from unknown causes. The breakdown for SUID has been reported as 38.7% SIDS, 24.3% suffocation, and 37% unknown.[5] The rate of SIDS has declined considerably in the United States, from 130.3 deaths per 100,000 live births in 1990 to 35.2 deaths per 100,000 live births in 2018, primarily following the National Institutes of Health "Back to Sleep" campaign (later renamed the "Safe to Sleep" campaign) promoting safe infant sleep.[5] Nevertheless, in 2018, there were still about 1,300 deaths due to SIDS with significant racial and ethnic differences. American Indians, Alaska Natives, and non-Hispanic Black Americans have a far higher rate of SUID than non-Hispanic white Americans (**Figure 39-2**); it is not clear whether the origin of these disparities lies in environmental, socioeconomic, or other factors.

Independent risk factors for SIDS include young maternal age, sleeping on a soft surface, maternal smoking during pregnancy, preterm birth/low birth weight, and prone sleeping position.[6]

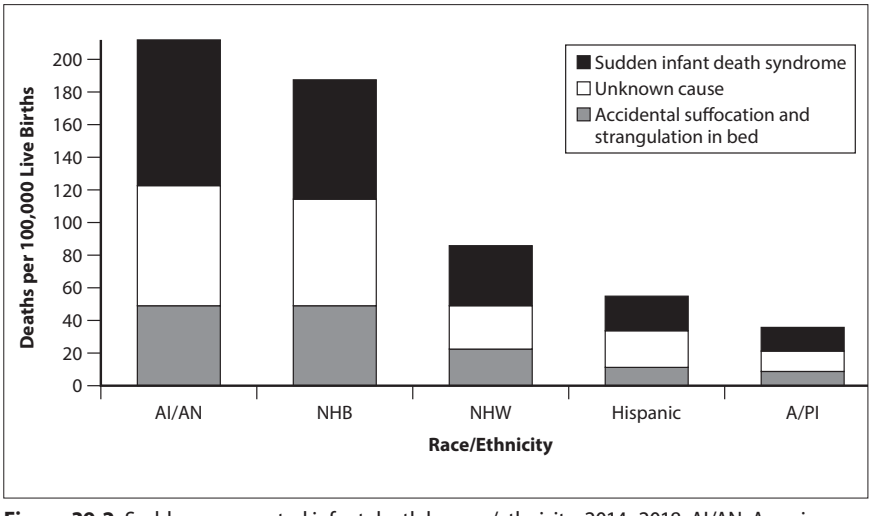


Figure 39-2. Sudden unexpected infant death by race/ethnicity, 2014–2018. AI/AN, American Indian/Alaska Native; NHB, non-Hispanic Black; NHW, non-Hispanic white; A/PI, Asian/Pacific Islander.

From Centers for Disease Control and Prevention. Sudden Unexpected Infant Death and Sudden Infant Death Syndrome: Data and Statistics. https://www.cdc.gov/sids/data.htm. Updated April 28, 2021. Accessed February 10, 2022.

Data source: Centers for Disease Control and Prevention (CDC)/National Center for Health Statistics, National Vital Statistics System, Period Linked Birth/Infant Death Data. Rates calculated via CDC WONDER using latest available data by subpopulation (2018).

Of note, a link between ALTE and SIDS has not been proven. There are not yet good data on any relationship between BRUE and SIDS. Whereas earlier studies suggested that infants presenting with ALTE or those with reduced heart rate variability were at high risk of SIDS, more recent studies reveal that SIDS cannot be predicted in an individual based on a history of apnea or "abnormal" cardiorespiratory events. Most infants who die from SIDS have no known predisposing causes, and few infants with ALTEs will die from SIDS.[7–10]

Epidemiology

Prevalence estimates for BRUE are difficult to ascertain given the variability in classification and heterogeneous nature of clinical presentation and ultimate diagnoses. Available literature suggests that the incidence of ALTE in the United States is 0.6 to 2.46 per 1,000 live births and represents 0.6% to 0.8% of all emergency visits for children less than age 1 year.[11,12] Recent literature suggests that 20% to 40% of infants with ALTE also meet criteria for BRUE.[12] The median age of infants who present with an ALTE has been reported as 6 to 8 weeks of age with equal sex distribution.[12–17] Risk factors described in infants with ALTE or BRUE are feeding difficulties, symptoms of a prior respiratory illness, infants under 2 months of age, history of a previous episode, premature birth, low birth weight, and maternal smoking.[15–18] Twelve percent to 14% of infants presenting with an ALTE will have symptoms significant enough to warrant hospitalization (particularly those with multiple ALTEs within the preceding 24 hours or those aged $\leq$1 month).[19] As opposed to SIDS, which has a higher incidence in the winter months, BRUE does not have a seasonal variation. The incidence of SIDS peaks at 1 to 4 months of age and rapidly decreases after that.

Pathophysiology

BRUE represents a chief complaint rather than a diagnosis and is, by definition, not explained by an underlying disease process. However, dysfunction in a diverse group of organ systems may be associated with BRUE. These include respiratory infections, non-accidental trauma, cardiac disease, gastrointestinal disorders (including gastroesophageal reflux and dysphagia), central nervous system disorders, and metabolic disorders.[18] Evaluation for these disorders associated with higher-risk BRUE is discussed in the following text.

Clinical Features

By definition, BRUEs are events not explained by underlying pathophysiology or disease processes, and there are no clinical features commonly associated with or unique to ALTE or BRUE. The inclusion and exclusion criteria for BRUE are listed in **Table 39-1**. Evaluation of infants with BRUE should include a comprehensive history and thorough physical examination aimed at identifying potential underlying causes of the event. History should ideally be obtained from a caregiver witness or medical first responder. A complete physical examination is necessary with a particular focus on signs of non-accidental trauma. This information will enable the provider to categorize infants into lower- and higher-risk groups (**Table 39-2**). Concerning findings may include historical features such as loss of consciousness, need for cardio-pulmonary resuscitation, evidence of trauma, history of similar events, family history of unexplained infant deaths, concern for non-accidental trauma, or an underlying known or suspected genetic syndrome or examination findings such as lethargy or toxic appearance.

Table 39-1. Brief, Resolved, Unexplained Events (BRUEs) Definition and Inclusion/ Exclusion Criteria

BRUE Clinical Features	Inclusion	Exclusion
Brief, resolved	Duration < 1 min Infant returned to baseline, normal vital signs and appearance. "Well appearing."	Duration ≥ 1 min Abnormal vital signs and/or appearance. Not "well appearing."
Unexplained	No identifiable medical condition.	Event or PE consistent with a medical diagnosis (eg, GER, child abuse).
Event characterization by observer	1. Central cyanosis or pallor. 2. Absent, decreased, or irregular breathing. 3. Marked change in tone (hypotonia or hypertonia). 4. Altered responsiveness.	1. Acrocyanosis, perioral cyanosis or rubor. 2. Periodic breathing of the newborn or breath-holding spell. 3. Tone changes associated with underlying medical condition (GER, seizures). 4. Loss of consciousness.

PE, physical examination; GER, gastroesophageal reflux.

Table 39–2. Characteristics of Lower-Risk vs Higher-Risk Brief, Resolved, Unexplained Events (BRUEs)

Lower-Risk BRUE	Higher-Risk BRUE
Age > 60 days	Age < 60 days
Gestational age ≥ 32 weeks (≥ 45 weeks post conceptual age)	Gestational age < 32 weeks (< 45 weeks post conceptual age)
First BRUE (no previous BRUE and not occurring in clusters)	Recurrent event or occurring in clusters
Duration < 1 minute	Duration ≥ 1 minute
No CPR by trained medical provider	CPR required by trained medical provider
No concerning historical features	Concerning historical features
No concerning physical examination findings	Concerning physical examination findings

CPR, cardiopulmonary resuscitation.

Adapted from Merritt JL, Quinonez RA, Bonkowski JL. A framework for evaluation of the higher-risk infant after a brief, resolved, unexplained event. *Pediatrics*. 2019;144(2):e20184101.

Diagnosis

The diagnosis of BRUE is based on documentation of an event meeting criteria for inclusion and exclusion of other underlying potential causes. Once a diagnosis has been established, BRUEs are classified as lower risk or higher risk. The basic questions are (1) Did something really happen, or did the parent misinterpret something normal? and (2) What was the cause of the event? The Collaborative Home Infant Monitoring Evaluation (CHIME) study showed that even normal, healthy newborns may have central apneas for as long as 30 seconds.[9] The purpose of a hospitalization is to evaluate the patient for a treatable cause of the event; one cannot "rule out apnea."

Management

There is no evidence to support routine hospitalization of all patients with BRUE. The decision to hospitalize infants should be guided by the findings during the initial assessment and categorization as lower vs higher risk. Infants presenting with lower-risk BRUE may not require hospitalization. Those classified as higher-risk BRUE require further evaluation and management tailored to their history and physical examination findings. The AAP has endorsed specific evaluation and management algorithms for lower-risk patients; suggestions for management of high-risk patients were published as a research paper.[2,19] Although studies are limited and evidence has evolved since the introduction of the term BRUE, a specific cause for the event may be identified in about 50% of infants presenting with ALTE (before BRUE was coined).[17,18]

Lower-Risk BRUE

Little intervention, other than reassurance, is typically required for lower-risk infants (those who are asymptomatic and well appearing). The AAP recommends against additional testing, hospital admission, or home cardiorespiratory monitoring for these infants.[2] Training of caregivers in cardiopulmonary resuscitation and close follow-up as an outpatient is warranted. Additionally, providers are encouraged to educate the family that there is no known association between lower-risk BRUE and SIDS and use this opportunity to reinforce safe sleep practices.[20]

Higher-Risk BRUE

Infants who do not meet criteria for lower-risk BRUE require additional evaluation. Testing depends on whether there are clinical features that indicate a specific diagnosis (based on history and examination). A suggested algorithm for evaluation of higher-risk infants is shown in **Figure 39-3**. Relatively common underlying disease processes that can present as BRUE include gastroesophageal reflux, respiratory infection, seizures, and nonaccidental trauma (child abuse). Rarer causes include systemic infections, disorders of ventilatory control, inborn errors of metabolism, cardiac abnormalities such as prolonged Q-T intervals, and toxic ingestions (intentional or unintentional).

Typically, higher-risk infants are monitored in the hospital for a brief period (24 hours), enabling close observation by medical personnel. Evaluation and testing are tailored to individual infants' needs based on signs or symptoms identified at presentation. Decisions regarding the need for home monitoring should be made on a case-by-case basis after discussing with the family the potential benefits, uncertainties, and stresses involved. Premature infants, those with severe or recurrent episodes, and those with chronic cardiopulmonary conditions may be candidates for home monitoring. It is important to understand that cardiorespiratory monitors ("apnea monitors") are not a treatment. They simply identify that the child needs attention. Monitors should be set at apnea and heart rate settings appropriate for age. It is important for the physician to personally review the downloaded recordings of "events" to be able to eliminate false alarms that may be due to a low amplitude signal or suboptimal lead placement. Monitoring with pulse oximetry may be more appropriate for some infants, although these too are prone to false alarms due to motion and cannot inform as to the cause of the desaturations.

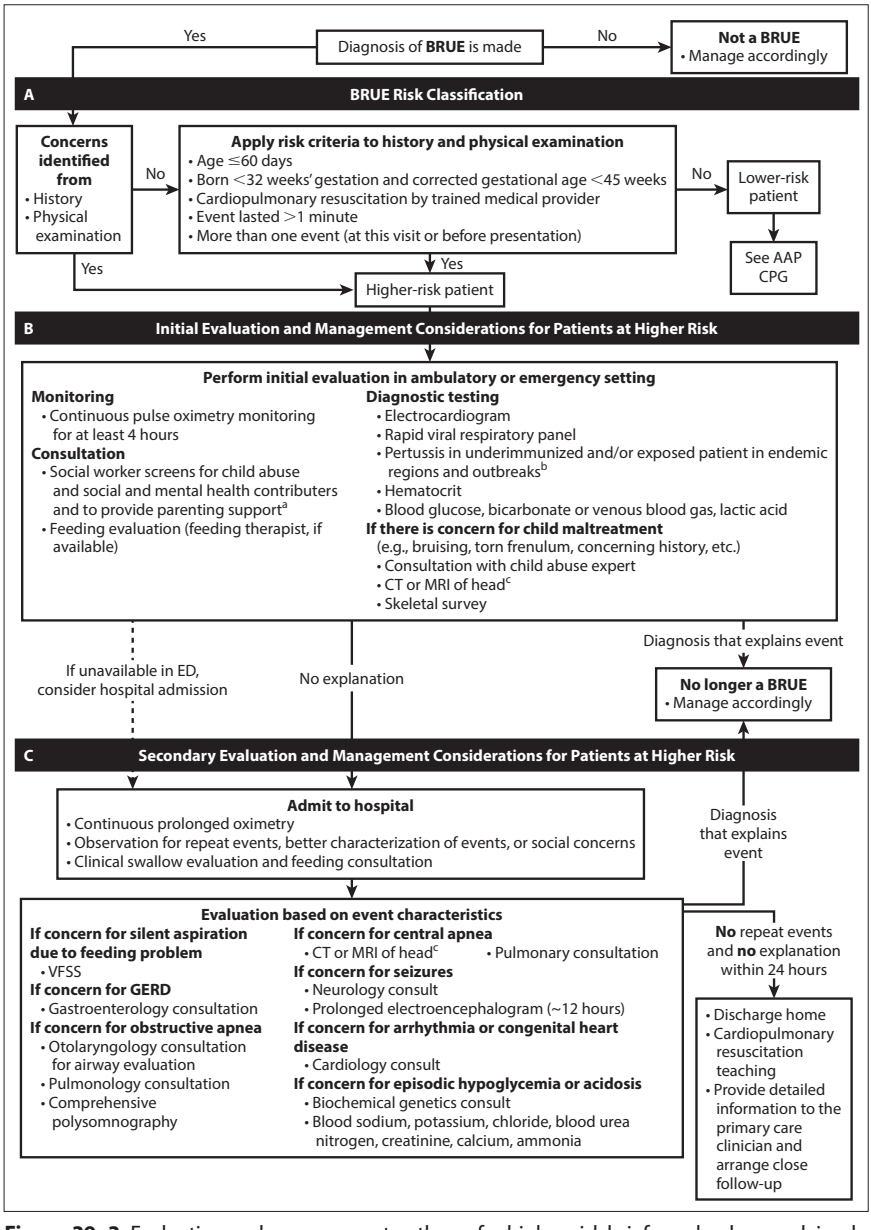


Figure 39–3. Evaluation and management pathway for higher-risk brief, resolved, unexplained events. If a social worker is not available, this may be performed by other health care workers with similar experience and skills. This assumes availability of pertussis results within a few hours. "Rapid" magnetic resonance imaging or computed tomography is preferred to avoid sedation risks.

From Merritt JL, Quinonez RA, Bonkowski JL. A framework for evaluation of the higher-risk infant after a brief resolved unexplained event. *Pediatrics*. 2019;144(2):e20184101.

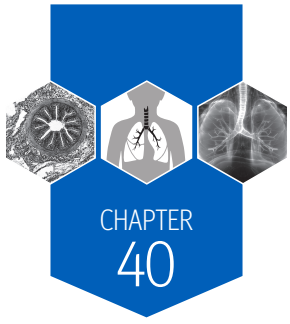
key points

- An ALTE/BRUE is a common, nonspecific disorder of infants that is usually self-limited, although, rarely, it may be a symptom of a potentially serious or life-threatening underlying disorder.
- A comprehensive history and complete physical examination are key in differentiating lower- vs higher-risk infants and determining next steps in management.
- No additional testing is indicated for lower-risk infants; however, higher-risk infants may need hospitalization and additional monitoring and testing.
- Education and guidance should be provided to all caregivers. Home monitoring is generally not indicated but may be considered in select infants.

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Congenital Central Hypoventilation Syndrome

Iris A. Perez, MD, FAAP
Emily S. Gillett, MD, PhD, FAAP
Thomas G. Keens, MD, FAAP

Congenital central hypoventilation syndrome (CCHS) is a rare genetic disorder of failure of automatic control of breathing and dysfunction of autonomic nervous system.[1–3] It is caused by a mutation in the PHOX2B gene that plays an important role in the migration of neural crest cells and development of the autonomic nervous system.[4,5] The most serious manifestation is significant hypoventilation that is always present during sleep but may also extend into wakefulness. Affected individuals commonly present at birth. Some patients present later, although the genetic defect is present at birth.[6–8] With advances in management, patients with CCHS can survive to adulthood.[9–12]

Pathogenesis

Congenital central hypoventilation syndrome is caused by a mutation in the PHOX2B gene, located in chromosome 4p12, which encodes a highly conserved homeodomain transcription factor that is essential in the development of the respiratory control neurons and autonomic nervous system.[1] Most CCHS cases are heterozygous for a polyalanine expansion repeat mutation (PARM) in the PHOX2B gene (24–33 alanines) resulting in 20/24 to 20/33 genotypes (normal 20/20 PHOX2B genotype).[1] The most common genotypes in CCHS are 20/25, 20/26, and 20/27 PARM. Approximately 10% of patients with CCHS have nonpolyalanine repeat mutations (NPARM), including missense, nonsense, frameshift and stop codon mutations. Most of these pathogenic variants are frameshifts in exon 3.[1] Less than 1% of cases have PHOX2B exon or whole gene deletion.[13]

Epidemiology

Congenital central hypoventilation syndrome is rare, with slightly more than 1,000 cases reported worldwide, but this is likely an underestimation. Recent reports estimate an incidence of 1 case per 148,000 live births in Japan[14] to 1 in 200,000 live births in France.[12] The male to female ratio is generally 1:1,[11,12,14,15] although more males (3:1 ratio) carry the PHOX2B 20/25 gene mutation.[15]

Genotype-Phenotype Relationship

The onset and severity of alveolar hypoventilation as well the need for ventilatory support can be anticipated by a patient's genotype. Patients who have CCHS with shorter PARMs (20/24–20/25) typically have more subtle symptoms and appear asymptomatic until a triggering event (ie, exposure to respiratory illness, sedation, or anesthesia) occurs that puts them in respiratory compromise. They generally present later, with some surviving to adulthood without need for around-the-clock ventilatory assistance.[16,17] They usually require assisted ventilation only during sleep. Patients with larger PARMs (20/26 PARM–20/30 PARM) are typically symptomatic at birth and require full-time ventilatory support.[1] Generally, they are not associated with variable penetrance or adult-onset presentations. However, an adult with 20/27 PARM genotype and mild phenotype was reported in 2018.[18] NPARM PHOX2B genotype is also generally associated with more severe alveolar hypoventilation, with patients typically requiring full-time ventilatory support.[1] Unlike the larger PARMs, NPARM mutations have variable expressivity and incomplete penetrance; some patients have no symptoms, while others need ventilatory support only during sleep.[19–22] It is postulated that frameshift variants located in the 3′ region of exon 2 and the 5′ region of exon 3 and nonsense variants in exon 1 are associated with a milder form of CCHS.[20,21,23]

Predisposition to certain autonomic nervous system dysfunctions may correlate with PHOX2B gene mutations. Hirschsprung disease is most prevalent in patients with NPARM mutations and, to a lesser degree, patients with PARM 20/27 and higher.[1,15,24] Although initial reports found life-threatening cardiac sinus pauses 3 seconds or greater requiring cardiac pacemaker placement in children who had CCHS with 20/26 PARM and 20/27 PARM,[25] recent reports indicate presence of these arrhythmias in those with 20/25 PARM and NPARMs.[19,26] Patients with NPARMs and longer PARM (20/28–20/33) genotypes are at higher risk for tumors of neural crest origin.[1] Pupillary abnormalities may be more frequent in patients with 20/26 and 20/27 PARMs than those with 20/25 PARM.[27]

Suboptimal school performance and/or neurodevelopmental impairment have been reported in patients with CCHS, appearing as early as preschool and

school age.[28,29] Bayley scores were noted to be essentially normal in children with 20/25 PARM and lower in the other PARM groups; those with more severe CCHS phenotype as indicated by cyanotic breath-holding spells, need for 24 hour ventilation, prolonged sinus pauses, and seizures had more severe neurocognitive delay.[28]

Clinical Presentation and Associated Features

Most patients with CCHS present in the newborn period with apnea or hypoventilation and require assisted ventilation. When placed on ventilatory support, extubation fails.[1,11,12,14,15] Others present at a later age with unexplained apneas, cyanosis, edema, or signs of right heart failure.[16] Some patients present in older childhood or adulthood, where a common presentation includes an adverse reaction to general anesthesia, respiratory infections, pneumonia, or other stressors.[7,8,16,30,31] Thus, any patient with a delay in waking or achieving adequate ventilation following general anesthesia or mild respiratory illness should raise a suspicion of having CCHS.

Patients with CCHS lack subjective and objective responses to hypoxia or hypercapnia,[32,33] thus they do not manifest respiratory distress, increased ventilation, retractions, nasal flaring, or a sense of dyspnea in response to hypoxia and hypercapnia. They may report remarkable ability to hold their breath for a prolonged period of time. As a result, hypoxia may be detected only much later, when it has already caused central nervous system depression with lethargy, cyanosis, or other complications. Some patients may present with seizures due to undetected hypoxemia or hypercapnia,[16,34] while others may have unexplained polycythemia or elevated serum bicarbonate as a presenting sign.[7,18,19,35,36] Older children and adults may present with unexplained pulmonary hypertension and cor pulmonale resulting from unrecognized and untreated hypoxemia and hypoventilation.[36,37]

The hallmark presentation of CCHS is alveolar hypoventilation, mainly during sleep but often also during wakefulness. Hypoventilation is always worse during sleep, particularly in non-rapid eye movement sleep where breathing is critically dependent on metabolic control.[38,39] There is a range of ventilatory support requirement in patients with CCHS. Those with PHOX2B 20/24, 20/25, and sometimes 20/26 PARM generally maintain adequate ventilation while awake and require ventilatory support only during sleep. Those with PHOX2B 20/27 PARM and higher and those with NPARM generally have a more severe respiratory phenotype and hypoventilate during wakefulness as well, requiring full-time ventilatory support.[1] However, some patients with these mutations have been able to maintain adequate ventilation while breathing spontaneously while awake, and require ventilatory support only during sleep.[9,11,19] More recently, some patients have been reported to

require no or minimal intervention with only supplemental oxygen as part of their supportive care.[18,40]

Congenital central hypoventilation syndrome is a generalized disorder of the autonomic nervous system, and it affects more than just control of breathing. Associated abnormalities include ophthalmologic,[41,42] cardiovascular, gastrointestinal, endocrine, and neurodevelopmental issues; tumors of neural crest origin; and temperature instability.[1] Characteristic features are a broad, flat face with box-like or rectangular appearance and inferior inflection of the lateral vermillion border of the upper lip (**Figure 40-1**).[43] Ophthalmologic conditions may include sluggish pupils, strabismus, iris abnormalities, and Marcus Gunn pupil.[27,41,42,44,45] Patients with CCHS may present with syncope, postural hypotension, reduced nocturnal blood pressure dipping, and reduced heart rate variability.[25,26,46–49] In patients with arrhythmias, syncope is the most common presentation, but some may be asymptomatic.[26] When CCHS is undiagnosed and long-standing hypoventilation is present, patients with CCHS may present with pulmonary hypertension and cor pulmonale.

Hirschsprung disease is seen in approximately 20% of patients, particularly in those with NPARM and PHOX2B 20/27 or higher PARM.[6,15,24,41] In one series, the pathologic segment was classic (rectosigmoid and left colic form) in 20% and long (above the splenic flexure) in 80%.[24] Thus, Hirschsprung disease, especially with total colonic aganglionosis, should raise suspicion of CCHS. In addition, patients with CCHS may have associated esophageal dysmotility and swallowing dysfunction.[41,50]

Patients with CCHS may present with associated hypoglycemia or hyperglycemia and hyperinsulinism. Infants and children with CCHS presenting with seizures or hyperhidrosis should be considered for dysregulated glucose homeostasis.[51–55]

Finally, patients with CCHS may have tumors of neural crest origin (neuroblastoma, ganglioneuroma, and ganglioneuroblastoma). Neuroblastoma is typically associated with NPARM, while 20/29 and 20/33 PARMs have been associated with ganglioneuromas and ganglioneuroblastoma.[1] However, a case of an infant with CCHS with neuroblastoma and PHOX2B 20/33 PARM has been reported.[56]



Figure 40-1. Characteristic facial features in a patient with congenital central hypoventilation syndrome.

Diagnostic Evaluation

PHOX2B gene mutation testing is required in establishing the diagnosis of CCHS.[1] PHOX2B testing methods include (1) PHOX2B targeted mutation analysis (PHOX2B screening test; fragment length analysis), (2) PHOX2B sequencing test, and (3) PHOX2B exon or whole gene deletion analysis.[1,13,57,58] PHOX2B targeted mutation analysis identifies all PARMs and most NPARMs, thus most pathogenic variants in CCHS. It is considered the most appropriate test in detecting low-level mosaicism in seemingly asymptomatic and mildly

symptomatic individuals. The PHOX2B sequencing test identifies all PARMs and all known NPARMs but may not detect low-level mosaicism. PHOX2B multiplex ligation-dependent probe amplification test identifies PHOX2B exon or whole gene deletion. When clinical suspicion is high, a combination of all 3 tests may be required in establishing the diagnosis. While awaiting the PHOX2B gene testing results, it is important to explore and rule out other causes of hypoventilation. Evaluation may include magnetic resonance imaging or computed tomography scans of the brain and brain stem to rule out gross anatomic lesions, as well as metabolic screen and neurologic evaluation because a variety of inborn errors of metabolism and neurologic conditions may cause apnea and hypoventilation. A polysomnogram with appropriately collected respiratory data, including end-tidal carbon dioxide (CO_2) is necessary to establish the presence of hypoventilation during sleep noninvasively. It is useful to gather data during wakefulness as well. Daytime blood gas during wakefulness will aid in establishing the presence of hypoventilation. Other tests to rule out primary lung disease, ventilatory muscle weakness, and cardiac disease, such as chest radiography, fluoroscopy of the diaphragms, echocardiogram, and muscle biopsy, may be performed.[1] Suggested evaluation of patients suspected of having a diagnosis of CCHS is seen in **Figure 40-2.** The increasing availability of whole exome sequencing with feasibility of obtaining fast results may result in earlier diagnosis.[59]

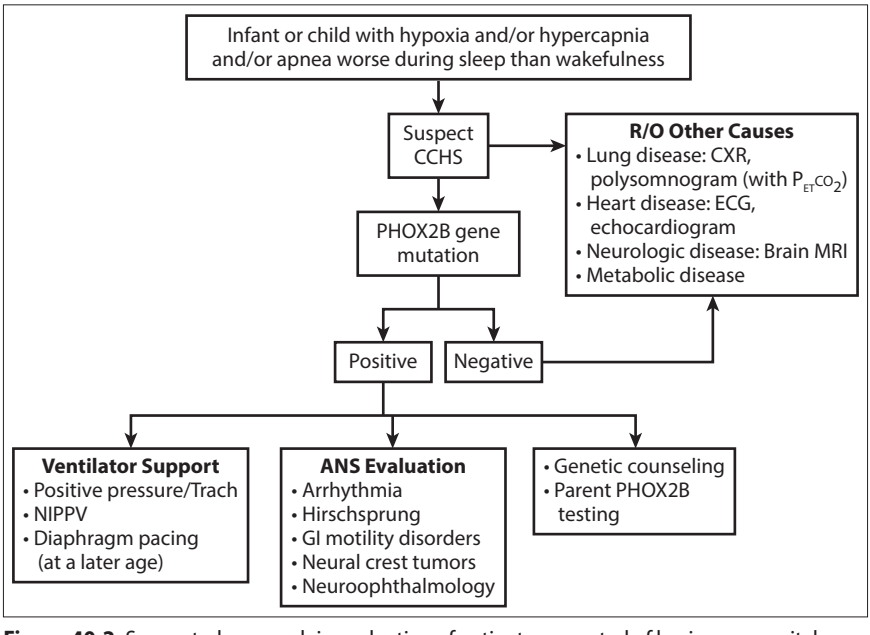


Figure 40-2. Suggested approach in evaluation of patients suspected of having congenital central hypoventilation syndrome.

Management

The fundamental goals in the treatment of CCHS are to ensure optimal oxygenation and ventilation at all times and anticipate occurrence of associated autonomic nervous system conditions.[1] Adequate oxygenation and ventilation can be achieved by maintaining end-tidal CO_2 less than 45 mmHg (< 5.99kPa) and SpO_2 95% or higher. Since patients with CCHS lack perception of dyspnea and do not manifest respiratory distress, oxygen saturation monitoring with pulse oximetry and CO_2 monitoring (end tidal or transcutaneous) are essential features in their management.

Modes of Ventilatory Support

Assisted ventilation is critical in CCHS management, because pharmacologic respiratory stimulants have been shown to be ineffective.[1] Positive-pressure ventilators via tracheostomy, noninvasive positive-pressure ventilation (NPPV) via face or nasal interface, negative-pressure ventilators, and diaphragm pacing are all options for these patients.[1,9,60–62] At present, the use of negative-pressure ventilators has largely been supplanted by the preponderance of invasive and noninvasive positive-pressure ventilators. For most patients, oxygen administration alone is inadequate because, although it relieves hypoxemia and cyanosis, hypoventilation may persist. In those who are treated with supplemental oxygen alone due to minimal or no hypercapnia, close monitoring is required with initiation of ventilatory support when hypoventilation develops or worsens.[40] There is no consensus on the choice of ventilatory support; it is necessary for the mode of ventilation to be individualized to meet the patient's needs, goals of treatment, and quality of life.

Positive-Pressure Ventilation via Tracheostomy

Positive-pressure ventilation (PPV) via tracheostomy is the most common form of ventilatory support in patients with CCHS.[1,11] It is particularly effective in infants and younger children because they have longer sleep periods and, therefore, require more hours of ventilatory support per day. The components of their respiratory system are still immature, predisposing them to significant respiratory instability in response to environmental stressors and minor respiratory infections. Because patients with CCHS do not increase their breathing frequency in response to hypercapnia and hypoxemia, the pressure control/assist control mode or synchronized intermittent mandatory ventilation (SIMV) with an appropriate rate is crucial to achieve ideal oxygenation and ventilation. Toddlers and older children who require 24-hour ventilation can be transitioned to diaphragm pacing at daytime to allow for mobility while continuing with PPV via tracheostomy at night.

Noninvasive Positive Pressure Ventilation

Patients can be ventilated by NPPV via mask (nasal or face) or nasal prongs using bilevel positive airway pressure[1,63,64] or average volume-assured pressure support ventilation mode.[60,65] Stable older children who have hypoventilation only during sleep are ideal candidates for NPPV.[1] Noninvasive positive-pressure ventilation allows stable patients who are ventilated only during sleep to be transitioned from PPV and be decannulated.[66] For patients ventilated by NPPV, only spontaneous/timed or timed modes with mandatory backup rates guarantee breath delivery. Because patients with CCHS do not increase their breathing frequency in response to hypercapnia or hypoxemia, spontaneous mode or continuous positive airway pressure is inappropriate. Long-term use of noninvasive ventilation by nasal mask can be associated with midface hypoplasia and dental malocclusion.[67] Therefore, patients should alternate between different interfaces and must be monitored with consideration for referral to a craniofacial team for monitoring of facial growth as well as dental malocclusion.

Diaphragm Pacing

Diaphragm pacing (DP) can provide daytime ventilatory support for those who are dependent on a ventilator 24 hours per day. It can be the sole ventilatory support for those who are dependent on a ventilator only during sleep and possibly may allow for tracheal decannulation.[1,9,62] With diaphragm pacing, the child's own diaphragm acts as the respiratory pump. A diaphragm pacer system involves 4 components: (1) monopolar electrodes that are surgically implanted bilaterally on the phrenic nerves, (2) receivers that are surgically implanted subcutaneously on the abdomen or chest bilaterally, (3) antennae that are placed over the receivers, and (4) an external battery-operated portable transmitter that generates electrical energy similar to radio frequency. The electrical energy generated by the external transmitter is transmitted via external antennae that are placed over the receivers. The receivers then convert the energy to electrical currents that are then conducted to the phrenic nerve, stimulating contraction of the diaphragm (**Figure 40-3**).[1,62]

A normal functioning diaphragm, intact phrenic nerves, little or no lung disease, normal airway, and healthy weight are essential for successful diaphragm pacing.[1,9,10] Patients who have overweight or obesity are not ideal candidates because the high amount of adipose tissue interferes with the antennae and receivers of the diaphragm pacers, resulting in variability in the signal inputs to the receiver.[9] When the goals for diaphragm pacing are decannulation and diaphragm pacing without tracheostomy, the following requirements must also be met: (1) ventilator dependence only during sleep, (2) not requiring daytime naps, (3) stable medical course with infrequent hospitalizations,

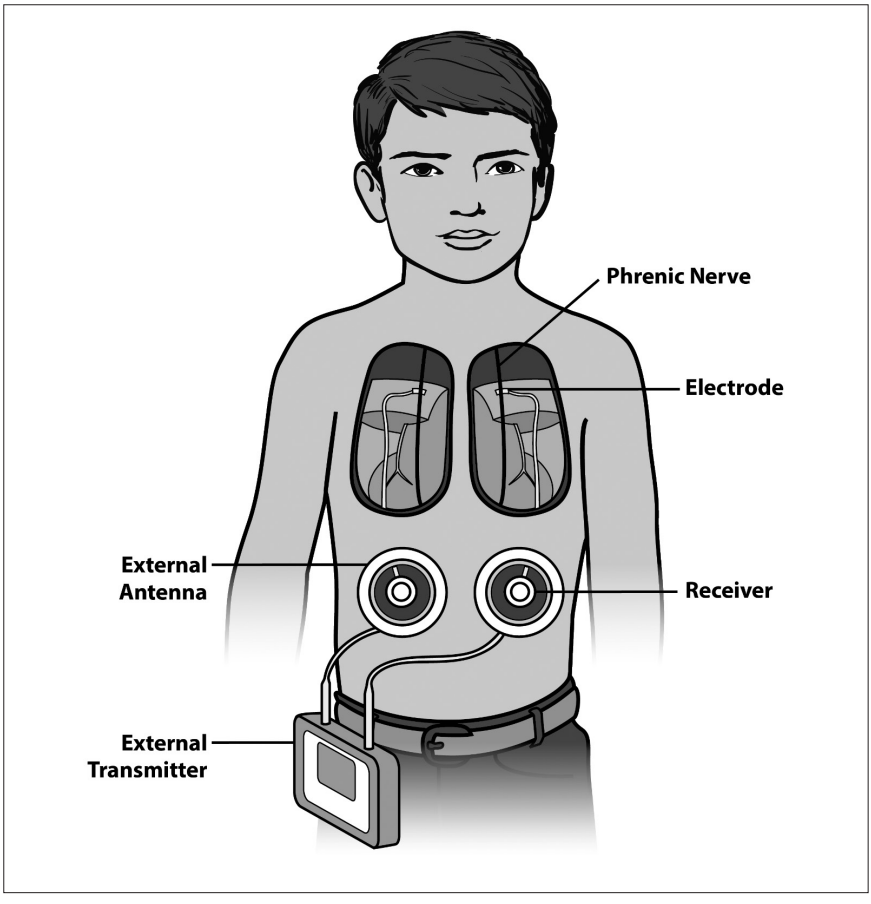


Figure 40-3. Components of diaphragm pacer system.

(4) not requiring full-time ventilatory support during respiratory illnesses, and (5) acceptance that DP is not a secure method of ventilation and intubations may be necessary for serious illnesses.[9] A disadvantage of diaphragm pacing without tracheostomy is the risk of obstructive sleep apnea and upper airway obstruction, which can occur due to the diaphragm contraction without concomitant upper airway muscle contraction.[10,68,69] However, obstructive sleep apnea can be alleviated by decreasing the diaphragm pacer amplitude settings to decrease the force of inspiration with each diaphragm contraction.[9,10] At present, diaphragm pacing without tracheostomy is not a viable mode of ventilatory support in younger children.[69] Because of the risk of diaphragm fatigue, diaphragm pacing is typically used only for up to 14 to 16 hours a day.[1] Therefore, during an acute illness, when additional time on assisted ventilation is necessary, a patient must have an alternative form of ventilatory support (NPPV or home ventilator).

Observation and Monitoring

Patients with CCHS require vigilant observation and monitoring at each sleep episode. Many patients, particularly those who are young, require at least 16 hours of home nursing per day. At home, pulse oximetry and capnography can aid in their monitoring. In this instance, the pulse oximeter is generally set to alarm at Spo_2 of 85% or less and heart rate at 50 beats per minute or less. The goal for these alarm settings is to decrease nuisance alarms while allowing sufficient time for caregivers to respond to potential emergencies. The pulse oximeter will also aid in monitoring changes in respiratory status. Apnea/bradycardia monitoring alone is not sufficient, because patients may continue to hypoventilate without being apneic.

Long-term Management

Once the diagnosis is established, patients who have CCHS with symptoms, or depending on their genotype, should be screened for associated autonomic dysfunction. These tests may include (1) barium enema or rectal biopsy to assess for Hirschsprung disease, (2) esophageal motility and swallowing evaluation, (3) ambulatory cardiac rhythm monitoring to evaluate for sinus pauses, (4) chest and abdominal imaging to assess for neural crest tumors, and (5) a comprehensive ophthalmologic evaluation. These will aid in early identification of abnormalities and allow intervention to prevent learning delay. Patients may demonstrate developmental delay and neurocognitive deficits as early as preschool age, indicating a need for neurocognitive evaluation and early intervention when necessary.[28,29,70]

Patients with CCHS are at risk for pulmonary hypertension and cor pulmonale; when present, these must be assumed to be caused by inadequate ventilation until proven otherwise. Yearly overnight in-laboratory polysomnography including capnography to assess optimal ventilator settings and echocardiogram should be part of anticipatory care.[1] The development of pulmonary hypertension while ventilator settings during sleep are appropriate suggests hypoventilation during wakefulness, indicating need for ventilatory support during wakefulness as well.

Due to the risk of life-threatening arrhythmias[25,26,49] and the presence of sinus pauses even in those who are asymptomatic, all patients would benefit from yearly cardiac ambulatory monitoring.

All individuals with CCHS require lifelong follow-up. Potential situations that predispose to ventilatory instability need to be anticipated. During exercise, they may not increase their ventilation normally to meet their increased oxygen consumption.[71] Activities that involve breath holding, such as swimming underwater, are particularly dangerous because individuals with CCHS will not perceive the asphyxia[32,33] that occurs with prolonged breath-holding.

Adolescent and young adult patients need to be counseled on alcohol abstinence because of the potential adverse outcomes, including coma and death.[72]

Genetic Counseling for CCHS

PHOX2B gene mutation in CCHS has an autosomal pattern of inheritance with variable penetrance.[1,19,58,73,74] Although most cases occur de novo, it is necessary to test the parents of the affected patient even if they do not report symptoms.[58] Genetic counseling is imperative for individuals diagnosed with CCHS because there is a 50% chance of inheritance with each child. Mothers with CCHS should undergo prenatal testing with each pregnancy. Prenatal testing will provide optimal information about the status of the fetus and aid the pregnant mother in making an informed decision; it also prepares the medical and nursing team to plan for smooth delivery and neonatal care.[1]

key points

- Congenital central hypoventilation syndrome is a lifelong disorder without known cure. It is caused by a mutation in the PHOX2B gene.
- PHOX2B gene mutation analysis is required to confirm the diagnosis, predict the CCHS phenotype, and guide management.
- A high index of suspicion is critical because early identification and application of intervention with modern techniques for home ventilation may result in most children surviving to adolescence and adulthood with a relatively good quality of life.
- Optimal care requires a multidisciplinary approach that is individualized for each patient.
- Successful outcomes require adequate oxygenation and ventilation at all times and vigilant monitoring and management of associated autonomic nervous system dysfunction.

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PART 8

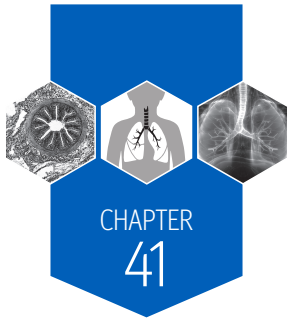
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Acute Aspiration and Chronic Aspiration–Related Lung Disease

Jade B. Tam-Williams, MD, FAAP

Introduction

Aspiration of materials into the lower respiratory tract can be both a chronic and an acute problem in children. Because the respiratory and gastrointestinal tracts share a common site of origin, and because of the complex interplay among breathing, chewing, and swallowing, the aspiration of both intrinsic and extrinsic oral contents can be more prevalent in children. The clinical picture of aspiration and aspiration-related lung disease depends on the amount and type of material aspirated, as well as timing; therefore, a child can present with an acutely life-threatening event, with recurrent respiratory disease, or with subclinical disease. The 3 major types of aspiration-related lung disease are (1) airway foreign body, (2) massive acute aspiration of chemical or liquid contents, and (3) recurrent small-volume aspiration. In this chapter, we will review the physiological mechanism of normal swallowing, the clinical presentation of the 4 major types of aspiration-related lung disease, evaluation of swallowing dysfunction, and possible treatments.

Physiological Mechanism of Swallowing

Normal swallowing is a complex process dependent on normal anatomy, as well as the normal neuromuscular function of cranial and cervical nerves.[1] Swallowing consists of 4 phases: oral preparatory phase, oral transit phase (bolus delivery), pharyngeal phase, and esophageal phase (**Figure 41-1**). Swallowing involves the aerodigestive tract, which is defined as the combined organs through which both air and food may pass: oral cavity, tongue, nose, pharynx, vocal cords, pyriform sinus, larynx, and upper esophagus. The oral phase is voluntary, including acceptance of the food bolus, preparation of the food bolus by chewing or sucking, and preparing the bolus on the tongue. The food bolus is then delivered via the tongue to the pharynx voluntarily in the oral transit phase. There can be spillage into the hypopharynx if oral movements are not coordinated. Once food bolus delivery occurs, the involuntary pharyngeal phase begins in order to protect the airway. The pharyngeal phase

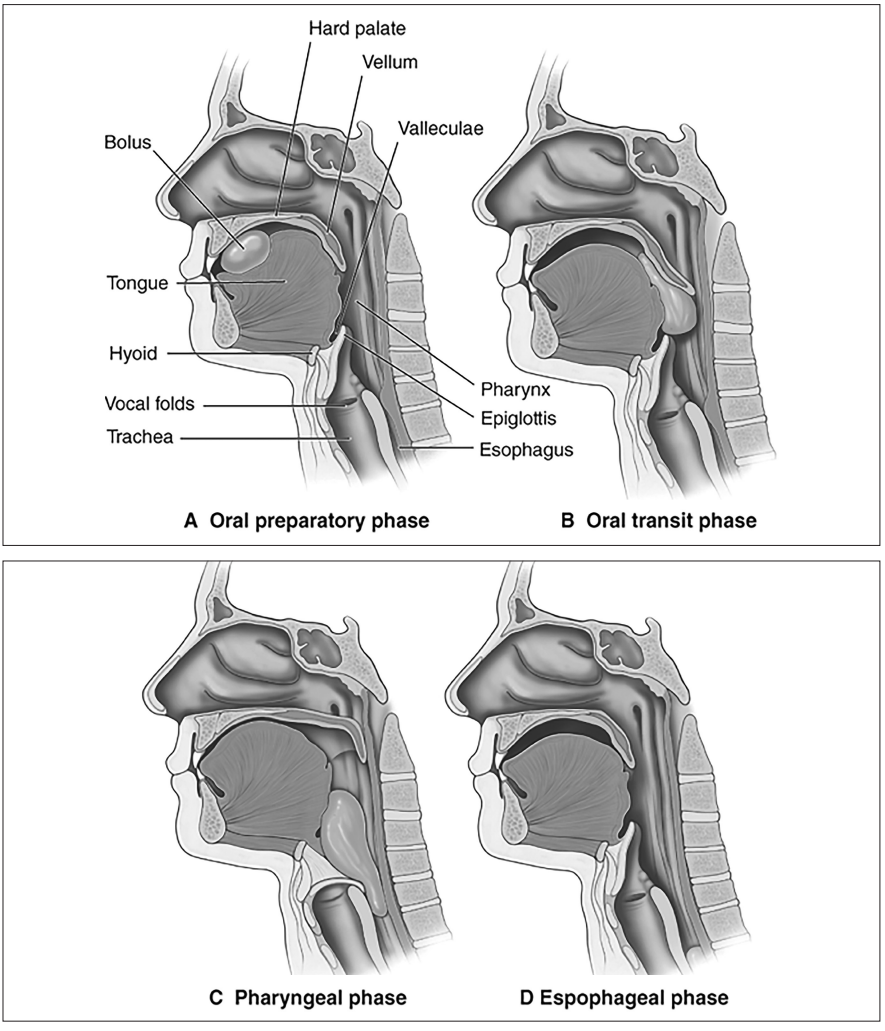


Figure 41-1. Swallowing can be separated into 4 phases: oral preparatory, oral transit, pharyngeal, and esophageal phases. Coordination difficulties in these phases are more likely to contribute to symptoms of dysphagia and chronic aspiration. **A,** Oral preparatory phase: The lips are sealed, and the tongue assists in mastication and mixing of food into a bolus formation. The velum meets the base of the tongue to prevent the bolus from moving posteriorly while mastication occurs. **B,** Oral transit phase: The tongue elevates and makes contact with the palate to squeeze the bolus toward the posterior oral cavity and into the pharynx while the velum starts to elevate. **C,** Pharyngeal phase: The velum elevates and prevents food from entering the nasal cavity; the vocal folds close, and the epiglottis deflects to protect the airway while the food bolus enters the esophagus. **D,** Esophageal phase: The epiglottis returns to the upright position with reopening of the vocal folds. The food bolus has passed the upper esophageal sphincter and is in the esophagus.

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includes brief cessation of breathing, adduction of the true vocal folds along with horizontal approximation of the arytenoid cartilages, closure of the false vocal folds, and retroversion of the epiglottis to protect the airway. The larynx then elevates and the intrinsic laryngeal muscles contract, diverting the food into the pyriform sinus region. The muscles of the pharynx then propel the food through the upper esophageal sphincter. Once the food bolus enters the esophagus, the larynx returns to resting position and the airway reopens. The food bolus then enters the esophagus in the esophageal phase and is pushed downward via peristalsis. This entire intricate process can be seen as early as 10 to 14 weeks of gestation but is not generally sustained until 32 to 34 weeks of gestation. Neurodevelopmental immaturity, difficulty with coordination of swallowing, and abnormal anatomy of any part of the aerodigestive tract can contribute to aspiration.

Aspiration of a Foreign Body

Approximately 80% of foreign body aspirations occur in children younger than 3 years, with a higher incidence in boys and a peak incidence between 1 and 2 years of age.[2] Food is the most aspirated material in toddlers, whereas small nonedible objects are more common in older children (**Box 41-1**). Aspiration of foreign bodies in children is usually due to children placing items in the mouth that are unable to be chewed or swallowed. Inhalation of a foreign body can occur if a child of any age is suddenly startled, although it is more likely in toddlers because of the tendency of this age group toward oral sensory behavior, poor mastication because they do not have molars to chew adequately, and immature oropharyngeal coordination.

CASE REPORT 41-1

A 20-month-old boy had a sudden onset of choking and coughing while his mother was on the telephone in the next room. The cough continued throughout the next 24 hours, and he developed intermittent wheezing for which she took him to the pediatrician. He had a prior history of wheezing with respiratory syncytial virus at age 6 months. She was not aware of any potential foreign bodies in his environment. At examination, he was afebrile, with a respiratory rate of 36 breaths/min, mild suprasternal retractions, and an oxygen saturation of 98%. Lung auscultation revealed a monophonic expiratory wheeze, which was transmitted equally throughout the chest. Chest radiography showed mild bilateral hyperinflation without infiltrates. He was referred to surgery for evaluation with rigid bronchoscopy. A tracheal foreign body was suspected from the history and physical examination results.

Box 41-1

Foreign Bodies Commonly Aspirated by Children

Food
- Peanuts
- Popcorn
- Seeds
- Hot dogs and hot dog pieces
- Vegetable material
- Hard candy
- Grapes

Nonorganic
- Toy parts
- Pen pieces
- Pins
- Crayons
- Tacks
- Nails
- Screws

Clinical Presentation

The most common presentation of foreign body aspiration is a history of a choking event followed by an acute cough, although parents will often not associate an acute coughing event with a foreign body. Many parents (≥25%) are not aware of any aspiration or choking event; therefore, a high index of clinical suspicion is necessary, and the lack of a witnessed event does not rule out foreign body.[3,4] There is often an asymptomatic period after the choking spell once the foreign body becomes lodged in the lower tracheobronchial tree.

This asymptomatic period could be hours, days, or months, leading to parents forgetting about the initial episode. A careful history should attempt to elicit the details surrounding the beginning of the cough. Transient or persistent cough is the primary symptom in approximately 75% of children with airway foreign bodies. Physical findings can include asymmetrical chest expansion, decreased breath sounds over the affected lung, or localized wheezing, or there may be no abnormalities at examination. A tracheal foreign body is more likely associated with monophonic wheeze on exhalation because it reflects obstruction in a single large central airway but may sound bilateral owing to reverberation. The presence of either monophonic or localized wheezing that is unresponsive to bronchodilators can help distinguish an

asthma exacerbation from a foreign body aspiration. Finally, foreign bodies lodged in the esophagus may push on the posterior membrane of the trachea, leading to respiratory symptoms.

Diagnosis

A plain 2-view chest radiograph is the first diagnostic test for a foreign body because it may quickly show radiopaque foreign bodies (**Figure 41-2**). An expiratory radiograph is particularly helpful in demonstrating air trapping on the affected side from a ball-valve effect, although tracheal or bilateral foreign bodies will not likely cause asymmetrical findings (**Figure 41-3**). Atelectasis may be a later finding. However, a normal chest radiograph does not exclude an airway foreign body because most foreign bodies aspirated by children are radiolucent and may not be detected. A normal radiograph is particularly common for tracheal, laryngeal, and smaller, more distal foreign bodies.[3] If the physical examination and a plain radiograph are not diagnostic, fluoroscopy, inspiratory and expiratory radiographs, or bilateral decubitus radiographs (particularly in the uncooperative young child) may be helpful. However, reviews of decubitus radiographs and fluoroscopic images showed them to be of limited predictive value for airway foreign bodies.[4,5] Hence, low-dose multidetector computed tomography (CT) is often used to investigate suspected foreign body aspiration further. Where available, virtual bronchoscopy using CT imaging software to recreate a virtual intraluminal evaluation of the tracheobronchial tree may be useful in identifying a foreign body, as well as assisting in the surgical removal of foreign bodies (**Figure 41-4**). Computed tomography imaging increases the likelihood of positive bronchoscopy results[6,7] and is also used to detect residual foreign bodies after bronchoscopy.[8]



Figure 41-2. A plain chest radiograph can easily reveal radiopaque objects; this example shows a nail lodged in the trachea.

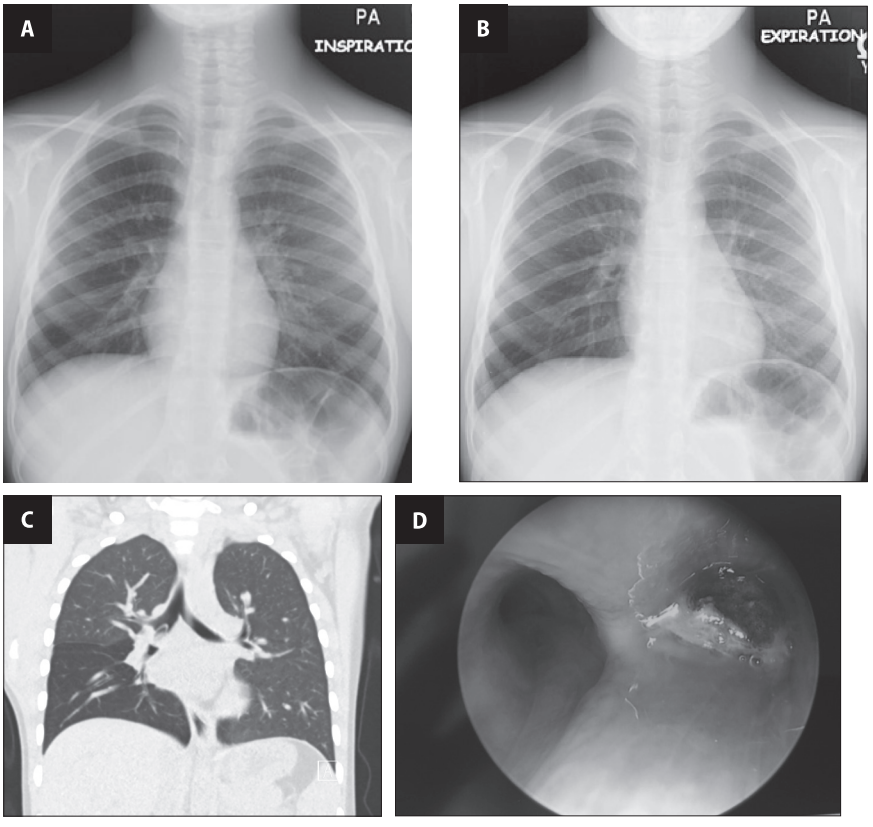


Figure 41-3. Inspiratory (**A**) and expiratory (**B**) chest radiographs show a right bronchus intermedius foreign body, demonstrating the ball-valve effect with right-sided air trapping on the expiratory radiograph. These images -are representative of a radiolucent foreign body trapped on the right side. **C,** Coronal computed tomography scan shows a foreign body in the right mainstem bronchus and air trapping in the right lower lobe. **D,** Image obtained during rigid bronchoscopy shows the foreign body was a sunflower seed.

Images C and D courtesy of Christopher Oermann, MD.

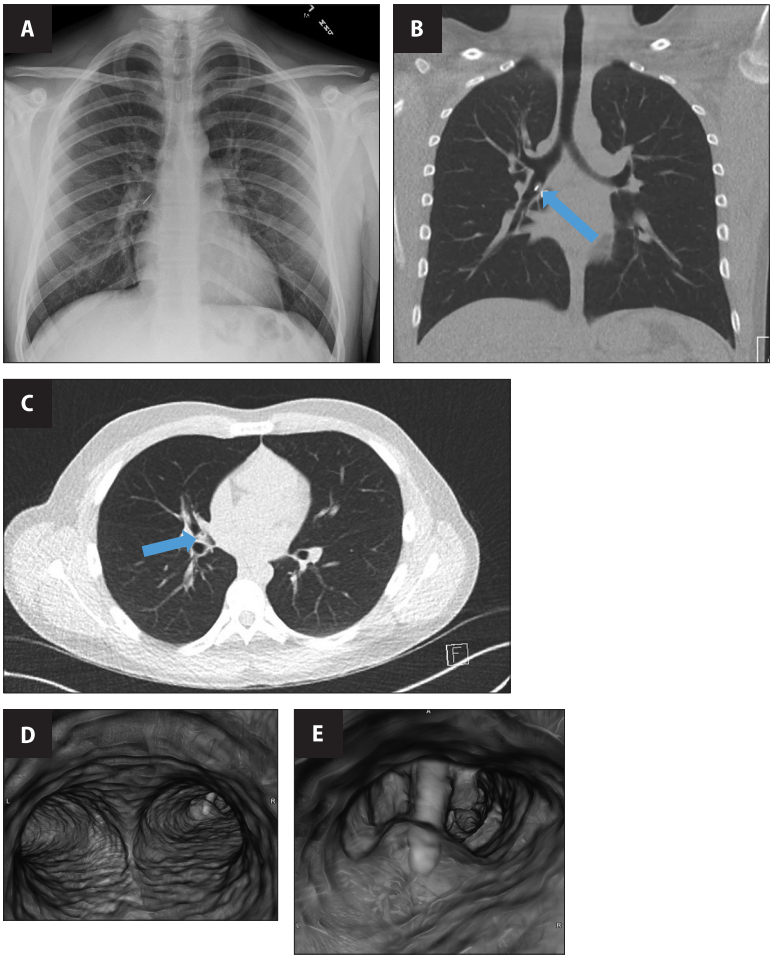


Figure 41-4. A, Posteroanterior view chest radiograph obtained for a shoulder injury. Note the incidental finding of a thin radiopaque metallic object near the right hilum. **B** and **C,** Computed tomography coronal (**B**) and axial (**C**) images obtained to follow up on the chest radiograph show a foreign body (arrow) with both a metallic bright component and a less radiopaque component in right mainstem bronchus. **D** and **E,** Virtual bronchoscopy images with reconstructed images of the foreign body. Note that the radiopaque metallic component is embedded in granulation tissue. After further history was obtained, the patient recalled aspirating a thumbtack several years previously, which explains the radiopaque metallic component and the radiolucent plastic component of the foreign body on the chest computed tomography images.

Courtesy of Jade Tam-Williams, MD, FAAP.

Management

If complete airway obstruction occurs with a witnessed choking event, abdominal thrusts (Heimlich maneuver) are indicated for children older than 1 year. For infants younger than 1 year, chest thrusts and back blows in the head-down position should be used. If a foreign body is likely based on the history, examination results, or radiographs, airway evaluation should be performed as soon as safely possible to prevent possible dislodgement into a more central and potentially life-threatening position in the airway. In these situations, the airway is evaluated with the patient sedated in the operating room via microlaryngoscopy and bronchoscopy (MLB), also colloquially referred to as *rigid bronchoscopy,* to describe the type of bronchoscope. Performing MLB is preferred for retrieval of foreign bodies because the larger hollow metal bronchoscope tube allows for introduction of instruments to secure foreign bodies. Small food-based foreign bodies may be especially troublesome because they can lead to inflammation and obstruction of distal airways, leading to recurrent pneumonia. These may necessitate treatment with antibiotics and aggressive airway clearance to help with retrieval because without reduction of local inflammation, the foreign body is difficult to remove. Other parenchymal lung complications include pneumothorax, atelectasis, and bronchiectasis. Small distal foreign bodies may require special instrumentation, and sometimes flexible bronchoscopy with a bronchoscope that can bend in multiple directions can help aid diagnosis or visualization of small objects. If the diagnosis is unlikely to be a foreign body, flexible bronchoscopy may also be beneficial to provide another diagnosis for respiratory symptoms. Very rarely, a lobectomy may be necessary to remove a highly embedded foreign body.

Preemptive education for parents of infants and toddlers should be standard in pediatric practice. This education includes advising that commonly aspirated objects, such as peanuts or similar-sized foods, be kept out of reach; food should be cut into small pieces; and latex-type balloons should not be allowed in the home.

When to Refer and Admit

Any child with sudden onset of choking followed by coughing, wheezing, or respiratory distress should be suspected of having an airway foreign body. After initial stabilization and imaging, consultation with an otolaryngologist or pediatric surgeon should be sought for foreign body airway evaluation via MLB. A history of acute choking should never be ignored. A child with a choking event but no further symptoms, such as cough, dyspnea, or fever, who has normal physical examination or chest radiographic findings, may not require foreign body airway evaluation but should undergo follow-up for possible late-onset symptoms.[9] If the child presents with chronic cough,

recurrent pneumonia, persistent chest radiographic abnormalities, or wheezing or cough unresponsive to asthma therapy, or if the diagnosis is in question, consultation with a pediatric pulmonologist is warranted. Flexible bronchoscopy should be considered in these cases as well.

Acute Large-Volume Aspiration

Large-volume aspiration is typically associated with vomiting, particularly with altered level of consciousness and diminished upper airway protective reflexes. It may occur during trauma, seizure, or general anesthesia, or with underlying neuromuscular disorders. Results from animal studies have shown that volumes greater than 1 mL/kg or pH less than 2.5 are associated with the most severe outcomes, although aspiration of particulate material also contributes to clinically significant lung injury.[10] When acute massive aspiration is suspected, immediate intervention is paramount.

CASE REPORT 41-2

An 8-year-old boy with developmental delay developed fever and upper airway congestion. He subsequently began vomiting and appeared to become dyspneic. Given his history of aspiration, his mother took him to their local hospital. His oxyhemoglobin saturation was 83% while receiving high-flow supplemental oxygen. Inspiratory crackles were audible in both lower lobes. While his evaluation was underway, he became increasingly tachypneic, dyspneic, and cyanotic. He subsequently underwent intubation and mechanical ventilation and was airlifted to a nearby children's hospital. His chest radiographs showed complete opacification of his right lower lobe with streaky infiltrates and haziness in his right upper and left lower lobes. He required intensive care with mechanical ventilation for 2 weeks and subsequently needed supplemental oxygen for several days thereafter. Multidisciplinary family-centered rounds with specialists in otolaryngology, pulmonology, and palliative care included discussion about whether tracheostomy placement would reduce morbidity from future aspiration events and improve his quality of life.

Clinical Presentation

There is no difficulty in establishing the diagnosis of acute massive aspiration when the patient is observed to have vomited a large volume, with choking and immediate respiratory distress. If the child has a tracheostomy tube, suctioning of the tube may return some formula or stomach contents, but evidence of vomitus may still be present in the oropharynx. In severe cases, asphyxia may occur with loss of consciousness or respiratory arrest. Generalized seizures may occur secondary to associated hypoxic encephalopathy.

Mendelson[11] first described acute large-volume aspiration of gastric contents as a complication of obstetric anesthesia, although this form of aspiration is uncommon in the modern day because of changes in anesthesia practice.[12] Clinical observation frequently reveals accessory muscle use and retractions, inspiratory coarse crackles, and polyphonic wheezing due to aspirate obstruction. Aspiration of high-acidity gastric contents may also lead to chemical pneumonitis due to lung injury and release of inflammatory mediators. These findings typically include coughing, wheezing, dyspnea, tachypnea, tachycardia, and possibly cyanosis. After a latent period of 1 to a few hours, fever and crackles may develop. Initial radiographic findings typically show bilateral multilobar infiltrates that worsen over the next 24 to 36 hours secondary to inflammatory response (**Figure 41-5**). Acute respiratory distress syndrome may develop, and bacterial infection is unusual initially, but superinfection may develop later. Chemical pneumonitis is less likely to occur from aspiration of tube feedings or blood because of the higher pH and lower likelihood of bacterial contamination.[12]

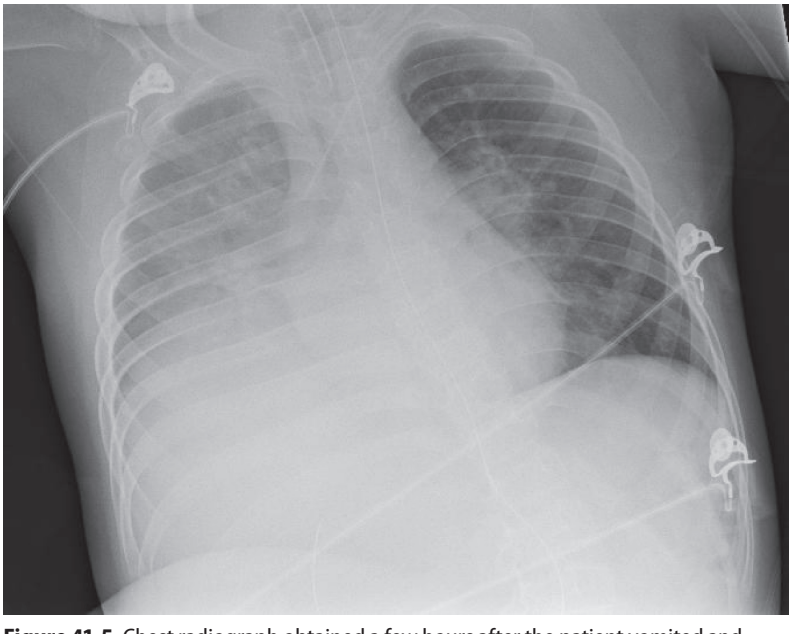


Figure 41-5. Chest radiograph obtained a few hours after the patient vomited and aspirated a large volume of gastric material.

Diagnosis

It may be difficult to differentiate between large-volume aspiration leading to aspiration pneumonia, chemical pneumonitis, and postobstructive pneumonia.[12] Radiographic imaging is warranted as a confirmatory first step and for monitoring. If a child is suspected of having inhaled substances with substantial particulate matter, bronchoscopy may be warranted. Identification and removal of large airway particles are of diagnostic as well as therapeutic value. If no large particles are seen in the airways, bronchoalveolar lavage (BAL) may still reveal diagnostic foreign material, such as meat or vegetable fibers. If lipid is aspirated, lipid-laden macrophages may be observed within a few hours after aspiration.[13]

Management

Bronchoscopy may play a role in some cases of massive aspiration. There is no value in attempting to neutralize acid aspiration because this occurs endogenously within seconds after the event. Routine corticosteroids are not beneficial for aspiration pneumonia or chemical pneumonitis.[12] Antibiotics are determined based on the clinical picture. Mandell and Niederman[12] proposed an algorithmic approach differentiating aspiration events between community versus hospital acquisition, with the recommendation to use broad-spectrum antibiotics if the patient was admitted recently, including coverage for gram-negative bacteria, methicillin-resistant *Staphylococcus aureus*, and anaerobes. However, in the immediate treatment for large-volume aspiration with mild to moderate symptoms, antibiotics can be withheld as long as the patient can be observed. General supportive measures, including supplemental oxygen, bronchodilators, and possible mechanical ventilation, are mainstays of acute treatment.

For patients at risk of vomiting and aspiration, gastric volume should be minimized. Whenever possible, gastric acid should be suppressed. If vomiting is witnessed in a patient with a poorly protected airway or artificial airway, immediate suctioning of the airway is critical. Elevation of the head of the bed to 30° to 45°, avoiding excess sedation (if possible), and monitoring gastric residual volumes during enteral feedings may be helpful preventive measures.

When to Refer and Admit

All patients who become rapidly dyspneic from large-volume aspiration should be admitted to a hospital. Unless the physical examination results, oxyhemoglobin saturation, and chest radiographs are normal, all patients suspected of having had large-volume aspiration ought to be admitted for close observation. If a patient is able to maintain near-normal blood oxygen levels with reasonable amounts of supplemental oxygen (fraction of inspired oxygen $<60\%$), is only mildly or moderately dyspneic, is not in an altered

neurological state, and can be monitored by experienced staff, that patient reasonably can be cared for in a community hospital. The patient should be observed closely for a minimum of 48 hours because late-onset deterioration can occur. A child whose condition deteriorates rapidly and who requires increasing oxygen supplementation, becomes obtunded, or requires intubation and assisted ventilation should be transferred to a center with pediatric pulmonary and critical care specialists. It is very likely that, in these situations, the patient will require prolonged and intensive treatment and will require close follow-up in specialty clinics.

Aspiration of Hydrocarbons

Some attention must be given to the uniqueness of aspiration of hydrocarbons because they are lipophilic, causing tissue damage and surfactant disruption quickly. In addition, they have intrinsic properties that allow them to spread throughout the lung easily.[14] Common household hydrocarbons include kerosene, furniture polish, paint, paint thinner, and gasoline. Aspiration can be accidental in children or intentional in adolescents and young adults. Once inhaled into the alveoli, these chemicals lead to fluid leak and bleeding with subsequent acute hypoxemic respiratory failure. Ventilation may require high pressures and high oxygen concentration. Acute hypoxemia may also affect neurological function. It can be difficult to assess these events because they may or may not be witnessed and the amount aspirated may be unknown. Treatment is generally supportive because there is no evidence that prophylactic steroids or antibiotics are helpful.[15] Antibiotics are reserved for superimposed bacterial infection. Induction of vomiting may lead to further aspiration of hydrocarbon into the lungs. Chest radiography is indicated in any patient suspected of having inhalation aspiration of hydrocarbons. Initial radiographic findings may be minimal or may reflect chemical pneumonitis with multiple patchy opacities with ill-defined margins. Radiographic findings typically peak by 48 hours after aspiration; therefore, serial imaging in patients suspected of having inhaled a hydrocarbon may be beneficial.[14] Once the patient has recovered, long-term complications may include pneumatocele or pulmonary fibrosis.

CASE REPORT 41-3

A 9-month-old boy presents with a recurrent cough that is present more days than not for the past 6 months. His newborn screening for cystic fibrosis was normal. He spits up after most feedings, more than his older siblings did. His cough seems to have no particular pattern, but with specific questioning, the mother states it may be more common toward the end of and after feedings. His physical examination results were normal except for transient inspiratory and expiratory wheezes after a feeding. Chest radiographs showed patchy infiltrates predominantly in the posterior right upper lobe and to a lesser extent in the apical left upper lobe and right lower lobe with mild to moderate hyperinflation. He has had intermittent low-grade fevers. His cough did not improve substantially with a course of amoxicillin. He was referred for a video-fluoroscopic swallowing study, which showed tracheal aspiration with thin barium and mild laryngeal penetration with nectar consistency barium.

Recurrent Small-Volume Aspiration (Gastroesophageal Reflux, Saliva)

Recurrent aspiration of small volumes of food or gastric, oral, or nasal contents leads to acute and chronic respiratory problems. Risk factors for chronic recurrent aspiration are listed in **Box 41-2**. However, chronic aspiration with isolated swallowing dysfunction can occur in otherwise apparently healthy young children.[16] Oropharyngeal incoordination has been reported to be the most common underlying problem associated with recurrent pneumonia causing hospitalization.[17]

Box 41-2

Risk Factors for Recurrent Aspiration

- **Vocal cord anomalies**
- **Congenital anomalies of the airways (eg, laryngomalacia, laryngeal cleft, vascular ring, and tracheoesophageal fistula)**
- **Craniofacial anomalies (eg, Pierre-Robin sequence, choanal atresia)**
- **Neurological or neuromuscular disease**
- **Dysautonomia**
- **Poor oral hygiene**
- **Poor feeding techniques**
- **Gastroesophageal reflux**
- **Swallowing immaturity**

Clinical Presentation

Small-volume aspiration, or *micro-aspiration*, is sometimes differentiated as being from above, or anterograde, such as oral intake (eg, saliva or formula), or being from below, or retrograde, such as gastroesophageal reflux (GER). Parents may describe cough, rattling, or noisy breathing after swallowing. A history of recurrent lower respiratory tract infections (pneumonia, bronchitis) may be present. Clinical clues to chronic micro-aspiration due to GER can include apnea, recurrent cough, wheezing, and esophageal discomfort, although children may not be able to communicate this to their parents. Nighttime symptoms may also be present. Aspiration of reflux causes airway inflammation due to acidity and the presence of gastric enzymes. Aspiration of material from the mouth can include lipids, oropharyngeal bacteria, salivary enzymes, and upper airway secretions. Other clinical clues to small-volume aspiration include the risk factors listed in **Box 41-2**. Although choking or coughing with feedings is common with aspiration from dysphagia, silent aspiration can also occur, especially in patients who are neurologically impaired. Chronic aspiration can also be a coincident finding in patients with other chronic conditions, such as cystic fibrosis, primary ciliary dyskinesia, and asthma.

Information to ask about in the history includes timing, duration, and frequency of respiratory symptoms. The patient may have a history of upper airway, gastrointestinal, or respiratory issues. Feeding habits such as positioning, bottle propping, or allowing the child to sleep with a bottle are important to assess, as well as subsequent spitting, vomiting, or arching behaviors. Other pertinent history includes difficulty with sucking, nasopharyngeal reflux with nasal congestion, changes in gag reflex, sialorrhea, or pooling of oropharyngeal secretions. The nose, oropharynx, and oral hygiene should be examined, along with auscultation of the lower airway. In addition, one should assess for neuromuscular weakness, dysmorphic features, and voice and cough quality. Observation of feeding during examination can provide valuable information and reduce the need for further workup.

Evaluation and Diagnosis

The intermittent nature of micro-aspiration and the fact that both aspiration and GER may be seen in healthy children without respiratory symptoms make it difficult to prove a cause-and-effect association of recurrent small-volume aspiration and lower respiratory tract disease. Considerable clinical judgment is required. The initial radiographic study for a child suspected of having recurrent aspiration is plain chest radiographs. However, there are no findings specific to aspiration, and the results may range from normal to hyperaeration with peribronchial thickening to classically described consolidations in dependent lobes or segments. Chest CT in children with chronic aspiration may

show persistent infiltrates or bronchiectasis in the posterior and medial lower lobes that is not evident on radiographs.

Depending on clinical suspicion, the next steps include either a simple barium esophagram and upper gastrointestinal series or a videofluoroscopic swallowing study (VFSS) or fiber-optic endoscopic evaluation of swallowing (FEES). A barium esophagram can depict gross anatomical abnormalities, such as hiatal hernia, tracheoesophageal fistula, vascular ring, and gross aspiration or GER; VFSS or FEES can provide an objective evaluation of oropharyngeal dysphagia.[18]

The VFSS is a well-described study for evaluating swallowing and oropharyngeal aspiration (**Figure 41-6**).[1,18,19] It should be performed with the assistance of a pediatric feeding specialist, a radiologist, and a parent. The purpose of this evaluation is to assess pharyngeal function and define motility problems in the oral cavity, pharynx, and upper esophagus. It is usually performed with the child seated in a normal eating position and using various consistencies of barium or food soaked in barium. Although VFSS is sensitive for oropharyngeal aspiration, it does not help evaluate lower esophageal motility or GER. Indications for use of VFSS include intolerance of FEES, suspected anatomical anomalies of the upper airway or esophagus, suspected swallowing disorders, and the need for a treatment plan to improve swallowing efficiency and decrease risk of aspiration. Contraindications include inability to be fed orally or never having been fed orally, inability to use the correct posture during examination for imaging, allergies to barium or iodine, and inability to transfer to the radiology department.[1]

Fiber-optic endoscopic evaluation of swallowing is useful in children and is of sensitivity similar to that of VFSS without the radiation.[18,20] With this test, the endoscopist observes multiple swallows of food of various consistencies through a small nasopharyngoscope located above the supraglottic area. This method allows both anatomical and functional evaluation of swallowing, except that nothing can be viewed during pharyngeal contraction because of airway closure, and there is no evaluation of the esophageal phase. It can be used in children with oral aversion, although some level of cooperation, or at least tolerance, is necessary with the nasopharyngoscope. In addition, properly trained staff must be available to perform the procedure; therefore, FEES is not as widely available as other diagnostic modalities. Fiber-optic endoscopic evaluation of swallowing has increased sensitivity for detection of laryngeal sensitivity for aspiration, but concerns have been raised regarding intrusion of the fiber-optic scope negatively affecting the swallowing process.[18,21] Both FEES and VFSS can only be used to assess a brief period, which can lead to both false-positive and false-negative results. An advantage to both is that they can assist with providing treatment recommendations, such as thickening of food or special positioning.

Other radiographic evaluations include gastroesophageal scintigraphy (milk scan); although offering the theoretical advantages of being more physiological and giving a longer window of viewing than the barium esophagram for detecting GER or aspiration, it is insensitive for detecting aspiration. The salivagram, another radionuclide scan, has been used to assess the aspiration of oropharyngeal contents. With this test, a small of amount of radionuclide is administered orally to mimic the amount of saliva in the mouth, and scanning is performed to look for tracheal or pulmonary aspiration. It may be more sensitive than gastroesophageal scintigraphy and has approximately the same sensitivity as VFSS.[22]

In patients with a tracheostomy or endotracheal tube, methylene blue used to be administered under the tongue or mixed in with food to help diagnose aspiration-related lung disease. Observation of stained tracheal secretions during subsequent suctioning was an indication of aspiration into the main airways. It is not advisable to add dye to large volumes of tube feedings because this has the potential for toxicity and larger amounts do not increase sensitivity for aspiration. This is a simple test that can be repeated multiple times, but caution is advised. Although they could not establish a causal relationship, the US Food and Drug Administration has issued an advisory regarding methylene blue use in these scenarios, with complications reported, including blue discoloration of the skin, urine, and feces; metabolic acidosis; and death, especially in patients who are seriously ill or have sepsis.[23]

Gastroesophageal reflux may produce respiratory symptoms such as chronic cough, with or without aspiration, through an exaggerated esophagobronchial response through shared vagal nerve innervation.[24,25] A cause-and-effect relationship between GER and respiratory symptoms is difficult to prove, as previously stated, because GER can exist without respiratory symptoms. An expert panel report from the American College of Chest Physicians in 2019 recommended that for children younger than 14 years with chronic cough (>4 weeks), a trial of GER medications should be attempted only if the child has signs of GER.[25]

Examination of BAL fluid obtained with flexible bronchoscopy or tracheobronchial aspirates from artificial airways can yield valuable information regarding aspiration, including analysis for pepsin, vegetable or meat fibers, bile, and lipid-laden macrophages. The use of biomarkers such as pepsin or lipid-laden macrophages to diagnose aspiration-related lung disease is limited owing to variations in study methodology and availability of testing.[24] Pepsin is a more specific biomarker of gastric pulmonary aspiration than are lipid-laden macrophages.[26] The usefulness of pepsin analysis in BAL fluid and sputum is unclear at this time, not only because there are no clinically validated assays but also because pepsin levels in BAL fluid did not differ between those with chronic cough and healthy control subjects in one study.[24] The finding of

lipid-laden macrophages is nonspecific for aspiration because it cannot help distinguish exogenous from endogenous lipids and results from studies evaluating the lipid-laden macrophage index have been inconsistent.[24] In one study, the lipid-laden macrophage index was higher in children with chronic respiratory symptoms than in healthy adults but did not seem to correlate with levels of inflammation.[27] With the use of proper histological techniques, the absence of lipid-laden macrophages highly suggests that lipid aspiration is not occurring.[28]

It is critically important to consider diagnoses other than aspiration as the cause of respiratory disease. Children with cystic fibrosis, asthma, interstitial pneumonitis, and primary ciliary dyskinesia, among other conditions, may present with an abnormal history or diagnostic assessment, which may indicate aspiration, thus delaying the primary diagnosis.

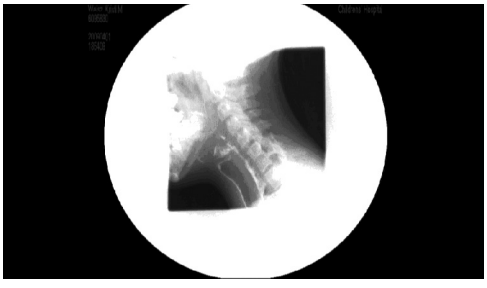


Figure 41-6. An image obtained during a videofluoroscopic swallowing study shows tracheal aspiration of a large volume of thin barium.

Management

Treatment should be directed at the underlying condition causing aspiration. Other treatments will depend on the severity of respiratory problems and whether they are caused by a swallowing dysfunction or GER. Conservative measures to prevent aspiration during swallowing include thickening or pacing of feedings, swallow stimulation, and change of feeding position. Thickening foods, upright positioning, avoidance of bottle propping and smoke exposure, and weight loss (if indicated) can be helpful in reducing GER. Medical treatment with proton pump inhibitors can reduce acid reflux but has not been shown to reduce nonacid reflux. Prokinetic agents available in the United States are metoclopramide and erythromycin. The efficacy of either drug is not well substantiated, and adverse effects are common with metoclopramide. A trial of nasogastric (NG) feedings can be used while waiting for temporary swallowing dysfunction to improve. Risks with NG tube feedings include nasopharyngeal lesions, sinusitis, insertion trauma or misplacement, esophagitis, GER due to stent placement that opens the lower esophageal sphincter, or gastrointestinal upset. With clinically significant GER, postpyloric feedings may be considered. Surgical treatment is reserved for patients with more severe morbidities, such as recurrent pneumonias requiring hospitalization or

evidence of progressive lung injury. Fundoplication can be considered and performed in conjunction with gastrostomy tube placement in children with clinically significant GER and/or oropharyngeal dysphagia. However, a preoperative decision must be made whether fundoplication should be performed at the same time as gastrostomy tube placement in children without clinically significant GER as some patients develop symptomatic GER after gastrostomy tube placement. Recurrent pneumonias may continue even after both fundoplication and gastrostomy tube placement because of continued aspiration of oral secretions, particularly in children who are neurologically impaired.

Anticholinergic agents, such as glycopyrrolate and scopolamine, may reduce excess salivation, but tolerance can develop, and adverse effects may occur, such as blurred vision, dry mouth, constipation, and urinary retention.[29] Excessive drying of tracheal and bronchial secretions can cause mucous plugging in the airways or life-threatening mucous plugs in tracheostomy tubes. Salivary gland injection of botulinum toxin can reduce salivation.[29] Investigators in a single-center study reported that injection of botulinum toxin to the salivary glands decreased or eliminated anticholinergic medications use as well as tolerance to injections for up to 9.6 years; they also reported decreased episodes of pneumonia and length of hospitalization stays.[30] Other minimally invasive interventions include salivary gland sclerotherapy, which is performed by an interventional radiologist. The salivary glands are identified, and then a sclerosing agent is injected to shrink the gland. Surgical intervention with salivary gland removal, ductal ligation, or laryngotracheal separation may be considered in children in whom more conservative therapy does not work.[22] Tracheostomy can be considered in a patient with chronic aspiration and airway clearance impairment leading to chronic lung disease or respiratory insufficiency. In this situation, tracheostomy is a means to improve pulmonary hygiene, as well as to provide ventilatory assistance and oxygen delivery.

Management of chronic aspiration can be multifactorial, and treatment is best individualized for the patient through close collaboration between the primary physician, pulmonologist, family, and team members from surgical subspecialties. As outlined, management can range from changing feeding behaviors to more invasive surgical interventions. In particular, when considering tracheostomy, it is important to take into account patient and family preferences, short- and long-term pulmonary needs, and upper airway anatomy, with consultation of otolaryngology subspecialists; consideration should be given to palliative care and pediatric pulmonology consultation for long-term care.

When to Refer and Admit

A child with recurrent pneumonia or persistent chest radiographic abnormality, dysphagia, coughing or choking with feedings, or recurrent wheezing not responsive to routine asthma therapy should be referred to a pediatric pulmonologist for further evaluation. Hospital admission would be indicated if there is clinically significant dyspnea, hypoxemia, worsening pulmonary signs or symptoms, equivocal history, or an acute life-threatening event. Any of these may indicate an acute or cumulative effect of chronic aspiration. If available, referral to a multidisciplinary aerodigestive team, generally consisting of a pulmonologist, otolaryngologist, gastroenterologist, and speech and language pathologist, should be considered for complex cases.

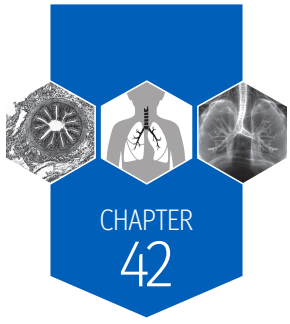
key points

- Oropharyngeal aspiration from swallowing dysfunction is the most common cause of recurrent pneumonia in children.
- A high index of suspicion is necessary for airway foreign bodies because the history, physical examination results, and radiographs may be normal. The ultimate diagnosis is often made only by means of MLB. Choking episodes should never be ignored.
- Clinical presentation for large-volume aspiration is generally associated with respiratory distress. Supportive care and observation should be provided, with the consideration of adding antibiotics, depending on severity of symptoms, underlying disease processes, and recent institutionalization or instrumentation of the airway. Routine use of corticosteroids is not indicated.
- Aspiration of hydrocarbons can cause surfactant disruption and tissue damage, quickly leading to acute hypoxemic respiratory failure. There is no support for routine use of oral corticosteroids or antibiotics.
- Evaluation for aspiration of foods includes physical examination during feedings, VFSS, and FEES. Both imaging modalities have limitations and benefits, but both allow for diagnosis of aspiration, as well as distinguishing safe consistencies of foods. There is no test for aspiration that is both highly sensitive and specific. Clinical judgment is always necessary to determine whether aspiration is a likely cause of existing respiratory disease.
- Small-volume aspiration, or micro-aspiration, of both oropharyngeal secretions and GER has been described and can be difficult to distinguish.
- Management of aspiration from feedings can include feeding therapies, thickening of food, or changing to enteral feedings via NG tube or gastrostomy tube.
- Management of aspiration from saliva or oropharyngeal secretions ranges from anticholinergic medications, botulinum toxin injections to salivary glands, and salivary gland sclerotherapy to more invasive measures such as salivary gland ligation or laryngotracheal separation.

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Lung Transplantation

Carol Conrad, MD

Introduction

The first pediatric lung transplant was performed in 1986. Lung and heart-lung transplants were prominent in the 1980s into the early 1990s, but because of improved surgical techniques, and in the interest of increased organ allocation, they are not as commonly performed in children as in adults. As of 2019, a total of 2,514 pediatric lung and 733 pediatric heart-lung transplants had been reported to the International Thoracic Organ Transplant Registry since its inception.[1] The registry reports a relatively stable number of pediatric lung transplants between 2010 and 2018 but a decrease in pediatric heart-lung transplants through the same period. Annually, the number of pediatric lung transplants has ranged between 97 and 136, and there has been a concomitant decrease in the number of centers that perform pediatric lung transplants. Pediatric lung transplant is a very specialized surgical procedure: fewer than 5 pediatric lung transplants are performed yearly at most of these centers.[1]

Survival after a lung or heart-lung transplant is lower in both children and adults than that for any other solid organ because the mechanisms that culminate in chronic graft dysfunction (ie, chronic lung allograft dysfunction [CLAD]) are not well understood. No new therapies have been introduced that readily prevent CLAD, although survival has improved slightly in recent years. Long-term survival for patients surviving 1 year after lung transplant is 9.1 years. This survival outcome compares favorably with the survival outcomes for adult recipients of lung transplants through 2009, but discrepancies are increasing, with noted worse survival rates in adolescents for the period from 2009 to 2017. During this period, adult lung transplant survival averaged 12.8 years, if the recipient survived to 1 year, but pediatric survival averaged 9.4 years, calculated with conditional survival to 1 year. For recipients of heart-lung transplants, the survival is slightly worse. The average survival of children with lung transplants varies by age group (**Figure 42-1**). Although the first-year mortality is much higher for infants younger than 1 year at the time of transplant, the mortality rate for all age groups is similar (**Figure 42-2**).[1,2]

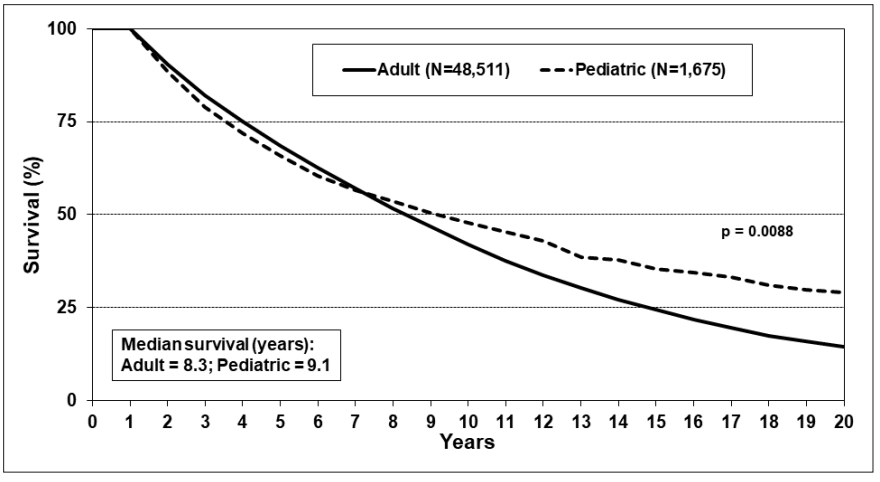


Figure 42-1. Pediatric lung transplant survival. Kaplan-Meier survival by age group is conditional on survival to 1 year by age group (transplants: January 1992–June 2017).

Reprinted from Hayes D Jr, Cherikh WS, Chambers DC, et al; International Society for Heart and Lung Transplantation. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: twenty-second pediatric lung and heart-lung transplantation report—2019; focus theme: donor and recipient size match. *J Heart Lung Transplant.* 2019;38(10):1015–1027. © 2019, with permission from the International Society for Heart and Lung Transplantation.

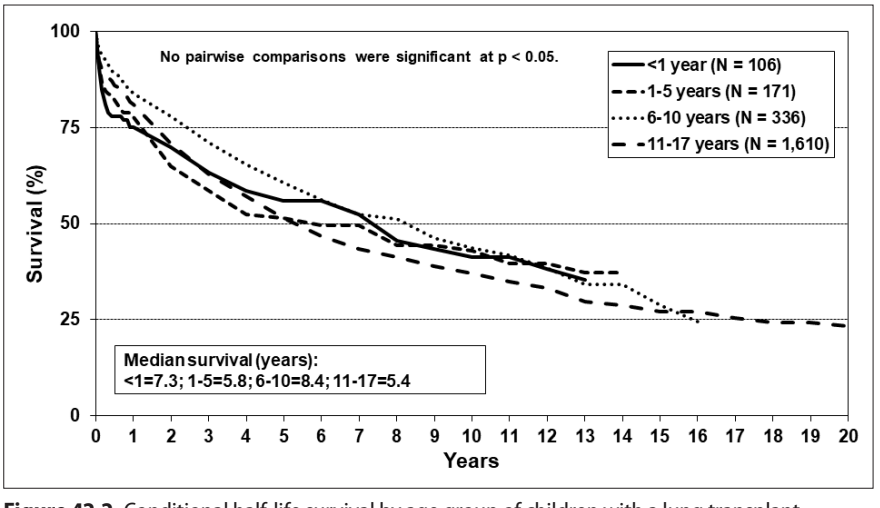


Figure 42-2. Conditional half-life survival by age group of children with a lung transplant (transplants: January 1992–June 2017).

Reprinted from Hayes D Jr, Cherikh WS, Chambers DC, et al; International Society for Heart and Lung Transplantation. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: twenty-second pediatric lung and heart-lung transplantation report—2019; focus theme: donor and recipient size match. *J Heart Lung Transplant.* 2019;38(10):1015–1027. © 2019, with permission from the International Society for Heart and Lung Transplantation.

The most life-limiting factor for recipients of lung and heart-lung transplants is chronic graft rejection that manifests histologically as obliterative bronchiolitis (OB) in the small airways, a restrictive disease characterized by parenchymal fibrosis, or a combination of the two. The clinical equivalent of OB is termed *bronchiolitis obliterans syndrome* (BOS). Obliterative bronchiolitis describes luminal obliteration of the bronchioles with accumulated fibrous tissue, which eventually leads to progressive respiratory failure once it has begun. Fibrosis of the lung parenchyma creates restrictive mechanics and is termed *restrictive allograft syndrome* (RAS). The fibrotic pathophysiology that characterizes both BOS and RAS is considered representative of the final common pathway of injury, occurring as a result of various forms of damage to the graft, which includes postoperative lung injury, including ischemia-reperfusion injury, primary graft dysfunction (PGD), immunologic phenomena such as acute cellular rejection (ACR) episodes, antibody-mediated rejection (AMR), and infection. The term *chronic lung allograft dysfunction (CLAD)* describes dysfunction of both types (BOS and RAS) and was coined in 2015.

Types of Lung Transplant

There are 4 major types of lung transplant: unilobar, bilateral, heart-lung, and living donor transplants. Unilobar lung transplants are uncommon in children because of previous outcomes with high mortality.[3] They are more commonly performed in adults with nonsuppurative chronic obstructive pulmonary disease and pulmonary fibrosis.

Bilateral lung transplant is the most common type of lung transplant performed in children. The most recent surgical technique for bilateral lung transplant is to transplant each lung individually via either median sternotomy or clamshell incision. These approaches minimize bypass time, which reduces related complications.

Pediatric heart-lung transplants performed per year have decreased to fewer than 12 annually worldwide, and totaled only 3 in 2017.[1] Because this type of graft may use up to 3 donor organs, it is reserved for children with advanced pulmonary vascular disease, complex congenital cardiac anomalies with Eisenmenger syndrome, lung disease due to abnormal left ventricular function, or cardiac anomalies with anatomy that cannot be fully corrected with bilateral isolated lung transplant and cardiac repair.[1] Patients with severe right ventricular dysfunction secondary to pulmonary hypertension but with preserved left ventricular function can tolerate transplant with isolated bilateral lung grafts because the right ventricle is often able to remodel and repair once the strain of working against the pulmonary arterial pressures is removed.[3,4]

Living donor lobar lung transplant was developed in the early 1990s to decrease waiting time of children who were severely ill awaiting lung

transplant. Waiting times were markedly reduced with the United Network for Organ Sharing's adoption of the new lung allocation score (LAS) in 2005, and advances in patient care before transplant have led to a decrease in waiting list deaths.[5] The institution of the new LAS system combined with the technical and ethical challenges associated with living lobar transplant have obviated the living donor lobar transplant procedure in the United States.[6]

General Clinical Indications

Guidelines for adult transplant have been firmly established, but the issues and the challenges regarding lung transplant for children are distinctly different than those for adults. In 2007, the International Pediatric Lung Transplantation Collaborative published the first set of guidelines on selection and referral criteria for pediatric candidates for lung transplant.[7] The indications vary by age group, but generally, lung or heart-lung transplant is a treatment strategy considered for children who have end-stage lung disease. Children should be referred if they have progressive lung disease or life-threatening pulmonary vascular disease that has no further options for remediation by means of medical or surgical therapy (**Table 42-1**) and for whom the life expectancy is severely limited. Complex congenital heart disease is the most common indication for infants, accounting for about 25% of transplants in this age group. Infants with primary pulmonary hypertension and pulmonary hypertension secondary to pulmonary vascular disease (eg, pulmonary venous obstruction, alveolar capillary dysplasia, Eisenmenger syndrome) constitute the next largest group. Infants with surfactant protein deficiencies B and C, surfactant deficiency (*ABCA3*), and pulmonary vascular malformations not manageable with surgical correction (pulmonary venous stenosis) constitute an increasing proportion of candidates. Interstitial pneumonitis accounts for the remainder of indications for lung transplant in infants. In the 1- to 5-year-old age group, primary pulmonary hypertension and interstitial pneumonitis are the predominant reasons for transplants, but for older children and adolescents, the principal cause for referral tends to be complications of cystic fibrosis (CF), closely followed by primary pulmonary hypertension. **Box 42-1** lists the most common reasons for referral of candidates for lung transplant.

Patients often have comorbid disorders that can complicate the procedure and affect the outcome. **Table 42-2** lists relative contraindications, but each center uses its own criteria. **Box 42-2** lists the criteria for absolute and relative contraindications to lung transplant. Most pediatric centers allow treatment with mechanical ventilation for patients who develop respiratory failure after listing, with certain exceptions, such as sepsis; however, this allowance poses an increased risk factor for mortality.[8]

Table 42-1. Indications for Lung Transplant in Children (January 2002–June 2018)

Indication	Age < 1 y (%)	Age 1–5 y (%)	Age 6–10 y (%)	Age 11–17 y (%)
Cystic fibrosis	-	3.4	48.1	85.4
Idiopathic pulmonary hypertension	11.3	26.7.2	10.0	8.9
Pulmonary hypertension other than idiopathic pulmonary hypertension	25.8	21.6	2.9	2.1
Retransplant not OB	-	4.3	2.9	3.4
Retransplant OB	-	3.4	2.9	2.8
Nontransplant OB	-	8.6	13.3	4.8
Interstitial lung disease	8.1	5.2	2.1	3.1
Interstitial lung disease (specific cause)	9.7	8.6	8.7	4.1
Surfactant protein B deficiency	22.8	3.4	1.2	0.2
Surfactant protein C deficiency	-	0.9	-	0.2
COPD/emphysema	3.2	0.9	1.2	0.9
Bronchiectasis	-	-	0.8	2.0
Other	4.8	4.3	4.6	2.1

Abbreviations: COPD, chronic obstructive pulmonary disease; OB, obliterative bronchiolitis.

Adapted from Hayes D Jr, Cherikh WS, Chambers DC, et al; International Society for Heart and Lung Transplantation. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: twenty-second pediatric lung and heart-lung transplantation report—2019; focus theme: donor and recipient size match. *J Heart Lung Transplant.* 2019;38(10):1015–1027. © 2019, with permission from the International Society for Heart and Lung Transplantation.

Box 42-1

Characteristics Associated With the Best Outcomes for Candidates for Lung Transplant

- **A well-defined diagnosis or projected trajectory of illness in which the child is at risk of dying without a lung transplant despite treatment with optimal medical therapy**
- **Adequate caregivers to provide support**
- **Satisfactory network of resources that ensure uninterrupted access to transplant services and medications after transplant**
- **Evidence that the patient and caregivers are motivated and that all demonstrate the ability to adhere to the rigorous therapy, daily monitoring, and an ongoing monitoring schedule of graft function after transplant**

Derived from Conrad C, Cornfield DN. Pediatric lung transplantation: promise being realized. *Curr Opin Pediatr.* 2014;26(3):334–342.

Table 42-2. Factors That Affect Prognosis of Lung Transplant in Children With Cystic Fibrosis

Factor	Measurement
Spirometric results	FEV_1, FVC
Poor exercise tolerance	Decreased 6-minute walk distance Desaturation during exercise Decreased maximal oxygen consumption
Abnormal blood gas results	Resting hypercarbia Resting hypoxemia
$\dot{V}/\dot{Q}$ mismatch	$\dot{V}/\dot{Q}$ scan
Pulmonary hypertension	Cardiac catheterization, pulmonary arterial pressure >30 mm Hg
Poor nutrition	Hypoalbuminemia Anemia Short stature Poor weight for height Low body mass index
Rapid decline	Rapid rate of decrease of FEV_1 Frequent exacerbations Young age
Female sex	-
Increased energy expenditure	Resting tachycardia
Multisystem involvement	Liver disease Diabetes mellitus

Since the early 2010s, extracorporeal support has been used to bridge pediatric and adult patients to transplant. Venovenous extracorporeal membrane oxygenation (ECMO)[9–11] and pumpless, low-resistance membrane oxygenator devices are preferred to venoarterial ECMO because the patient can more often participate in physical therapy while awaiting a donor. The outcome of lung transplant after use of venoarterial ECMO as a bridge to transplant was poor, with an overall survival rate of only 40%.[12] However, expertise and experience have led to improved outcomes with use of venovenous ECMO as a bridge, and with careful selection and emphasis on rehabilitation, the short-term survival is similar to that of patients who did not require venovenous ECMO before transplant.

The setting in which an optimal outcome is most assured is a center that incorporates experienced physical therapists, both before and after lung transplant; centers have reported that these patients are often ambulatory less than 1 week after transplant.[11–13] Some centers use central transthoracic placement of the ECMO catheters to allow patients to move their heads freely and ambulate

Box 42-2

Absolute and Relative Contraindications to Lung Transplant[a]

Absolute

- Active malignancy
- Sepsis
- Active tuberculosis
- Severe neuromuscular disease
- Documented, refractory nonadherence
- Multiple organ dysfunction
- Immune deficiencies, including hypogammaglobulinemia
- Hepatitis C with histologically proved liver disease
- Infection with HIV

Relative

- Pleurodesis
- Renal insufficiency
- Markedly abnormal body mass index (overweight or underweight)
- Mechanical ventilation
- Severe scoliosis or kyphosis
- Poorly controlled diabetes mellitus
- Osteoporosis
- Chronic airway infection with multiple resistant organisms
- Fungal infection or colonization
- Hepatitis B surface antigen positivity
- Long-term steroid use (eg, prednisone ≥ 10 mg daily)
- Use of illicit drugs

[a] These contraindications have been derived primarily from adults and can vary from center to center in some respects.

From Faro A, Mallory GB, Visner GA, et al; American Society of Transplantation. American Society of Transplantation executive summary on pediatric lung transplantation. *Am J Transplant.* 2007;7(2):285–292.
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more easily. An important advantage to using this method is that recirculation is prevented and minimal damage to the tricuspid valve occurs.[14]

Another device used more rarely to sustain survival to transplant is paracorporeal membrane oxygenation, which has been used in some infants and children with severe pulmonary arterial hypertension (PAH). A membrane oxygenator is interposed between the pulmonary artery and left atrium and acts as a pumpless oxygenator that allows for extubation and rehabilitation and potentially affords some right ventricular rest while the patient awaits lung transplant.[15]

Timing of Referral

There are no guidelines that determine the most appropriate time to refer a patient for a lung or heart-lung transplant. Before 2005, all lung candidates for transplant were prioritized according to the length of time they had been waiting to receive organs. This system led to inappropriate and early listing of patients who were considered too well for transplant; subsequently, a long waiting list at all centers filled with potential candidates but created a high waiting list mortality rate among the patients who were most severely ill. In an effort to minimize mortality on the waiting list, and to prioritize donors to the patients most likely to benefit from transplant, the LAS was conceived by transplant physicians in the community of the United Network for Organ Sharing (UNOS). The LAS was inaugurated in 2005 for patients aged 12 years or older. A complex formula was devised to account for variables, including the candidate's health, diagnosis, and lung function, and assign a level of illness severity to calculate the survival benefit and target the patients who could benefit the most. A similar formula has not been created for children younger than 12 years because of difficulties in measuring the lung function of toddlers and infants. In addition, children have fewer comorbid conditions to be accounted for than adults have. Instead, the previous system is used, and organs are targeted to candidates with time accumulated on the waiting list. However, some prioritization is granted within UNOS policy that allows for the organs from pediatric donors to be allocated first to children. Other factors that are considered include ABO blood type (although infants can receive ABO-incompatible organs), sensitization to human leukocyte antigens (HLAs; major histocompatibility tissue antigens), appropriate size matching of the lungs to the recipient's thoracic dimensions, and distance of the donor from the transplant center.

Selection of Candidates for Transplant

The single most important aspect of a successful lung transplant outcome is ensuring the most appropriate candidates are selected to undergo the procedure. Candidates for transplant should have generally good medical health and well-controlled comorbid medical conditions. Generally, if the candidate has clinically significant end-organ damage in more than 1 other solid organ, they are rarely, if ever, considered for listing because morbidity and mortality complicate the postoperative outcome in the short and longer terms. Acceptable medical conditions include systemic hypertension, diabetes mellitus, and peptic ulcer disease. Relative and absolute contraindications to lung transplant are listed in **Box 42-2**.

Selection Guidelines for Candidates for Transplant With Specific Diseases

Cystic Fibrosis

The criteria for referral of patients with CF are based primarily on the results of a longitudinal study by Kerem and colleagues[16] from 1992. They evaluated predictors of mortality in a large, single-center retrospective study. They were able to define that the patients at the greatest risk of mortality were those with an FEV_1 less than 30% predicted, a Pao_2 less than 55 mm Hg, and/or a Pao_2 more than 50 mm Hg. These patients had a 2-year mortality rate higher than 50%. The investigators found that the most statistically significant factor to predict mortality was the FEV_1; this factor became the foundation for the 1998 guidelines for patient referral for lung transplant, most of which have been maintained since (**Table 42-2**).[17]

Slightly broader criteria are used to recommend referral of patients to a transplant center than to recommend transplant. During the evaluation, consideration is based on the following criteria: (1) the trajectory of loss of lung function predicts less than a 2-year survival, (2) transplant is likely to improve the patient's quality of life, (3) no absolute contraindications to transplant have been identified, and (4) the patient is fully informed and committed to proceeding. Most pediatric transplant centers assess quality of life with qualitative consideration given to whether the child can participate in usual daily activities; whether the child has exercise intolerance; the amount of time spent in the hospital and treatment of disease exacerbations; whether oxygen supplementation is required at rest, during exercise, or with sleep to maintain normal oxygen saturation levels; and the patient's functional status as determined by means of the New York Heart Association Functional Classification System (class I, no symptoms or limitations in ordinary physical activity; II, mild symptoms and slight limitation; III, marked limitation due to symptoms; IV, severe limitations and symptoms even at rest).[18]

Physicians performing transplants attempt to balance the patient's life expectancy after transplant with life expectancy predicted without the procedure when considering the most optimal time for listing, although this aspect of care is not a science. The physician estimates the likely waiting time for a suitable organ to become available with the known survival statistics. In essence, early referral for transplant assessment is best because it allows for the evaluation to proceed in an organized manner, for the patient's treatment plan to be considered through a thorough multidisciplinary dialogue among team members, and for ensuring a thorough understanding of the

process on the part of patients and caregivers. This approach allows time for the patient, the family, and the referring center to develop trust and a good working relationship with the transplant center. For some children, it is the first occasion they and their family have had to discuss openly the possibility of their death. This situation can be quite stressful, especially for children, and an early referral allows time for their parents and caregivers to consider the complexities and the opportunities that transplant provides and make an informed decision.

Microbiological Issues in Patients With Cystic Fibrosis

Most patients are colonized with organisms that have developed resistance to many classes of antibiotics. Pretransplant colonization with multidrug-resistant organisms does not preclude transplant and can often be successfully treated with antibiotic therapy. In the era of routine use of inhaled antibiotics (aminoglycosides or colistimethate) and recent development of others (eg, amikacin, aztreonam), sputum in patients with CF is commonly colonized with species such as *Staphylococcus aureus*, both methicillin resistant and methicillin sensitive; *Pseudomonas aeruginosa*; *Xanthomonas* (formerly *Stenotrophomonas*) *maltophilia*; and *Achromobacter* (formerly *Alcaligenes*) *xylosoxidans*. The latter 2 organisms tend to be innately resistant to most classes of antibiotics. In vitro detection of panresistant species may be considered a relative contraindication because these findings often do not correspond to in vivo responses. Microbiological review of sputum should be performed routinely, at least at 3-month intervals during the pretransplant waiting period. If the organism is developing increasing patterns of resistance, the length of antibiotic use after transplant may be reconsidered.

Few data are available from pediatric transplant centers regarding the effect of colonizing organisms present before transplant on survival and other outcomes in pediatric transplant. Unless otherwise noted, the data that follow are culled from studies on adult recipients of transplants.

Burkholderia cenocepacia *Complex*

Colonization with *B cenocepacia* (formerly *B cepacia* genomovar III) has a marked severe and negative effect on posttransplant survival. There have been no peri- or postoperative antibiotic interventions that prevent recolonization of the lower airways after transplant.[19–21] Results from a 2008 study using data from patients referred for transplant in the United States suggest that the risk of poor outcome is limited to patients colonized with nonepidemic strains of *B cenocepacia*; posttransplant mortality was also increased in patients infected with *Burkholderia gladioli*.[22] Therefore, these organisms being cultured from the patient's sputum remains a strong relative, if not absolute, contraindication to lung transplant internationally.

Fungus and Molds

Results from a retrospective analysis in pediatric recipients of lung transplants demonstrated an increased risk of mortality from pulmonary fungal infections the first year after lung transplant. Risk factors for pulmonary fungal infection included pretransplant colonization.[23] For patients whose cultures previously had grown certain fungi, such as *Aspergillus fumigatus* and *Scedosporium apiospermum*, secondary prophylaxis should begin in the immediate perioperative period because these species can become invasive infections in patients who are immunosuppressed. *Scedosporium* species, in particular, are inherently resistant to most antifungal medications but may retain sensitivity to voriconazole.[24,25]

Nontuberculous Mycobacteria

There are few data with regard to mortality associated with mycobacterial infection or colonization. Experience with adult transplant patients who have CF is limited and mostly anecdotal or in case series. Study results indicate that although nontuberculous mycobacteria disease causes clinically significant morbidity in a small number of patients after transplant, it can be successfully treated and does not influence posttransplant survival. However, the incidence of BOS is higher in patients with nontuberculous mycobacteria.[26] The isolation of nontuberculous mycobacteria before transplant in patients with CF may not necessarily exclude those patients from consideration for lung transplant, but it should alert the clinician to prepare patients for the risk of recurrence after transplant and for the possibility of the ongoing use of intravenous antibiotics for successful control in the setting of immunosuppression. For this reason, centers vary in their acceptance of patients colonized with nontuberculous mycobacteria.

Surfactant Deficiencies

Infants with surfactant protein B deficiency should be referred to a pediatric lung transplant center immediately on diagnosis because mortality is nearly 100% during the perinatal period. Surfactant protein B deficiency manifests as unrelenting respiratory failure or progressive interstitial lung disease with respiratory insufficiency and is unresponsive to medical interventions. However, treatment requiring ECMO may be a contraindication to transplant, particularly if there is other organ insufficiency, such as a comorbidity, or if cerebral hemorrhage has occurred. The other surfactantopathies often manifest with less severe symptoms and may be possible to treat with medical therapy. Genetic testing capabilities are rapidly improving and are less expensive than in the past, but the phenotypic variation of children born with these mutations that were previously suspected to confer lethality seems to be widening. The severity of the defect may not be discernable solely with gene mutation analysis to predict the long-term outcome, and watchful waiting may be merited.[27,28]

Idiopathic Pulmonary Hypertension and Pulmonary Arterial Hypertension

Patients with idiopathic pulmonary hypertension or PAH should be referred to a lung transplant center if they are considered to be at New York Heart Association functional class III or IV despite treatment with intravenous, oral, or inhalational vasodilator therapy. Similarly, if the candidate has a low tolerance to exercise or oxygen desaturation with a 6-minute walk test, recurrent syncopal episodes, hemoptysis, or right-sided heart failure, referral should be initiated. Some patients present to medical care with severe symptoms, and they should be referred for lung or heart-lung transplant at the same time that they begin treatment for PAH. Major comorbidities that are a contraindication for single-organ transplant include renal failure and liver failure with hyperbilirubinemia. Dual-organ transplant may be necessary. Identifiable causes of the PAH must be sought and include collagen vascular disease, primary pulmonary disease, chronic thromboembolic disease (rare in children), and pulmonary venous obstruction that can be treated with surgical correction.

Eisenmenger Syndrome

Children with Eisenmenger syndrome should be referred to a transplant center if they have profound hypoxemia despite ameliorative therapy. Contraindications for lung transplant in these children include the presence of major comorbidities, left ventricular failure, irreparable congenital heart defect (heart-lung transplant should be considered), or history of previous thoracotomies because the consequent scarring from those surgeries can substantially increase intraoperative mortality due to hemorrhage. Patients with Eisenmenger syndrome should be referred when their cardiac function is worsening or they have impaired exercise tolerance and a worsening quality of life.

Other Pulmonary Vascular Disorders

Patients with other congenital malformations of the pulmonary vasculature should be referred for evaluation because there are no effective medical strategies for treatment. Infants born with total or partial anomalous pulmonary venous return who undergo surgical repair but for whom the follow-up echocardiogram demonstrates rapid recurrence of obstruction should be referred for urgent evaluation.

Diffuse Parenchymal Lung Disease

Diffuse parenchymal lung diseases arise from heterogeneous causes and include alveolar capillary dysplasia with misalignment of the pulmonary veins and other idiopathic diffuse lung diseases that demonstrate unremitting progression despite optimal medical management. Contraindications for

transplant in patients with diffuse parenchymal lung disease include the presence of systemic disease that might later affect the allograft. These potential candidates should be referred early in the course of their disease process.

Evaluation of the Donor

Box 42-3 describes the criteria used to define an ideal donor. These criteria have been developed largely from clinical experience rather than multicenter trials.[29] Specific criteria for donors to children have not been established. However, it is generally accepted that the ideal lung donor for children should be a nonsmoker of the same height (particularly of chest dimensions) and ABO-compatible blood type. The donor should have no clinically significant history of lung disease, including asthma. Donors who have sustained pulmonary trauma or infections are rarely selected. Gas exchange should be minimally impaired, and ischemic time between organ harvest and implantation should be minimal, although the optimal time frame has not been established. Some pediatric lung transplant centers may apply more stringent criteria if the candidate in question is reasonably stable. Organs from donors younger than 55 years are desirable in most instances.

Depending on the need of the candidate, donors who are considered nonideal, also referred to as *extended* or *marginal* donors, may be accepted. Data are limited to either support or prohibit the use of lungs from a nonideal donor. There is no evidence that organs from a marginal donor will have any effect

Box 42-3

Features of the Ideal Donor

- **Age < 55 y**
- **ABO compatibility**
- **No human leukocyte antigen antibody sensitization by recipient**
- **Clear chest radiographs**
- **Pao_2 > 300 on FIo_2 = 1.0, PEEP = 5 cm H_2O**
- **Nonsmoker (never smoked)**
- **Absence of chest trauma**
- **No evidence of aspiration or sepsis**
- **No prior cardiopulmonary surgery**
- **Absence of organism and polymorphonuclear cells on sputum Gram stain**
- **Absence of purulent secretions at bronchoscopy**

Abbreviations: FIo_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure.

Reproduced from Bhorade SM, Vigneswaran W, McCabe MA, Garrity ER. Liberalization of donor criteria may expand the donor pool without adverse consequence in lung transplantation. *J Heart Lung Transplant.* 2000;19(12):1199–1204. © 2000, with permission from the International Society for Heart and Lung Transplantation.

on either immediate or long-term morbidity or mortality, except in egregious cases, including if bronchopneumonia or purulent secretions of the lower airway are detected in the donor during bronchoscopy. Lungs obtained from donors older than 50 years who have a significant smoking history are at risk for developing malignancy in the setting of immunosuppression.

Posttransplant Care

Postoperative Management

Immunosuppression

Successful lung transplant is achieved if acute lung allograft dysfunction and CLAD can be prevented. Acute allograft dysfunction recorded after the first month is most commonly associated with acute allograft rejection by the recipient and is most commonly mediated by activation of recipient T lymphocytes to the allograft. Transplanted lungs still contain bronchus-associated lymphoid tissue, which is intimately associated with the bronchi and, thus, cannot be completely removed at the time of organ harvesting. This fact, along with higher immunogenicity and constant exposure of the lungs to the environment compared with what is seen with other solid organ transplants, are possibly the main reasons for the higher rate of ACR in the transplanted lung. Transplanted lungs are also much more easily infected because the recipient receives high doses of immunosuppression after lung transplant. If too aggressively implemented, strategies to prevent rejection often result in infection. Conversely, more liberal approaches to immunosuppression to allow for recovery from infection or Epstein-Barr virus (EBV)–associated posttransplant lymphoproliferative disorder (PTLD) may result in acute rejection.

Induction Therapy

Recurrent trauma to the allograft, such as can be sustained with acute rejection episodes, infections, and inhalation injury, contributes to the development of CLAD. Chronic lung allograft dysfunction affects most recipients of lung transplants, and its emergence is detectable in 20% of recipients within the first 2 years after lung transplant. Most adult and pediatric transplant centers apply induction immunotherapy at the time of transplant to decrease the risk of acute rejection; it is presumed this will protect from both ACR and CLAD, but evidence for these effects is lacking in the survival data.[1]

Maintenance Immunosuppression

On the basis of adverse effects in children and efficacy, the International Pediatric Lung Transplant Collaborative has adopted a standard immunosuppressive protocol consisting of tacrolimus, mycophenolate mofetil, and prednisone as the cornerstone of maintenance immunosuppression.[1]
The most widely accepted regimens still rely on a calcineurin phosphatase inhibitor, in combination with a cell cycle inhibitor and a corticosteroid. The 2 main calcineurin phosphatase inhibitors currently in use are cyclo-

sporine and tacrolimus, with approximately 20% of patients receiving cyclosporine and 80% receiving tacrolimus. Both work similarly, and both have clinically significant systemic adverse effects. There is no clear benefit of one over another in preventing OB or affecting survival. Adverse events associated with tacrolimus treatment include hyperglycemia, alopecia, and possibly PTLD; cyclosporine-based regimens are associated with hypercholesterolemia, hypertension, hirsutism, and gingival hyperplasia. The cosmetic effects, in particular, often lead to medication nonadherence among the adolescent cohort.

Since 2010, the combination of tacrolimus and mycophenolate mofetil or mycophenolic acid has been the maintenance immunosuppressive regimen of choice, with 82% of patients receiving that combination at 1-year post-transplant follow-up; the next most common combinations are tacrolimus and azathioprine (7%) and single-agent therapy with tacrolimus (5%).[1] Almost all pediatric lung transplant programs include steroids as part of a triple-drug immunosuppression regimen. The steroid dose is tapered to decrease the incidence of complications, which often include osteopenia, fractures, and hyperglycemia.

Long-term Follow-up After Transplant

The prognosis after a successful lung transplant is guarded. Mortality due to complications is 10% to 15% in the first year. Most complications occur in the first 6 months after transplant.[1] Early graft dysfunction occurs as a result of ischemia-reperfusion injury and previously accounted for most deaths within the first month after transplant. Most recipients of lung transplants have some clinical evidence of PGD due to ischemia-reperfusion injury, and the expression is usually most prominent during the first 72 hours after the transplant. The syndrome manifests as various levels of severity of graft dysfunction, from mild hypoxemia to fulminant graft failure. Primary graft dysfunction is noted histologically with neutrophil infiltration. The incidence of higher grades of PGD is much less common because organ preservation techniques at the time of organ harvesting have been optimized. Ischemia-reperfusion injury that progresses to severe PGD is very likely to result in early emergence of CLAD.[30]

Long-term Monitoring

Care for children who have received a lung transplant is complex. Monitoring the patient and the allograft function requires the coordination of care among several services. The transplant team components include the patient and family; a pulmonary function laboratory that is familiar with working with children; and ancillary services, including radiology, interventional radiology, pharmacy, laboratory, social work, specialty nursing, and committed primary care and pulmonary physicians. Most transplant centers monitor patients routinely with laboratory tests, surveillance bronchoscopy for assessment of

rejection and infection, spirometry and comprehensive pulmonary function tests, exercise studies, and frequent imaging. Because of the limitations of infant pulmonary function testing and the fact that sedation is required for many of these diagnostic procedures, follow-up of infant recipients of lung transplants presents additional challenges. Transbronchial biopsies are the primary means by which ACR is diagnosed; they can safely be performed by experienced personnel.

Rejection

Children who have received lung transplants may experience 1 or more of 4 types of rejection. See **Box 42-4**.

Box 42-4

Types of Lung Transplant Rejection

1. **Hyperacute rejection (immediately after transplant): This is a rare event that occurs when human leukocyte antigen sensitization to the donor antigens is present.**
2. **Acute cellular rejection (most common in the first 6–12 months): This is the most common type of rejection; it occurs with highest frequency in the first year after transplant.**
3. **Humoral rejection: This is antibody-mediated rejection that occurs when donor-specific antibody develops.**
4. **Chronic airway rejection: The process begins in most recipients within the first or second year, and progression depends on host factors and on immunologic factors related to the graft; chronic vascular rejection occurs in the cardiac graft in heart and lung transplants and is the equivalent of chronic airway rejection.**

Hyperacute Rejection

Hyperacute rejection is rare but can cause complete rejection of the lungs within 24 hours. It is caused by antibodies to the allograft formed by the recipient after a sensitizing event (blood transfusion, pregnancy, connective tissue disease, or previous transplant). The mechanism of hyperacute rejection involves the binding of preformed antibodies against major allograft antigens, usually HLA. Hyperacute rejection manifests clinically as severe graft dysfunction immediately postoperatively with worsening oxygenation, a decrease in lung function, fever, pleural effusions, pulmonary edema, and diffuse parenchymal infiltrates; it can manifest as diffuse alveolar damage.[31] The incidence has decreased dramatically with increased understanding and surveillance for HLA hypersensitivity and avoidance of donors to whom the candidate is sensitized.[32]

Acute Cellular Rejection

Acute cellular rejection occurs when T lymphocytes identify foreign proteins on the surface of cells in the transplanted lung and cause injury to those

cells. This is a normal function of the immune system and is important as a response to control the growth of tumors and viral infections, but it is diminished with the use of immunosuppressants.

Acute cellular rejection usually occurs in the first 6 to 12 months and is usually detected at a mild stage because of increased surveillance with bronchoscopy and biopsy procedures during the first 6 months after transplant. Transplant centers differ in their surveillance protocols for transbronchial biopsy. Generally, most centers schedule these monthly for the first 3 months, at the sixth month, and then again at 12 months. There is controversy as to when or if transbronchial biopsies should be performed after the first year. Many centers perform surveillance bronchoscopy annually thereafter and obtain biopsy specimens if clinically indicated, such as when ACR or infec-tion is suspected. Indications for bronchoscopy are to assess for the presence of infection or when AMR is suspected when acute graft dysfunction is measured and is coincident with an elevation of antibody levels to HLAs of the donor.

Acute rejection is graded according to how far the lymphocytes extend into the tissue surrounding the blood vessels (**Figure 42-3**). Acute rejection can occur with or without outward symptoms. If symptoms are present, they are quite similar to those of a lung infection, and signs can include fever, cough, dyspnea on exertion, decrease in spirometric test results (FVC and FEV_1),

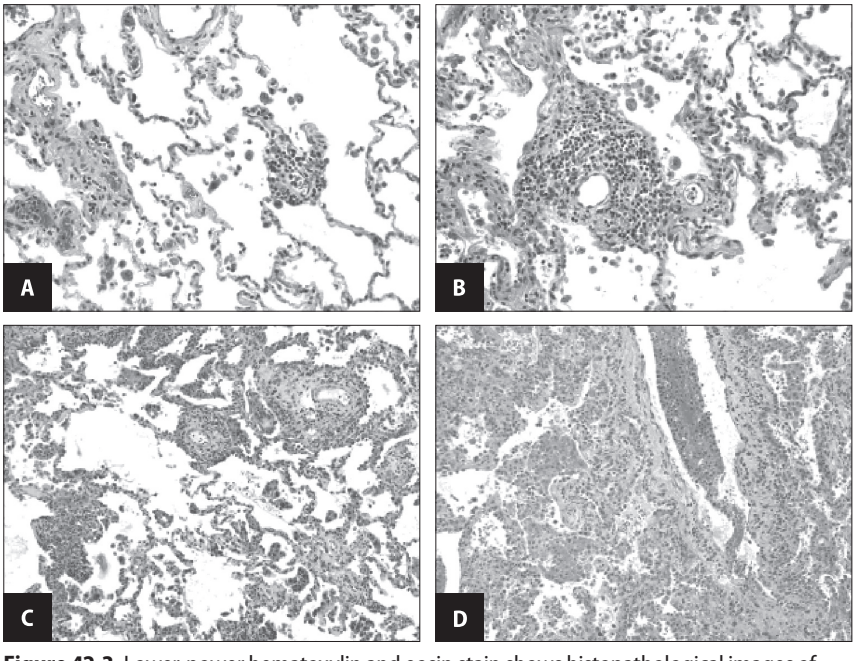


Figure 42-3. Lower-power hematoxylin and eosin stain shows histopathological images of acute cellular rejection and grades of severity. Grade A1 (**A**) indicates minimal acute cellular rejection, grade A2 (**B**) indicates mild acute cellular rejection, grade A3 (**C**) indicates moderate acute cellular rejection, and grade A4 (**D**) indicates severe acute cellular rejection.

increase in the white blood cell count, and abnormal changes noted on chest radiographs (pleural effusion or new opacifications).

Most initial low-grade episodes of acute rejection respond to treatment with high doses of steroids, and lung function often returns to baseline once treated. If the disease is classified as grade A2 or worse, treatment is initiated with a pulse of intravenous corticosteroid once a day for 3 days, and follow-up bronchoscopy and transbronchial biopsy are performed within 4 weeks after completing treatment to confirm response. If rejection is still present at the follow-up biopsy, and it is not grade A1 or improved, some centers may use monoclonal antibodies or antilymphocytic antibody (rabbit anti-thymocyte globulin), and they may alter or increase the oral immunosuppressive agents.

Most patients experience at least 1 asymptomatic episode of acute rejection in the first year, although the risk may be lower in children younger than 1 year. If ACR is treated early and is low-grade (A2 or better), allograft dysfunction can be avoided. In most patients, mild acute rejection resolves after treatment.

Chronic Lung Allograft Dysfunction

Extended survival is compromised by CLAD. Chronic lung allograft dysfunction was previously termed *BOS*, which described obstructive graft dysfunction due to fibrotic obliteration in the smallest airways. In 2015, a consensus conference convened to define better the chronic rejection in lung transplant. The acronym *CLAD* was originated to encompass all types of graft dysfunction. It encompasses the several forms of CLAD defined by pulmonary mechanics, including restrictive, obstructive, and mixed phenotypes.[33] It is thought that CLAD eventually emerges as a result of various injuries to the graft that produce chronic active inflammation. A dysregulated injury response results, and CLAD is noted. Bronchiolitis obliterans syndrome is characterized by progressive airflow obstruction due to fibrotic obliteration of the small airways.[34] Restrictive allograft syndrome is characterized by restrictive lung function mechanics. Often, study results demonstrate elements of both. Within 5 years after transplant, fewer than 50% of recipients are free from BOS (**Figure 42-4**). Investigators have made substantial efforts to identify, prevent, or treat the causes of CLAD, yet its pathophysiological mechanism is not well characterized. Treatments are generally palliative rather than curative.[35,36]

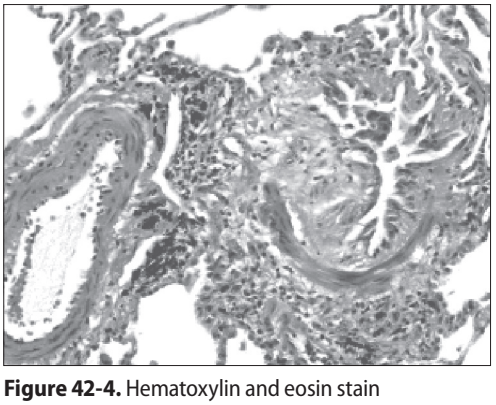


Figure 42-4. Hematoxylin and eosin stain demonstrating obliterative bronchiolitis.

Bronchiolitis Obliterans Syndrome

The symptoms of BOS include shortness of breath and low oxygen saturation levels. Patients who develop OB may have chest cold symptoms or initially may have no symptoms at all. It is detected clinically with the use of pulmonary function testing and/or imaging.

The most useful early indicator of OB is a decrease in lung function—specifically, the FEV_1 and the FEF 25%–75% of FVC that is not otherwise explained. See **Table 42-3** for grading criteria for BOS. The potential-BOS stage (0-p) alerts the physician to the need for close functional monitoring and assessment. Symptoms of more severe OB include onset of a dry or productive cough that is not related to an infection, a new onset of shortness of breath with or without exercise, and a decrease in lung function (FEV_1) that is otherwise unexplained. A decrease in oxygen saturation measured eventually occurs but is a late sign.

Transbronchial biopsy samples often do not indicate the histological presence of OB because it most often initially is a sporadic process and the pieces obtained during biopsy are very small. If present, OB appears as dense eosinophilic intraluminal scarring, primarily involving the bronchioles. Advanced BOS stages are associated with fibrointimal scarring that also can be present in the pulmonary arteries and veins (**Figure 42-4**).

Table 42-3. Classification and Staging of Bronchiolitis Obliterans Syndrome

Stage	Definition
0	FEV_1 >90% of baseline *and* FEF 25%–75% >75% of baseline
0-p	FEV_1 81%–90% of baseline *and/or* FEF 25%–75% ≤75% of baseline
1	FEV_1 66%–80% of baseline
2	FEV_1 51%–65% of baseline
3	FEV_1 ≤50% of baseline

Abbreviation: 0-p, potential BOS.

Reprinted from Estenne M, Maurer JR, Boehler A, et al. Bronchiolitis obliterans syndrome 2001: an update of the diagnostic criteria. *J Heart Lung Transplant.* 2002;21(3):297–310. © 2002, with permission from the International Society for Heart and Lung Transplantation.

Restrictive Allograft Syndrome

Historically, chronic lung graft dysfunction was thought to manifest only as BOS and lead to a decrease in the FEV_1, but, in 2005, a novel subtype of graft dysfunction was described.[37] Since then, various phenotypes of CLAD with distinct prognostic importance have been described. The entity Pakhale and colleagues[37] described is now known as RAS. Restrictive allograft syndrome fibrosis occurs predominantly in the peripheral lung tissue rather than in small airways, resulting in a decrease in total lung capacity, FVC, and FEV_1.

Phenotypes of CLAD are characterized with a combination of pulmonary function testing and chest computed tomography. Eighty percent of patients with CLAD have no identifiable cause for chronic graft failure, yet identifiable causes of graft dysfunction must be sought and fully treated. These causes include AMR, ACR, chronic infection, aspiration, obesity, gastroesophageal reflux disease, and ongoing chronic inflammation. Distinct phenotypes of CLAD have individual prognostic importance. For example, neutrophilic reversible allograft syndrome can often be arrested with a prolonged course of oral azithromycin and attention to airway clearance techniques. However, RAS is rapidly progressive, difficult or impossible to slow, and associated with a low survival rate.

Treatment Options for CLAD

There is no maintenance immunosuppression protocol known to prevent CLAD. As stated before, using an induction regimen at the time of transplant has not proved preventive. Once graft dysfunction is established, intervening with more immunosuppression is ineffective to treat BOS or RAS. Bronchiolitis obliterans syndrome, if not associated with AMR, infection, or inflammation, may be slowed with maintaining good chest physiotherapy to prevent postobstructive pneumonia and chronic inflammation. Many physicians resort to substituting cyclosporine for tacrolimus, attempt a trial of azithromycin for 3 months or longer, or proceed to fundoplication of the gastroesophageal junction if gastroesophageal reflux continues despite optimal medical treatment. These steps tend to result in limited success. Photopheresis, in the setting of recurrent ACR, or plasmapheresis in the setting of AMR, may slow the rate of graft deterioration. If these approaches fail, retransplant is indicated in selected cases.[37,38] No formal guidelines for treatment of RAS exist. Pirfenidone is a medication approved by the US Food and Drug Administration in 2014 to slow the process of idiopathic pulmonary fibrosis (IPF). Pirfenidone has a potent effect in vivo and an antifibrotic effect in vitro. The mechanism by which pirfenidone acts is to inhibit the synthesis of transforming growth factor β and tumor necrosis factor α, which has a downstream effect that leads to a lessening in fibroblast proliferation, less collagen synthesis, and thus a slower decrease in lung function in animal models of fibrosis and in patients with IPF.[39] The treatment is currently experimental, but results from case reports have confirmed some beneficial effects (ie, mild improvement of interstitial changes and lung function) of pirfenidone.[40,41]

Nintedanib is a drug also developed to treat IPF by targeting cellular receptors that have been implicated in the pathogenesis of IPF. If blocked, these receptor and nonreceptor tyrosine kinases no longer serve to activate fibroblast growth factor receptor, platelet-derived growth factor receptor, and vascular endothelial growth factor receptor, and the intracellular signaling required for the

proliferation of fibroblasts is blocked.[42,43] Nintedanib has not been tested in placebo-controlled trials in patients receiving lung transplants.

Extracorporeal photopheresis (ECP) has emerged as an effective option in arresting BOS. It has been used with success in treating cutaneous T-cell lymphoma and graft-vs-host disease.[44] Extracorporeal photopheresis induces DNA cross-linking in T cells with the use of psoralen in the patient; then the patient's plasma is passed over an ultraviolet light source. This treatment results in apoptosis of T lymphocytes, including natural killer cells. The dying apoptotic lymphocytes are then eliminated on reinfusion by dendritic cells, decreasing the population of activated T cells. The first successful treatment with ECP in lung transplant occurred in 1993.[44] Results from various studies have shown that ECP modulates dendritic cells, alters cytokine profiles, and induces specific T-cell subpopulations. Results from small studies[45–47] have validated efficacy to treat CLAD, but conclusions are limited because the studies have been small and have not included comparison with other modes of immunosuppression.[45] Nonetheless, ECP is used in most centers as rescue treatment for BOS.[46]

Posttransplant Lymphoproliferative Disorder

All patients receiving lung transplants are at risk for developing PTLD, a form of cancer in children naïve to EBV infection before transplant but who become exposed afterward. It can also develop in children who were previously infected with EBV. In those previously exposed, in the normal host, the virus remains dormant in the B-lymphocyte cells. The EBV is more easily reactivated when the child is immunosuppressed. When this happens, lymphoid nodules form as the B cells multiply rapidly.

Posttransplant lymphoproliferative disorder occurs in about 10% to 15% of pediatric recipients of lung transplants. It most commonly occurs in the first 2 to 3 months after transplant at the time of highest immunosuppression but may occur many years after transplant. Most patients do not have symptoms, and the tumor is discovered during a routine physical examination. Other patients have flu-like symptoms associated with a primary infection, and disease manifestations might be due to the location of the tumor (eg, diarrhea, pharyngitis, hepatitis, cough). The prognosis depends on the amount and location of tumor formation and the response to treatment. In a small number of cases, PTLD is fatal. Patients who are EBV positive or who have a donor who is EBV positive are tested frequently for EBV viremia with an EBV DNA polymerase chain reaction test.

There are several types of treatment options for PTLD. Most often, the doses of immunosuppressive medicines are decreased, which may cause the tumor to shrink or even disappear. More often, chemotherapy is administered in

addition so that patients may recover without the risk of rejection. In some cases, surgery is necessary to remove large, bulky tumors.

Survival

Chronic lung allograft dysfunction is the most common and clinically significant reason for poor long-term survival among recipients of lung and heart-lung transplants. Bronchiolitis obliterans syndrome is the most common expression of CLAD. Children who survive 1 year after transplant have good functionality of the allograft, although approximately 13% have BOS and the occurrence increases over time.[1] Bronchiolitis obliterans syndrome occurs in more than 50% of recipients of lung transplants, both adults and children, who survive 5 years after transplant. Recipients of living donor lobar transplants more commonly die from complications of infection.[48] Overall survival is equivalent regardless of the source of the transplant.

Children with lung transplants experience similar complications as do adults, but growth and developmental issues are unique to children. For adolescents, nonadherence is a frequent problem, leading to the lowest survival in this age group. The 5-year survival rate after lung transplant in children is about 60% (**Figure 42-2**).[1] Survival among children whose primary lung dysfunction was due to noninfectious lung disease (ie, other than CF) is better than that in patients with pulmonary vascular disease or CF.[48] Infants have a higher 1-year mortality, although long-term survival in infants is similar to that in other pediatric recipients. Retransplant has much lower first-year and long-term survival than that of primary transplants in children and adults; thus, few patients qualify.[1,38,39] Risk factors for poor survival after lung transplant include mechanical ventilation or ECMO at time of transplant; a diagnosis of congenital heart disease; and repeat transplant, particularly for treatment of RAS.

key points

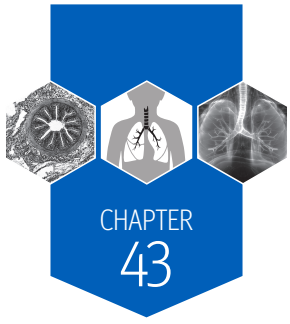
- Lung and heart-lung transplant are indicated in children who have developed end-stage lung disease, who have no other medical or surgical treatment options, and for whom life expectancy is less than 2 years.
- Children and adolescents are most frequently referred for transplant because of end-stage diseases of CF and PAH.
- Lung transplant is elected as an option after careful consideration and extensive education and does not occur emergently.
- Postoperative care is complex and requires close interaction between the primary care clinician and the transplant team for the rest of the recipient's life.
- Immunosuppression consists of a triple-drug regimen, including a calcineurin phosphatase inhibitor, a T-lymphocyte antiproliferative medication, and corticosteroid therapy. These are continued for the rest of the patient's life.
- The maintenance medication regimen's dosage carefully maintains a balance between preventing rejection and preventing infection.
- The most important life-limiting complication that restricts long-term survival of recipients of lung and heart-lung transplants after the first year is CLAD.
- Lung and heart-lung transplant extend and improve the quality of life, but because of the occurrence of CLAD, they are not a likely means to extend life beyond approximately 7 to 10 years.

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Asthma and Other Respiratory Disorders Associated With Obesity

Mutasim Abu-Hasan, MD
David Fedele, PhD, ABPP

Introduction

Asthma and obesity are both major public health problems with high prevalence and increasing incidence in children and adults.[1–3] Both illnesses have serious short- and long-term health consequences.[4] There is an increased interest in understanding the interaction between asthma and obesity and in establishing a diagnostic and treatment approach specific to patients who have both illnesses.

The association between asthma and obesity is well established by results from several epidemiological studies.[5] The incidence of asthma diagnosis is higher in patients with obesity than in patients without obesity,[6] and the incidence of obesity in patients with asthma is higher than that in individuals with no asthma.[7] More importantly, patients with asthma and obesity have more severe asthma than do patients without obesity.[8,9] Results from interventional studies have also shown that weight loss in patients with obesity and asthma results in improvement of asthma symptoms, lung function, and asthma-related quality of life.[10,11]

There are 3 possible explanations for the strong association between asthma and obesity: (1) a common etiologic and pathophysiological pathway; (2) a positive interaction between the 2 disease processes, by which obesity enhances the pathophysiological characteristics of asthma and/or asthma worsens obesity; or (3) an overlap of respiratory symptoms between asthma symptoms and other obesity-related respiratory disorders (eg, restrictive lung disease, obesity hypoventilation syndrome, obstructive sleep apnea [OSA]) that makes patients with obesity more likely to have asthma misdiagnosed.

Atopy and Airway Inflammation in Asthma and Obesity

Despite the strong association between asthma and obesity, there are many more patients with asthma who do not have obesity than who have it, and, vice versa, there are more patients with obesity who do not have asthma than who have asthma.[12] This discrepancy suggests that asthma and obesity are separate disease entities and do not share a common cause. However, patients with obesity and asthma have overlapping pathological and physiological abnormalities that can potentially explain their strong association (**Table 43-1**).

Atopy and allergic sensitization have been implicated as a potential common pathway between obesity and asthma. Even though atopy is generally high in both disease entities, investigators in epidemiological studies have failed to demonstrate a direct link.[13–15] The increased asthma prevalence among children with obesity appears to be unrelated to atopy status in these patients.[16]

Airway inflammation has also been suggested as a possible link between asthma and obesity. Increased systemic inflammation is present in patients with obesity as indicated by increased blood levels of interleukin 6 and C-reactive protein, which contributes to the cardiovascular complications of obesity.[17] This heightened systemic inflammation in patients with obesity can potentially contribute to airway inflammation and increased asthma symptoms and asthma diagnosis. However, there is no evidence of direct correlation between systemic inflammation and airway inflammation in patients with obesity and asthma.[18,19] Furthermore, there is no evidence that patients with obesity have increased

Table 43-1. Differential Effects of Asthma and Obesity on the Physiological Characteristics of the Respiratory System

Physiological Characteristic	Asthma	Obesity
Restrictive lung disease	Absent	Present
Upper airway obstruction	Absent	Present
Small airway obstruction	Present	Absent
Airway inflammation	Present	Absent
Airway hyperresponsiveness	Present	Present

airway inflammation compared with patients without obesity that can explain their predisposition for asthma. For example, results from several studies showed no increase in fractional exhaled nitric oxide (FeNO) concentration, a biomarker of eosinophilic airway inflammation, in individuals who were obese compared with that in those who were not.[20,21]

Airway inflammation might be common in patients with metabolic syndrome, which is a specific phenotype of obesity characterized by dyslipidemia, metabolic dysregulation, and tissue resistance to insulin, as well as systemic inflammation.[22,23] Patients with metabolic syndrome have a higher risk of developing asthma compared with patients with obesity who do not have metabolic syndrome.[24] Through increased availability of biochemical precursors to inflammatory mediators, hyperlipidemia in particular has been proposed as the possible link between asthma and metabolic syndrome.[25,26] However, study results have failed to show the presence of higher levels of adipokines such as leptin or adiponectin in patients who have asthma.[27,28] As mentioned previously, a direct link between airway inflammation and systemic inflammation has not been established either.

In contrast to airway inflammation, which does not seem to link obesity to asthma, there is stronger evidence that airway hyperresponsiveness is a pathophysiological characteristic shared by asthma and obesity. Patients with obesity have increased airway hyperresponsiveness to bronchoconstrictive agents, as do patients with asthma.[29] This airway hyperresponsiveness in patients with obesity is more likely related to the decreased lung volumes from increased weight on the chest and abdomen.[30] These low lung volumes can decrease the outward tethering of the small airways by the lung parenchymal tissue, leading to decreased airway caliber and affecting the length–strength properties of small airway smooth muscles in a manner that leads to increased bronchoconstriction. However, airway hyperresponsiveness in asthma is linked to airway inflammation and is not related to low lung volumes.[31] Therefore, even though airway hyperresponsiveness is a common pathophysiological characteristic between asthma and obesity, it appears to originate from 2 separate pathways.

The role of the gut microbiome in the development of asthma and obesity also suggests a possible common etiologic or pathophysiological link between the 2 illnesses.[32] However, more extensive longitudinal studies and interventional trials are needed to establish a strong link between the 2 illnesses based on gut dysbiosis.

In summary, there is not yet any strong evidence for common etiologic or pathophysiological pathways that can satisfactorily explain the high association between the 2 disease entities. Further research is needed in this field.

Physiological Interactions Between Asthma and Obesity

Despite the fact that asthma and obesity are separate disease entities that originate independently, there is strong evidence for the presence of a positive interaction between the 2 disease processes. Obesity affects physiological characteristics of the respiratory system in a way that worsens asthma, and, vice versa, asthma influences rapid weight gain. These interacting processes may explain the strong association between the illnesses.

Obesity affects physiological characteristics of the respiratory system primarily through decreasing compliance of the thoracic cage, which leads to lower lung volumes.[33] The decrease in lung volumes correlates strongly with body mass index and is gravity dependent and more prominent in the supine position or during exercise.[34–36]

This decrease in lung volumes can worsen respiratory symptoms in patients who have obesity and asthma because of (1) increased work of breathing and exaggerated perception of breathlessness,[37] (2) worsening of gas exchange abnormalities because of decreased ventilation,[38] and (3) exaggeration of airway hyperresponsiveness because of the effect of low lung volumes on decreased airway caliber.

The direct measurement of chest wall compliance in patients with obesity is cumbersome and requires insertion of an esophageal balloon. However, lung volume can be easily measured using spirometry and lung volume measurements (plethysmography or gas dilution). A decrease in all lung volumes is expected in patients with obesity, including decrease in vital capacity, FVC, total lung capacity, and FEV_1.[39] The ratio of FEV_1 and FVC (FEV_1/FVC) should be normal. However, a low FEV_1/FVC ratio can occur owing to decreased airway tethering. Functional residual capacity (FRC) is usually low. Residual volume (RV) can be normal or low. Because of the decrease in FRC and the normal RV, expiratory reserve volume is typically decreased in individuals with obesity and is the most commonly found lung function abnormality.[40] The pattern of lung function abnormalities can differ between children and adults with obesity, as well as between male and female patients.[41]

Unlike the restrictive physiology seen in obesity, asthma is characterized by reversible obstructive pulmonary defects. Airway obstruction is typical in asthma and affects airflow measures such as FEV_1, FEV_1/FVC ratio, and

$FEF_{25\%–75\%}$.[42,43] Lung volumes such as total lung capacity, FRC, and RV are usually normal or higher than normal in patients with asthma.[44,45]

The deleterious effects of asthma on patients who have obesity are primarily through decreased exercise capacity, especially in patients with severe asthma and airway obstruction.[46] Exercise-induced bronchospasm in patients who have exercise-induced asthma can lead to exercise avoidance and a sedentary lifestyle, which can contribute to accelerated weight gain.[47] Also, the need for repeated treatments with systemic corticosteroids or high doses of inhaled corticosteroids can contribute to exaggerating weight gain, especially in patients with poorly controlled asthma and frequent acute exacebations.[48]

Symptom Overlap Between Asthma and Other Obesity-Related Respiratory Disorders

Obesity can be associated with respiratory disorders other than asthma as a result of the effects of obesity on the physiological characteristics of the respiratory system.[49] These disorders can manifest with symptoms that mimic those of asthma and can be easily misinterpreted as asthma. One example is OSA. Patients with OSA typically present with snoring, gasping, and restless sleeping, but they can also present with nighttime cough and shortness of breath, which overlap with asthma symptoms.[50] Both obesity and asthma are known risk factors for OSA.[51] The physiological effects of obesity on decreasing upper airway patency during sleep are well described; however, the mechanism for the association between asthma and OSA is less clear but could be related to the influence of gas exchange abnormality on control of breathing during sleep.[52]

Obesity hypoventilation syndrome (OHS), another obesity-related respiratory disorder, is characterized by alveolar hypoventilation and increased carbon dioxide level with or without OSA.[53] Besides having fractured sleep and daytime sleepiness, patients with OHS may report shortness of breath during sleep or with exercise, similar to experiences with asthma.[15] The symptoms of obesity hypoventilation syndrome are mainly due to severe restrictive lung disease and decreased thoracic wall compliance, not lower airway obstruction, as is the case with asthma.[54]

Severe cardiovascular deconditioning is also a common morbidity in patients with obesity because of a sedentary lifestyle and can potentially lead to exercise-induced symptoms.[55] Exercise limitation due to cardiovascular deconditioning may contribute to higher diagnoses of asthma in patients with obesity. However, exercise-induced symptoms in patients with asthma are primarily due to exercise-induced bronchospasm.[56]

Obesity is also associated with increased frequency and severity of lower respiratory tract infections (LRTIs), including pneumonia.[57,58] This association was greatly highlighted during the COVID-19 pandemic as obesity was recognized to be a major risk factor for increased mortality and severe LRTIs.[59] In some patients, symptoms of recurrent viral LRTIs, such as cough, mucus production, and shortness of breath, can overlap with symptoms of recurrent asthma exacerbations.

Gastroesophageal reflux disease (GERD) is highly prevalent in patients with asthma and in patients with obesity and can indicate an overlap between the 2 illnesses and contribute to their strong association.[60] Although the relationship between obesity and GERD is well established, the cause-and-effect relationship between GERD and asthma is highly controversial.[61] Despite the overlap in symptoms between GERD and asthma, it is unlikely that GERD contributes to the increased incidence of asthma in patients with obesity.[62] However, the increased associations among the 3 comorbidities and the overlap of their symptoms support the need for evaluation for GERD in patients who have obesity and respiratory symptoms.

Evaluation of Patients With Asthma and Obesity

Asthma diagnosis in patients with obesity can be challenging because of the heterogeneity of asthma manifestation and the overlap between asthma symptoms and other obesity-related respiratory conditions. The main goal of evaluating patients with obesity and respiratory symptoms is to determine whether the respiratory symptoms are due to asthma or to other obesity-related respiratory disorders. Obtaining a detailed history and performing a physical examination in search of distinctive signs and symptoms of these overlapping respiratory diseases can help direct further investigation and lead to proper diagnosis (**Figure 43-1**). For example, a clear history of snoring, apnea, and gasping during sleep is suggestive of OSA, even if the patient has nighttime cough or shortness of breath as well.[50,63] Also, a clear history of shortness of breath during exercise that is not associated with wheezing and that resolves with rest and without any need of a bronchodilator is unlikely to be due to asthma. In this case, restrictive lung disease or cardiovascular deconditioning should be considered.

Besides the detailed history and physical examination, diagnostic tests can help diagnose asthma and differentiate between asthma and other obesity-related respiratory disorders (**Table 43-2**). Office-based spirometry testing can help differentiate asthma from other obesity-related disorders. Demonstration of airway obstruction that is reversible by albuterol supports the diagnosis of asthma, whereas the presence of a restrictive physiological pattern (ie, low FVC) is unlikely to be due to asthma. If lung function is normal, other tests

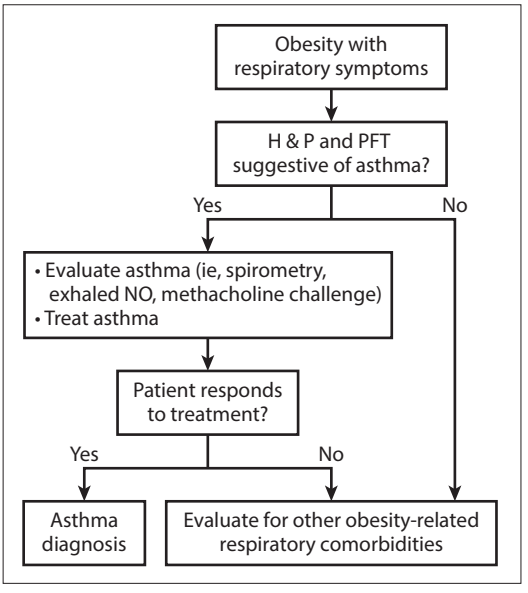


Figure 43-1. Algorithm for evaluating patients with obesity and respiratory symptoms. Abbreviations: H&P, history and physical examination; NO, nitric oxide; PFT, pulmonary function test.

Table 43–2. Overlap of Respiratory Symptoms of Obesity and Asthma

	Obesity-Related Respiratory Disorders Mimicking Asthma			
Symptoms and Tests	**OSA**	**Cardiovascular Deconditioning**	**GERD**	**Restrictive Lung Disease**
Asthma-like symptoms	Nocturnal cough Nocturnal dyspnea	Exertional dyspnea	Cough Wheezing	Exertional dyspnea
Distinctive symptoms	Snoring Witnessed apnea	Fatigue	Heartburn Postprandial symptoms	Orthopnea
Diagnostic tests	Sleep study	Exercise airway provocation testing Cardiopulmonary exercise testing	Swallowing studies Esophageal pH or impedance studies	Pulmonary function testing Cardiopulmonary exercise testing

Abbreviations: GERD, gastroesophageal reflux disease; OSA, obstructive sleep apnea.

can help with the diagnosis of obesity-related respiratory disorders.[42] Elevated levels of FeNO suggest the presence of eosinophilic airway inflammation and support the diagnosis of atopic asthma.[64] However, FeNO levels can also be high in patients with allergic rhinitis and are not specific for asthma diagnosis.[65] Normal levels of FeNO suggest that the symptoms are not from atopic asthma and that other causes should be considered.

Empiric treatment with a short course of oral steroids or inhaled steroids has been advocated as a quick and safe approach to diagnosing asthma if symptoms are strongly suggestive (see Chapter 12, Asthma). If empiric treatment fails, other obesity-related respiratory disorders should be considered.

Exercise testing may be needed to determine the cause of exercise-induced symptoms in patients with obesity. A clinically significant decrease in FEV_1 after exercise, which is associated with reproduction of symptoms and their reversibility with bronchodilator, is considered diagnostic of exercise-induced asthma.[66] If exercise testing cannot be performed or results are inconclusive, a negative methacholine challenge test is specifically helpful in ruling out an asthma diagnosis.[67] If asthma was excluded as the cause of exercise-induced symptoms in patients with obesity, then cardiopulmonary exercise testing is required to evaluate whether these symptoms are due to other obesity-related disorders such as restrictive lung disease or cardiovascular deconditioning, the latter being the most likely.[68–70]

Because of the high associations between obesity, asthma, and OSA, the diagnosis of nighttime symptoms can be challenging. Nighttime symptoms can be misinterpreted as asthma in patients who have OSA, and, vice versa, asthma symptoms can be misinterpreted as OSA. Therefore, careful consideration of the nighttime symptoms, review of home video recordings, and use of validated questionnaires will help direct the physician to the most likely diagnostic testing. Polysomnography is the gold standard test to confirm the diagnosis of OSA.[71] Polysomnography, including end-tidal CO_2 measurements and morning blood gas analysis, can help differentiate OSA from OHS as the cause of nighttime symptoms.[72]

Esophageal pH and impedance studies can be helpful in establishing the diagnosis of GERD in patients with obesity who present with postprandial heartburn, cough, and wheezing. Alternatively, empirical therapy with H_2- blockers or proton pump inhibitors can be both diagnostic and therapeutic.

Treatment of Asthma and Obesity

Once the diagnosis of asthma is confirmed in patients with obesity, treatment of both illnesses can be challenging due to the compounded effect of both diseases on the physiological characteristics of the respiratory system and the positive interaction of the 2 illnesses. Because of the chronic nature of both

illnesses, their treatment requires maintenance medications and sustained changes in lifestyle. Socioeconomic disadvantage, which is associated with both conditions, can impede effective treatment.[73] Some of the socioeconomic obstacles to effective treatment of both illnesses are related to disparity in access to quality food, exercise facilities, and quality health care. Low self-efficacy due to lack of health education can also affect adherence to treatment regimens. Such challenges are more pronounced in children than in adults because children lack autonomy.

A multidisciplinary approach to managing asthma and obesity by physicians, dieticians, and psychologists is advisable. The primary goal of management is to treat both illnesses simultaneously to maximize the chance of treatment effectiveness. A comprehensive approach can help alleviate anxiety, low self-esteem, depression, and poor adherence, which are prevalent in both diseases. However, few treatment programs are designed to incorporate a combined approach to treat asthma and obesity.[74]

Weight loss in patients with asthma and obesity results in a decrease in asthma symptoms and asthma exacerbations and an improvement in lung function and asthma-related quality of life.[11] Several weight loss programs for children with obesity have been developed and evaluated, most of them focusing on increasing physical activity and promoting dietary changes and eating habits.[75,76] The active participation of the child can be helpful in the development of self-efficacy.[77] Structured programs at home, in the health care setting, at school, or through monitored web-based or mobile devices can help improve adherence to dietary and physical activity recommendations.[78–81] Patient motivation can be developed through use of educational and motivational interviewing conducted by trained individuals with the help of written material or interactive software applications.[82–84] The increased availability of electronic wearable devices that monitor physical activity and other health-related parameters also provides an opportunity for their use in weight loss programs.[85]

Use of medications such as metformin, sibutramine, fluoxetine, and orlistat for weight reduction is associated with adverse effects, and these medications are not approved for use in young children. Furthermore, the long-term effectiveness of these medications is not known.[86] Bariatric surgery, including laparoscopic Roux-en-Y gastric bypass, vertical sleeve gastrectomy, and gastric banding, is associated with postoperative complications and should be reserved for adolescents with morbid obesity in whom behavioral therapy has failed.[87]

Treatment of asthma in patients with obesity facilitates weight loss. Successful control of symptoms can be achieved in most patients by using inhaled corticosteroids with or without long-acting β-agonists (see Chapter 12, Asthma). Use of high-dose inhaled corticosteroids or daily oral corticosteroids should be avoided in patients with obesity if possible. Treatment with monoclonal anti–immunoglobulin E antibodies should be considered as an alternative therapy

to avoid further weight gain.[88] Improvement of patients' adherence to medications and inhaler technique can result in good control of asthma and prevent escalation of steroid therapy. Once asthma is well controlled in patients with obesity, weaning asthma medications should be attempted as soon as possible. For patients with obesity and asthma, close monitoring and frequent clinic visits are important.

Alleviation of symptoms from exercise-induced asthma promotes increased physical activity and weight loss in patients with obesity. Most exercise-induced symptoms can be prevented by the use of short-acting albuterol before exercise. Inhaled corticosteroids should be considered in patients with evidence of airway inflammation.

Treating obesity-related disorders such as OSA, OHS, and GERD is important once the diagnosis of any of these disorders is confirmed. Treatment of OSA may require use of continuous positive airway pressure at night. However, evaluation and treatment of allergic rhinitis and surgical removal of enlarged adenoids and/or tonsils, if present, may alleviate the need for continuous positive airway pressure. Obesity hypoventilation syndrome is a serious medical condition and should be treated with noninvasive ventilation such as bilevel positive airway pressure or invasive ventilation through a tracheostomy tube. Finally, GERD should be treated with H_2-blockers or proton pump inhibitors.

key points

- The incidence and prevalence of asthma are high in patients with obesity, which can be partially explained by the effect of obesity on respiratory system mechanics, including decreased chest compliance, decreased lung volumes, and increased airway responsiveness.
- Obesity can develop in patients with asthma because of decreased physical activity and steroid therapy.
- Symptoms of obesity-related respiratory disorders other than asthma, such as OSA, OHS, cardiovascular deconditioning, recurrent chest infections, and GERD, can mimic asthma symptoms in patients who are obese and potentially be misdiagnosed as asthma.
- Reaching an accurate diagnosis of asthma versus other obesity-related respiratory disorders in children requires a detailed history and physical examination and may require further diagnostic testing, including spirometry, exercise testing, polysomnography, and esophageal pH impedance.
- Treatment of obesity requires a multidisciplinary clinical and psychological approach with a focus on behavioral changes through motivational techniques, family involvement, and use of digital technology. Specific treatments for obesity-related respiratory disorders should be initiated concomitantly.

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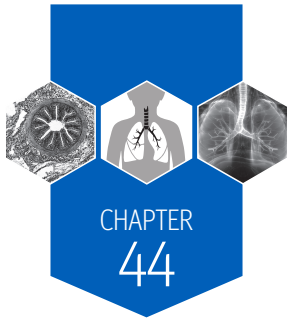
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Functional Respiratory Disorders

Miles Weinberger, MD, FAAP
Manju S. Hurvitz, MD, FAAP
Mutasim Abu-Hasan, MD

Introduction

Functional respiratory disorders (FRDs) are characterized by symptoms without medical explanation. Those likely to be encountered in children include chronic cough, dyspnea, and dysfunctional breathing; other clinical symptoms of FRDs include sighing, chest or throat tightness, and pain. Functional respiratory disorders should not be considered diagnoses of exclusion. They have recognizable characteristics that permit identification. Routine investigation for all other causes of the same symptoms is usually not justified and only causes unnecessary testing and treatment. For each of the FRDs discussed in this chapter, the unique presentation is described, diagnostic criteria presented, and the treatment approach provided.

Habit Cough Syndrome

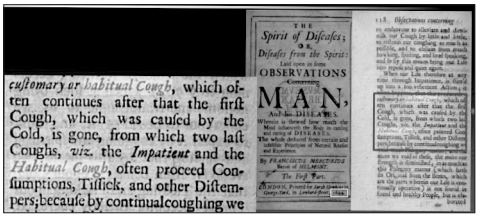
There are multiple causes of a chronic cough (**Table 44-1**). Habit cough is an involuntary chronic cough without medical explanation. Terminology that has been used for this disorder includes *cough tic, psychogenic cough,* and *somatic cough disorder*. In considering these alternative terms, it is important to understand that the symptom patients experience is obvious to an observer as a cough, not a tic. While some patients might have a psychogenic basis, there is little evidence to support that for most. Somatic cough disorder is a general description, not a specific diagnosis. The term *habit cough* had its origin in a 1966 publication by Boston allergist Bernard Berman, who identified 6 children in his practice over a 5-year period who were cured with "the art of suggestion."[15] A further advantage of the term is its benignity in explaining the disorder to children and their parents.

Table 44-1. Etiologies of Chronic Cough Among Diagnoses of 346 Children[a]

Cause	Percent of 346 children
Protracted bacterial bronchitis[1]	41.0
Asthma[2]	15.9
Spontaneous resolutions without diagnosis	14.0
Bronchiectasis[3]	9.0
Tracheomalacia[4]	6.1
Habitual[5]	4.3
Pertussis[6]	3.5
Aspiration[7]	2.3
Mycoplasma	1.4
Pneumonia[8]	0.9
Cystic fibrosis[9]	0.3
Primary ciliary dyskinesia[10]	0
Uvula impinging on epiglottis[11]	0
Tonsils impinging on epiglottis[12]	0
Achalasis[13]	0
Diffuse panbronchiolitis[14]	0
Tuberculosis	0

[a]Chang AB, Robertson CF, van Asperen PP, et al. A multicenter study on chronic cough in children: burden and etiologies based on a standardized management pathway. *Chest.* 2012;142(4):943–950.

The presentation is a repetitive cough, often occurring several times per minute though with interpatient variability, classically harsh and barking, and continuing for many hours that can include all waking hours. Habit cough commonly follows a viral respiratory infection, a common cold. Caregivers often describe an initial typical cough of a cold that changes after 1 to 2 weeks. That description is present in a 1694 publication (**Figure 44-1**).[16] It becomes the repetitive barking cough characteristic of this disorder. The cough may interfere with going to sleep, but a *sine qua non* of this disorder is the cough's total absence once the patient is asleep.[15,17–19] Habit cough has continued to be described in this manner since the Berman publication in 1966,[15] sometimes with different terminology but with the same presenting characteristics.[15,17–22] Variations seen in one series found about 10% with a softer cough manifested by a repetitive throat-clearing sound.[18]


customary or habitual Cough, which often continues after that the first Cough, which was caused by the Cold, is gone, from which two last Coughs, viz. the *Impatient* and the *Habitual Cough*, often proceed Consumptions, Tisick, and other Distempers; because by continual coughing we

THE
Spirit of Diseases;
OR,
Diseases from the Spirit:
Laid open in some
OBSERVATIONS
Concerning
MAN,
And his DISEASES.
Wherein is treated how much the Mind influenceth the Body in causing and curing Diseases.
The whole delivered from certain and infallible Principles of Natural Reason and Experience.
By *FRANCISCUS MERCURIUS*
Baron of HELMONT.
The First Part.
LONDON, Printed for Lodwick Lowndes, over-against the Inner-Temple-Gate, 1694.

Figure 44-1. Description of habit cough in a 1694 medical book.

The median age of children with habit cough at several centers has been about 10 years with a range from 4 to 18 years.[18,19] The prevalence of habit cough at major referral centers has been an average of 9 per year at the University of Iowa[18] from 2003 to 2014 and 9 per year over 6 years at the Brompton Hospital in London, England.[19] The variable cough presentation can be seen and heard at https://www.youtube.com/watch?v=U7p2B_Zt6AM.

The diagnosis of habit cough is based on the unique presentation of the daily repetitive cough that is absent once asleep. None of the other causes of chronic cough in **Table 44-1** have that characteristic presentation. Other proposed causes of chronic cough are sinusitis,[23] postnasal drip (aka upper airway cough syndrome),[24,25] and gastroesophageal reflux,[26,27] all of which diminish as legitimate causes of chronic cough when critically examined. Although asthma sometimes presents with cough, it rarely mimics the repetitive cough of habit cough that is absent during sleep. Moreover, a short course of an oral corticosteroid can readily distinguish the steroid-responsive cough of asthma from the habit cough.[28] (See also Chapter 12, Asthma.)

Various forms of suggestion therapy have been used to treat habit cough.[15,18,22,29] Suggestion therapy was used most extensively over a 40-year period at the University of Iowa Pediatric Allergy & Pulmonary Clinic.[19] A guide to the 15-minute session commonly used is in **Box 44-1.** A demonstration of the method is available at www.habitcough.com. The prognosis for habit cough with suggestion therapy is good, with long-term remission in most cases.

Absence of a specific treatment plan can result in prolonged symptoms. In a report from Mayo Clinic (Rochester, MN), 44 of 60 patients diagnosed with habit cough required an average of 6 months beyond the diagnosis for spontaneous resolution, and 16 continued to be symptomatic for a mean duration of 5.9 years.[30] A report from the Brompton Hospital looked at the outcome from reassurance alone. Cough subsequently resolved in 59% of patients within 4 weeks but persisted, on average, significantly longer when the parents were skeptical or did not accept the diagnosis.[19] In contrast, the cough can be abated after about 15 minutes of suggestion therapy, with residual symptoms fading over the next few days or weeks.

CASE REPORT 44-1

D.J. is a 12-year-old boy who is brought to your office by his mother with a complaint of cough for 3 months without systemic symptoms. A trial of inhaled corticosteroid and a short-acting bronchodilator have not produced improvement. The cough is present throughout the waking hours. It is not present once he is asleep. It is disruptive of activities, including school; he had been sent home multiple times. Your examination findings are normal except for a dry, harsh, "honking" cough. The referring physician had performed chest radiography, sinus radiography, and spirometry. Are all normal.

Comment: The presentation is diagnostic of the habit cough syndrome. While the chest radiograph and spirometry were reasonable, though not essential, to ensure there is no other explanation for the cough, the sinus radiograph is not indicated since it will provide neither positive nor negative information.[23,31] The indicated treatment is suggestion therapy, which was associated with a 95% success rate among 85 children seen at the University of Iowa Pediatric Allergy & Pulmonary Clinic by 6 clinicians.[18]

Box 44-1

Guide for Suggestion Therapy Treatment of Habit Cough

- **Express confidence, communicated verbally and behaviorally, that the therapist will be able to show the patient how to stop the cough.**
- **Explain the cough as a vicious cycle of an initial irritant, now gone, that had set up a pattern of coughing that caused irritation and further symptoms.**
- **Encourage suppression of the cough to break the cycle. The therapist closely observes for the initiation of the muscular movement preceding coughing and immediately exhorts the patient to hold the cough back, emphasizing that each second the cough is delayed makes further inhibition of cough easier.**
- **An alternative behavior to coughing is offered in the form of inhaling a generated mist or sipping body-temperature water with encouragement to inhale the mist or sip the water every time the patient begins to feel the urge to cough.**
- **Repeat expressions of confidence that the patient is developing the ability to resist the urge to cough.**
- **When some ability to suppress cough is observed (usually after about 10 minutes), ask in a rhetorical manner if the patient is beginning to feel that they can resist the urge to cough (eg, "You're beginning to feel that you can resist the urge to cough, aren't you?").**
- **Discontinue the session when the patient can repeatedly answer positively to the question, "Do you feel that you can now resist the urge to cough on your own?" This question is only asked after the patient has gone 5 minutes without coughing.**
- **Tell the patient that what we just did can be done by the patient on their own at home.**

Reprinted from Lokshin B, Lindgren S, Weinberger M, et al. Outcome of habit cough in children treated with a brief session of suggestion therapy. *Ann Allergy.* 1991;67(6):579–582. Copyright © 1991, with permission from Elsevier.

Habit Throat Clearing

Habit throat clearing appears to be related to the habit cough syndrome. Of 140 children diagnosed with the habit cough syndrome over a 20-year period at the University of Iowa, a repetitive, softer throat-clearing sound rather than the more typical barking cough was the presenting symptom in 10% of the patients; 11% exhibited both the barking cough and the softer throat-clearing patterns of coughing.[18] Habit throat clearing has been attributed by some to gastroesophageal reflex (GER). However, an association of GER and habit throat clearing was not found in 186 patients referred for possible GER disease who underwent consecutive ambulatory impedance studies.[32] Response to suggestion therapy was as effective in these patients as in those with the harsh barking cough.

Habit Sneezing

Habit sneezing is a much less common disorder than the habit cough syndrome, but there have been a substantial number of case reports. In the oldest reported case, a 40-year-old woman had repetitive sneezing that was eventually stopped by suggestion.[33] Two case reports in children were published (8- and 10-year-old girls).[34] Both children experienced severe repetitive sneezing multiple times per minute that was absent once asleep. Habit sneezing generally appears more as a cough through the nose than a true sneeze. There is no mucus excretion; it is essentially a dry sneeze. As with habit cough, a precipitating factor is likely to have been present (an irritant in the case of the 40-year-old woman). In a 9-year-old girl observed by one of this chapter's authors, the initiating factor was a bug up her nose. Suggestion therapy similar to that used for habit cough was rapidly effective.

Functional Causes of Dyspnea

Dyspnea is the subjective experience of uncomfortable breathing that can vary in quality and intensity. Dyspnea can occur for many reasons (**Box 44-2**). Pulmonary, cardiac, and neuromuscular disorders can cause dyspnea when they decrease appropriate ventilation and gas exchange. Functional disorders associated with dyspnea are those that have no physiologic basis.[35] Dyspnea is also perceived during hyperventilation attacks that involve a medically unexplained

Box 44-2

Causes of Dyspnea

Physiologic Dyspnea	Functional Dyspnea
Bronchospasm from asthma	Vocal cord dysfunction
Obstructive pulmonary disease	Hyperventilation
Restrictive pulmonary disease	Exertional dyspnea
Cardiac abnormalities	Dyspnea perception without physical correlate
Anemia	

increase in a normal function (breathing). Functional dyspnea can also occur without any physiologic dysfunction.

Vocal cord dysfunction (VCD) has an anatomic component, but the cause of that anatomic component is functional in that there is no organic reason for the dysfunction. Normal functions of the vocal cords include protection of the airway by adduction to prevent aspiration, permitting unrestricted flow of air into the lungs by abduction, and speech. The movement of the vocal cords is controlled by the intrinsic laryngeal muscles. All intrinsic laryngeal muscles except the cricothyroid muscle are innervated by the recurrent laryngeal nerves, which are branches of the vagal nerves.[36] Although much of the function of the vocal cords is reflexive and automatic, they must interact with volitional control at higher levels of the central nervous system. The precise interactions between cortical and subcortical control systems and reflexive pattern generators are essential for normal laryngeal function.

Dyspnea occurs with VCD when the dysfunction results in airway obstruction at the level of the larynx. That occurs because there is failure of the vocal cords to open and allow air to enter the lungs during inspiration. Essentially, the complex interaction of the vagal and central nervous system goes awry. There are 2 physiologic abnormalities of VCD: adduction of the vocal cords during inspiration and persistent adduction during both inspiration and expiration. Videos of both are available for viewing at https://www.milesweinberger.com/copy-of-exercise-induced-dyspnea.

The most common abnormality is adduction of the vocal cords during inspiration. The vocal cords should abduct to permit free flow of air during inspiration. Adduction during inspiration is essentially a paradoxical movement of the vocal cords, causing stridor on inspiration and dyspnea because of

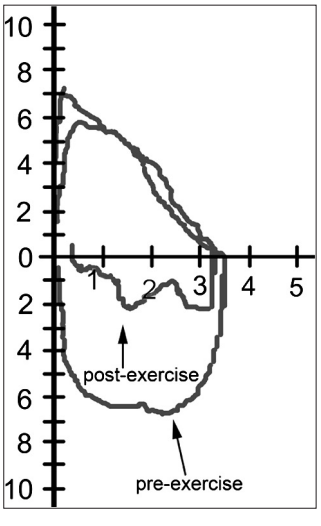


Figure 44-2. Spirometry before and after exercise of a 15-year-old girl showing a marked decrease in the inspiratory portion of the flow-volume loop in association with dyspnea and an inspiratory wheeze-like sound (technically a high-pitched stridor; see video with audio at https://www.milesweinberger.com/copy-of-exercise-induced-dyspnea).

From Weinberger M, Abu-Hasan M. Pseudo-asthma: when cough, wheezing, and dyspnea are not asthma. *Pediatrics.* 2007;120(4):855–864.

increased resistance to airflow on inspiration. Spirometry shows marked flattening of the inspiratory portion of the flow-volume loop as a result of marked obstruction to airflow only during inspiration (**Figure 44-2**).[37]

Persistent adduction during both inspiration and expiration results in interference of airflow to and from the lungs during both phases of respiration, causing stridorous sounds on both phases (**Figure 44-3**).[37] Because of the persistent decrease in airflow throughout the whole respiratory cycle, dyspnea is much more severe and alarming when there is persistent adduction.

A report in adults indicated a third pattern where adduction occurs only on expiration.[38] That has not been reported in children. An American Thoracic Society podcast discussing how dyspnea from vocal cord dysfunction can be distiguished from other causes of dyspnea can be heard at https://www.thoracic.org/about/ats-podcasts/evaluation-and-management-of-vocal-cord-dysfunction.php.

There are 2 distinct phenotypes of vocal cord dysfunction. Some patients have VCD limited to being exercise-induced (EIVCD). Others have spontaneously occurring vocal cord dysfunction (SVCD) that may or may not occur also with exercise.[39] The latter (SVCD) is more distressing to the patient since there is not a predictable trigger for the disorder. Speech therapy by skilled speech pathologists is reported to have been effective in enabling those with SVCD to control the problem.[40]

The use of speech therapy has also been reported for EIVCD, but the practicality of that during competitive activity raises questions of its actual value. Based on the vagal innervation of the vocal cords,[39] a trial of an anticholinergic aerosol, ipratropium metered-dose inhaler, has been used prior to planned exercise with success in preventing EIVCD.[37] Evidence that vagal stimulation can cause abnormal function of the vocal cords provides further rationale for

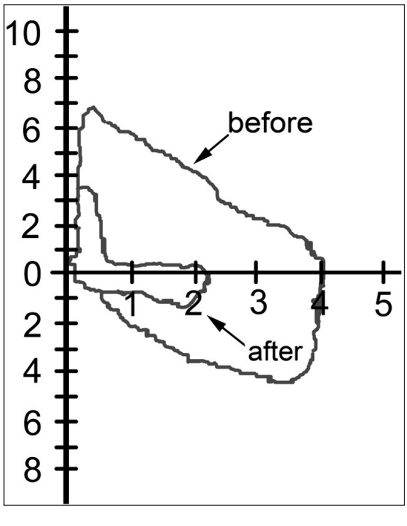


Figure 44-3. Spirometry before and after the spontaneous onset of dyspnea in a 14-year-old girl showing marked decrease in both the inspiratory and expiratory portion of the flow-volume loop in association with an inspiratory wheeze-like sound (technically a high-pitched stridor on inspiration) and a monophonic wheeze on expiration (see video with audio at https://www.milesweinberger.com/copy-of-exercise-induced-dyspnea).

From Weinberger M, Abu-Hasan M. Pseudo-asthma: when cough, wheezing, and dyspnea are not asthma. *Pediatrics.* 2007;120(4):855–864.

this approach.[41,42] While not subjected to a controlled clinical trial, multiple patients with well-documented EIVCD have experienced effective blocking of their paradoxical vocal cord movement.[37,40]

Extended follow-up in 28 patients with VCD found 26 patients asymptomatic when contacted a median of 5 months (range of 1 week to 5 years) after the evaluation and diagnosis.[39] Two of 17 patients with EIVCD were still using ipratropium metered dose inhaler prior to exercise for prevention. All 11 patients with SVCD were no longer having VCD symptoms when contacted.

An imitator of EIVCD is exercise-induced laryngomalacia (EIL).[43] In some cases, this may be a residuum of infantile laryngomalacia.[44] Inspiratory stridor occurs in patients with EIL only when vigorous exercise results in sufficient air movement to invaginate the arytenoids or pull down the epiglottis over the airway, depending on the specific anatomy.[45] When exercise testing identifies upper airway obstruction, visualization is necessary to distinguish EIVCD from the much less common EIL.[46] The treatment of EIL, if needed, is supraglottoplasty (**Figure 44-4**).[47,48]

In summary, VCD can occur with paradoxical vocal cord adduction during inspiration instead of the normal abduction. Some will have persistent adduction during inspiration and expiration. VCD can be limited to occurring only

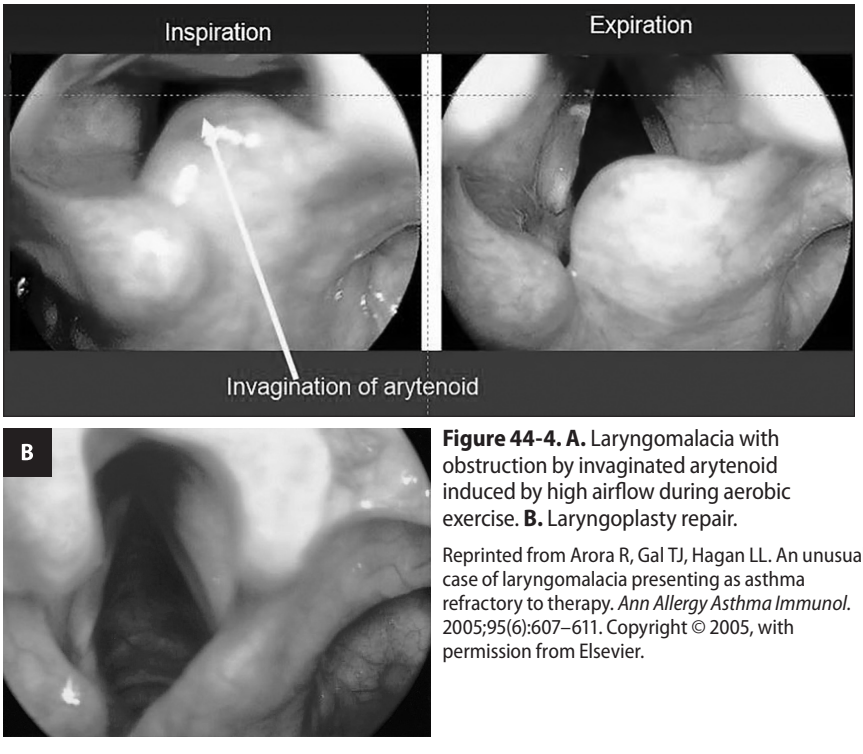


Figure 44-4. A. Laryngomalacia with obstruction by invaginated arytenoid induced by high airflow during aerobic exercise. **B.** Laryngoplasty repair.

Reprinted from Arora R, Gal TJ, Hagan LL. An unusual case of laryngomalacia presenting as asthma refractory to therapy. *Ann Allergy Asthma Immunol.* 2005;95(6):607–611. Copyright © 2005, with permission from Elsevier.

with exercise or can occur spontaneously. While these are often distinct phenotypes, some patients will manifest both SVCD and EIVCD. Speech therapy can provide the patient with SVCD with the ability to stop VCD when it occurs. Pre-exercise treatment with an anticholinergic appears to be an effective prevention for EIVCD. A high rate of natural resolution occurs for both forms of VCD.

Exertional Dyspnea Other Than EIVCD

Physicians may be predisposed to attribute exertional dyspnea to asthma because it is a common cause. However, in the absence of other symptoms of asthma, present or past, it is unlikely to be the cause of exercise-induced dyspnea (EID). Even in the presence of a modest degree of measurable exercise-induced bronchospasm (EIB), EID does not necessarily warrant a diagnosis of asthma. EIB is a pathophysiological response that can be measured using lung function testing. Exercise-induced asthma (EIA), on the other hand, is a clinical diagnosis based on demonstration of EIB as the cause of EID. This issue was demonstrated by Burnett et al[49] who reported an EIB prevalence of 43% in college athletes, most having no dyspnea or any respiratory symptoms. This raised the question of the clinical relevance of a modest degree of EIB in the absence of dyspnea on exertion or other symptoms of asthma.[50]

Evaluation of exercise-induced dyspnea first warrants a trial of pre-exercise use of a bronchodilator, such as albuterol. The complete and reliable prevention of exercise-induced dyspnea supports the diagnosis of asthma. The absence of complete and reliable prevention does not justify any other attempts at asthma pharmacotherapy. Instead, if there is minimal or no improvement in dyspnea from a trial of albuterol, alternative diagnoses should be considered, and cardiopulmonary exercise testing is needed to identify other causes of EID.[46]

Of 117 children and adolescents referred to the pulmonary clinic at the University of Iowa Children's Hospital because of EID, 100 had been previously diagnosed with asthma. They were referred because they had not responded to usual treatment for EIA. Symptoms were reproduced during exercise testing and the etiology identified. Although most of the patients previously had been diagnosed with asthma, only 11 could be demonstrated to have EIA. Other diagnoses associated with reproduced EID included vocal cord dysfunction in 13 patients, laryngomalacia in 2 patients (1 of whom had unilateral vocal cord paralysis), exercise-induced hyperventilation in 1 patient, and supraventricular tachycardia in 1 patient. Restrictive abnormalities suggestive of a minor degree of chest wall stiffness were seen in 15 patients. Seventy-four of those 117 patients demonstrated only normal physiologic exercise limitation; 48 of these 74 had normal to high cardiovascular conditioning, and 26 had poor conditioning (**Figure 44-5**).[51]

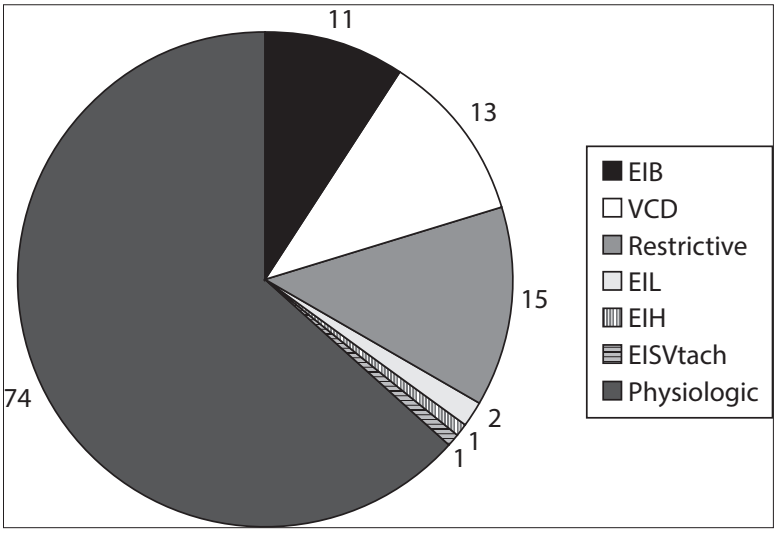


Figure 44-5. The diagnoses among 117 sequential children and adolescents evaluated for exercise-induced dyspnea. Diagnoses determined by treadmill exercise testing with physiologic monitoring.

Abbreviations: EIB, exercise-induced bronchospasm; EIH, exercise-induced hyperventilation; EIL, exercise-induced laryngomalacia; EISVtach, exercise-induced supraventricular tachycardia; Physiologic, normal physiologic limitation without other abnormality; Restrictive, apparent restriction of chest wall movement; VCD, vocal cord dysfunction.

From Weinberger M, Abu-Hasan M. Pseudo-asthma: when cough, wheezing, and dyspnea are not asthma. *Pediatrics*. 2007;120(4):862; with permission. Original data from Abu-Hasan M, Tannous B, Weinberger M. Exercise-induced dyspnea in children and adolescents: if not asthma then what? *Ann Allergy Asthma Immunol*. 2005;94(3):366–371.

Normal physiologic exercise limitation occurs when lactic acidosis increases during anaerobic metabolism, resulting in an attempt to compensate for this metabolic acidosis by increasing ventilation to create respiratory alkaloses. However, this increased respiratory drive occurs when maximal ventilation already has been reached. That is associated with a low pH that cannot be compensated by a respiratory alkalosis from further increasing ventilation. That causes progressive dyspnea, which is interpreted by even some well-conditioned children and adolescents as pathologic rather than normal physiologic limitation. Successful athletes in aerobic sports learn to adjust their activity when necessary to maintain a maximal tolerated level that may be increased with further conditioning. The treatment is counseling to explain the physiology of exercise so that the patient understands the etiology of their dyspnea and the necessity of pacing in addition to conditioning.

Dyspnea Without Physiologic Correlates

Although not associated with physiologic abnormality, a patient's perception of dyspnea may still be troublesome. The sensation of dyspnea is stronger in patients with anxiety and has been reported in patients with anxiety disorders

in the absence of cardiopulmonary disease.[52] These observations demonstrate the importance of cerebral cognition in this complex symptom. Patients with this disorder have been misdiagnosed as having asthma and treated as such. Once recognized by a physician, treatment of the anxiety is the appropriate measure.

Dysfunctional Breathing

Hyperventilation

Hyperventilation refers to an increase in alveolar ventilation in excess of metabolic needs. That can result in respiratory alkalosis with a reduction in arterial partial pressure of carbon dioxide below the normal range for age ($Paco_2$ <4.66 kPa [<35 mm Hg]) and a consequent rise in pH above 7.4. The resulting respiratory alkalosis with its effect on calcium ionization causes feelings of light-headedness, numbness, or tingling periorally and on the fingers or toes. It can progress to carpopedal spasm.

While some drug overdoses, such as aspirin, can create increased ventilation, which can also occur from metabolic disorders (eg, Kussmaul breathing during diabetic ketoacidosis), the details of those are beyond the scope of this publication. Hyperventilation in children typically presents as a spontaneous event related to anxiety, panic, nervousness, or stress. The term "acute hyperventilation" is used to describe these brief episodes, which can occur in children and adults. Chronic hyperventilation is a documented entity in adults but not described in the pediatric population.[53] Hyperventilation can be associated just with anxiety or can be a part of a panic attack. There is characteristically an abrupt onset of intense fear or discomfort that reaches a peak within minutes. Symptoms can include palpitations, sweating, and trembling along with the sensation of dyspnea that provokes the hyperventilation.[54] Somatic complaints can also occur.[55]

On examination, children and adolescents appear anxious or distressed with usually rapid deep breathing that can involve the use of accessory muscles of respiration. The apparent increased work of breathing and description by the patient that they are experiencing air hunger can cause a misdiagnosis of asthma. Lower airway sounds are unusually clear with absence of the polyphonic wheezes that characterize asthma. The presence of a normal pulse oximetry, 95% or greater, is reassuring to the examiner encountering this patient. A blood gas (capillary or venous is adequate) can confirm hyperventilation if the pH is high and the Pco_2 is low.

Immediate treatment of acute hyperventilation can include rebreathing into a bag. That increases the Pco_2, decreases the pH, and thereby eliminates symptoms caused by the alkalosis. Reassuring and calming the patient can further decrease the anxiety and fear associated with an anxiety-induced panic

attack. For a patient prone to have such episodes, counseling and explaining what is being felt are essential so that future episodes are not mistaken for acute asthma or some other illness.

Repetitive Sighing

Sighing is a normal activity, sometimes as an expression of relief. It involves taking a deep inspiration followed by exhalation and a subsequent normal breathing pattern. Repetitive involuntary sighing is known as the *sighing syndrome*.[56] As with other habit disorders, the sighing is absent once asleep. Anxiety and stress are speculated to be associated. Although one young child is reported to have sighing associated with asthma,[57] another report that included both adults and children suggested the potential for mistakenly diagnosing repetitive sighing as asthma.[58] When asked why they are sighing, the common answer is just that they felt more air was needed. While the syndrome is called *sighing dyspnea* in some publications, the child with recurrent sighing generally does not express a feeling of dyspnea. The sighing occurs most commonly when the patient is quiet, does not interfere with activity, and does not seem to disturb the child as much as the parent.

This generally appears to be a benign condition that nonetheless disturbs the parents who bring the child to a physician for evaluation. The child, however, is often unconcerned and experiencing no distress. No treatment is needed other than explaining the benignity of this minor functional deviation from usual respiration. Since it is harmless and generally self-limited, repetitive sighing generally warrants only benign neglect.

Dysfunctional Breathing Complicating Asthma

Dysfunctional breathing can occur in children with asthma and complicate the clinical assessment of severity and control of the disease.[59–61] However, dysfunctional breathing seems to occur much less frequently in children with asthma than in adults with asthma.[62] A study of 203 children with asthma, aged 5 to 18 years, used a Nijmegen Questionnaire[63] and related that to the results of an Asthma Control Questionnaire.[64] Although the Nijmegen Questionnaire is primarily used to assess hyperventilation in adults, the results demonstrated 5% of children at a specialized asthma clinic had a high Nijmegen score that correlated with poor asthma control. That suggests that poor asthma control warrants investigation for dysfunctional breathing.

Breathing retraining has been used for adults with asthma and dysfunctional breathing with benefit.[65] While that has also been suggested as of value for children with asthma,[66] controlled trials have not been performed. Nonetheless, poor asthma control justifies observation to determine if the patient's symptoms or breathing pattern were disproportionate to the degree of measured airway obstruction or gas exchange.

key points

- Functional respiratory disorders are symptoms without medical explanation.
- Functional respiratory disorders are not diagnoses of exclusion; they are based on specific characteristics.
- Misdiagnosis results in overtreatment of the symptoms.
- The treatment of functional disorders is behavioral, not pharmacologic.

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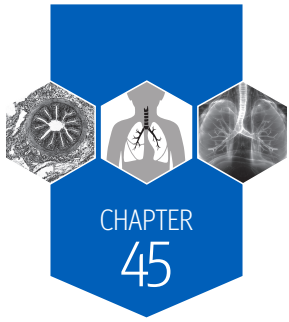
PART 9

Genetic Disorders

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Cystic Fibrosis

Michael S. Schechter, MD, MPH, FAAP

Introduction

Cystic fibrosis (CF) was, in the past, typically described as the most common lethal genetic disease in the white population, but the outlook for people with a CF diagnosis has improved dramatically with advancements in treatment, and new therapies are expected to lead to even greater changes. The US Cystic Fibrosis Foundation (CFF) median projected survival age in 2019 (before generalized availability of highly effective modulator therapies, described later, in Management) was 48.4 years (95% CI, 45.9–51.5 years) (**Figure 45-1**).[1] Birth prevalence varies with racial or ethnic background; CF occurs in approximately 1 in 3,000 white Americans (constituting 93.4% of the US population with CF), 1 in 4,000 to 10,000 Hispanic Americans (9.4% of the US population with CF), and 1 in 15,000 to 20,000 African Americans (4.7% of the US population with CF).[1] Internationally, the prevalence is quite low (but poorly ascertained) among the people of Africa, Asia, and Oceania.[2]

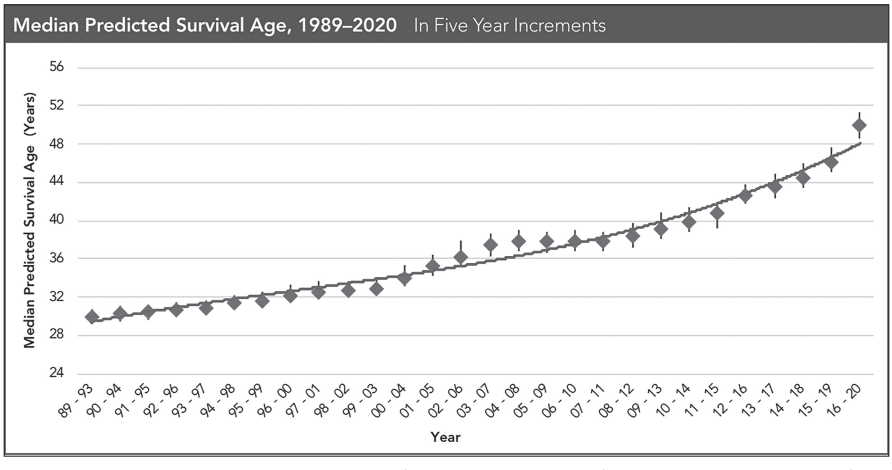


Figure 45-1. Median predicted survival age for people with cystic fibrosis in the United States for the period from 1989 to 2020 in 5-year increments.

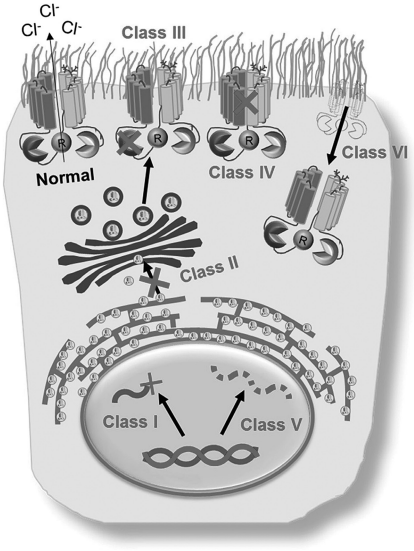
From *Cystic Fibrosis Foundation. Cystic Fibrosis Foundation Patient Registry: 2020 Annual Data Report.* Cystic Fibrosis Foundation; 2021:75. Accessed July 18, 2022. https://www.cff.org/sites/default/files/2021-11/Patient-Registry-Annual-Data-Report.pdf. ©2021 Cystic Fibrosis Foundation.

Pathogenesis

Genetics

Cystic fibrosis is an autosomal recessive disease caused by an abnormal gene on the long arm of chromosome 7. The gene product, called *CF transmembrane conductance regulator* (*CFTR*), localizes to the apical cell membrane and regulates ion transport by way of a blend of Na^+ absorption and Cl^- secretion.[3] Although there have been more than 2,000 *CFTR* mutations identified, about 50% of patients with CF with a Northern European background are homozygous for the F508del mutation (involving the deletion of phenylalanine, which is normally the 508th amino acid in the protein), and 35% are compound heterozygous with 1 F508del mutation.[1] The mutation frequency of *CFTR* varies from population to population, and the F508del is less common in non-European populations, but no single mutation other than F508del occurs in a frequency greater than approximately 5%.[1]

The *CFTR* mutations have been grouped into 6 classes (**Figure 45-2)**.[4] Class I mutations include nonsense mutations (associated with a premature termination codon) and splice mutations. Most (but not all) mutations with designations ending in *X*, such as G542X, are nonsense mutations. Class II mutations are protein-processing mutations, wherein a deleted or incorrect amino acid leads to an abnormal 3-dimensional configuration and failure of the cell to recognize and traffic the protein to the apical cell surface. This is the class to which F508del belongs and is therefore by far the most commonly seen mutation class. Class III mutations, such as G551D, are gating mutations; CFTR protein localizes to its proper position on the apical cell membrane, but the chloride channel does not open normally. Class IV mutations, such as R117H, are conduction mutations, which allow some chloride conduction, but not enough to allow normal function. Similarly, class V mutations, such as A455E, allow some, but inadequate, CFTR function because of underproduction, and class VI mutations produce an unstable protein with a shortened half-life. Some classification systems combine classes V and VI together. Class IV, V, and VI mutations are typically associated with enough residual CFTR activity to allow for normal pancreatic function, and patients with pancreatic sufficiency tend to have milder pulmonary disease. However, in any given individual, *CFTR* mutation is a much better predictor of pancreatic function than of lung involvement because lung disease is also influenced by nutritional status, sociodemographic and environmental factors, and variations in health care interventions to an extent that blurs distinct genotype–phenotype associations.[5] In addition, the presence of gene modifiers (polymorphisms in non-*CFTR* genes that control the inflammatory response, such as mannose-binding lectin, tumor necrosis factor, and alpha-1 antitrypsin) may also affect the severity of lung disease in patients with CF.[6]



	Class I	Class II	Class III	Class IV	Class V	Class VI
Molecular Defect	Synthesis	Processing	Gating	Conductance	mRNA Stability	Protein Stability
Defect Results	No mature CFTR protein	CFTR degradation	Channel opening defect	Reduced Cl^- conductance	Reduced synthesis of CFTR	Decreased CFTR stability
Mutation Examples	G542X	F508Del	G551D	R117H	A455E	Rescued F508Del
	R553X	N1303K	V530F	R334W	c.1680-886A>G	Q1412X
	W1282X	G85E	S549R	S1235R	c.2657+5G>A	
Modulator Treatment	NONE	Corrector + Potentiator	Potentiator	Potentiator	NONE	NONE

Figure 45-2. Classes of *CFTR* mutations. Abbreviations: Cl–, chloride ion; CFTR, cystic fibrosis transmembrane conductance regulator; mRNA, messenger RNA.

From Harutyunyan M, Huang Y, Mun KS, Yang F, Arora K, Naren AP. Personalized medicine in CF: from modulator development to therapy for cystic fibrosis patients with rare *CFTR* mutations. *Am J Physiol Lung Cell Mol Physiol*. 2018; 314(4): L529–L543. © 2018 The American Physiological Society.

Pathophysiology

There are several hypotheses regarding how *CFTR* dysfunction leads to the phenotypic manifestation of CF, but the most well accepted is the so-called low volume hypothesis, which holds that a combination of excessive reabsorption of sodium and deficient chloride secretion, along with passive movement of water, results in the dehydration of airway surface materials and reduced airway surface liquid depth.[3] This situation in turn leads to a reduction in the lubricating layer between the epithelium and mucus with compression of cilia and inhibition of normal ciliary and cough clearance (**Figure 45-3**). Mucus adherent to the underlying epithelium forms plaques with hypoxic niches that can harbor bacteria, particularly *Pseudomonas aeruginosa*. Recently, an increased appreciation has developed regarding CFTR's role as a bicarbonate

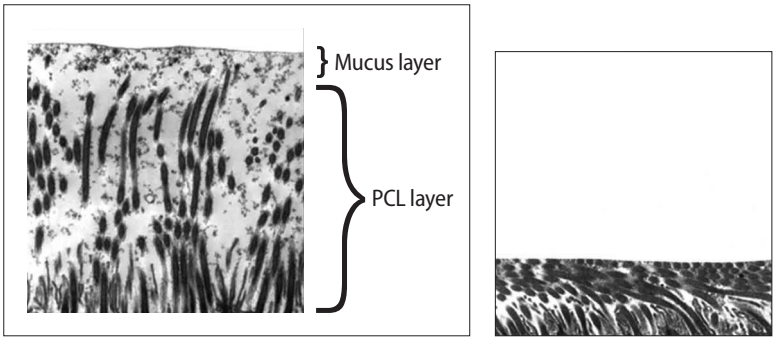


Figure 45-3. A, Mechanical clearance via mucus transport provides the primary innate defense against inhaled bacteria. The promotion of efficient mucus transport is facilitated by the maintenance of a well-defined periciliary liquid (PCL) layer that exhibits an optimal height (ie, the height of extended cilia) and viscosity for effective ciliary beating and cell surface lubrication to clear inhaled organisms. CFTR is key to this process. **B,** Absence of CFTR leads to isotonic reduction in the airway surface liquid, depleting the PCL layer and compromising ciliary function and the system of mucociliary clearance.

channel and a driver of chloride–bicarbonate exchange, and thus a modifier of local pH, which leads to mucin abnormalities in the airway, dysbiosis in both the airway and gastrointestinal tract, and pH dysregulation in the gut.[7] There is also evidence of intrinsic dysregulation of the host inflammatory response.[8] Results from lung lavage studies show that inflammation is present in children as young as 4 weeks who are apparently free of infection.[9]

This CFTR dysfunction in the airways thus leads to susceptibility to bronchial infection. Persistent infection leads to the elaboration of chemotactic cytokines, which recruit large numbers of polymorphonuclear cells into the airways that necrose and release DNA, leading to increased sputum viscosity; this process is termed *neutrophil extracellular trap formation*.[10] Bacterial exotoxins and products of the damaged neutrophils spur further polymorphonuclear cell recruitment, more inflammation, and increased tissue damage. This vicious cycle of cellular events leads to obstruction and bronchiectasis, persistence of infection and inflammation, and eventual respiratory failure (**Figure 45-4**). Outside of the airway, abnormalities in ion transport cause decreased water content in pancreatic and male reproductive tract secretions, leading to ductal obstruction (pancreatic insufficiency [PI] and congenital bilateral absence of the vas deferens [CBAVD]), decreased pH of the small intestinal secretions, and excessive salt content of the sweat.

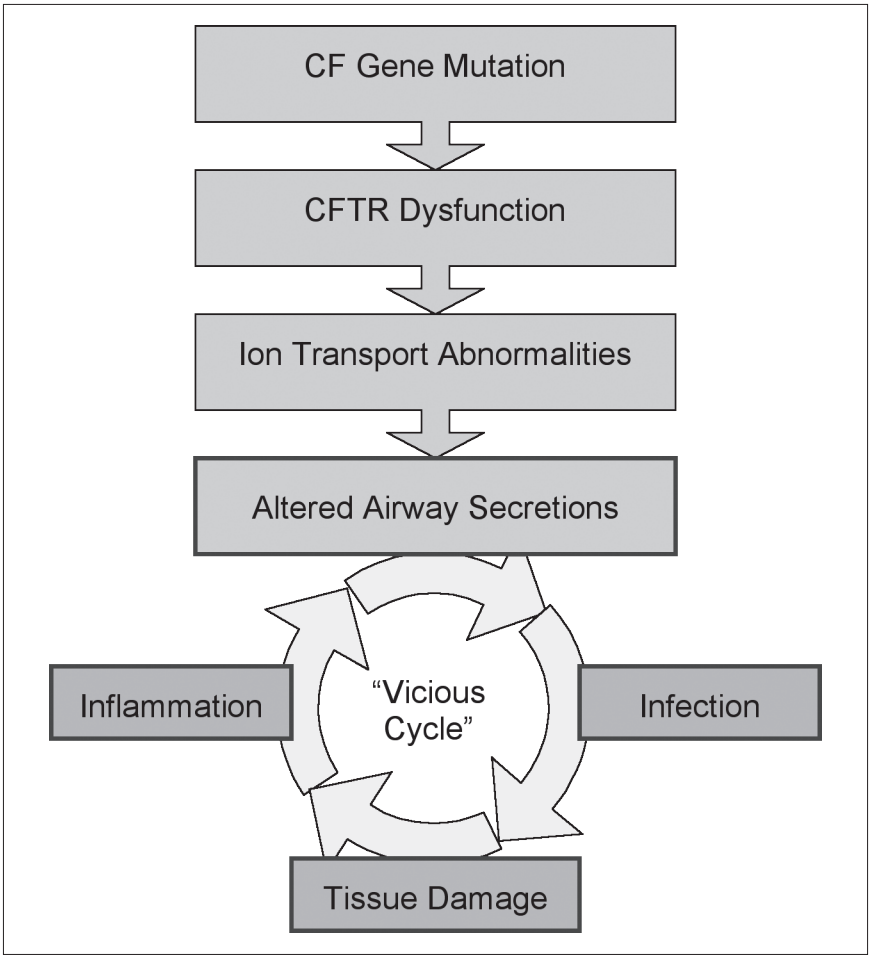


Figure 45-4. Pathogenesis of cystic fibrosis. Abbreviations: CF, cystic fibrosis; CFTR; cystic fibrosis transmembrane conductance regulator.

Clinical Features

Diagnosis

Before the universal adoption of newborn screening (NBS) in the United States in the late 1990s, the median age at diagnosis was 6 months but the mean age at diagnosis was 3 years because of the patients whose diagnosis was missed until late childhood or adulthood. The most common features leading to diagnosis in the pre-NBS era were respiratory symptoms (50%), failure to thrive or malnutrition (34%), and steatorrhea or abnormal stools (26%). Meconium ileus, which is present in about 20% of newborns with CF, remains an important diagnostic marker of CF. Cystic fibrosis continues to be

diagnosed in adults born before NBS; the typical presentation of these patients includes unexplained chronic bronchitis or bronchiectasis, CBAVD, and recurrent pancreatitis.[11]

Cystic fibrosis is diagnosed through the recognition of clinical characteristics, documentation of CFTR dysfunction, and a search for genetic mutations of *CFTR*.[12] The sweat test remains the most readily available and clinically useful approach to establishing the diagnosis of CF, provided it is performed at a laboratory that adheres to strict guidelines using pilocarpine iontophoresis and a quantitative determination of chloride concentration.[13] A sweat chloride test result greater than 60 mmol/L (60 mEq/L) is almost always diagnostic of CF. Patients with a sweat chloride test result in the so-called intermediate range (30–59 for infants younger than 6 months, 40–59 years for older patients) often have abnormalities in CFTR function and should be referred to an accredited CF center for further evaluation. Sweat testing is feasible and reliable in patients by 3 days of age, although it might be more difficult to obtain adequate sweat in young infants, especially those of low birth weight.[14] There are limited causes of false-negative or false-positive sweat test results, and most of these are clinically apparent (**Box 45-1**). In practice, the most common cause of incorrect sweat test results is poor laboratory proficiency, which is unfortunately common in laboratories not associated with CFF-accredited care centers.[15]

Box 45-1

Conditions Associated With a False-Positive or False-Negative Sweat Test Result

False positive

- Atopic dermatitis (eczema)
- Malnutrition
- Congenital adrenal hyperplasia
- Mauriac syndrome
- Fucosidosis
- Ectodermal dysplasia
- Klinefelter syndrome
- Nephrogenic diabetes insipidus
- Adrenal insufficiency
- Hypothyroidism
- Autonomic dysfunction
- Environmental deprivation
- Munchausen syndrome by proxy

False negative

- Dilution of sample
- Malnutrition
- Peripheral edema
- Low sweat rate (quantity not sufficient)
- Hypoproteinemia
- Dehydration
- *CFTR* mutations with preserved sweat duct function (eg, 3849+10kb C→T, R117H-7T)

A number of analytic methods for *CFTR* mutation detection are commercially available. In general, use of a discrete panel of mutations is faster and less costly than expanded mutation analysis, and incorporation of approximately 40 of the most frequent disease-associated mutations can help detect more than 90% of individuals who are affected in most populations. However, the diagnosis will be missed if the subject is affected by a mutation that is not included on the panel in use. Full sequence analysis can help detect virtually all *CFTR* mutations, but its interpretation is sometimes difficult because it often uncovers polymorphisms and novel mutations the importance of which is not known, so genetic testing still requires confirmatory testing of CFTR dysfunction.[12] This confirmatory testing may include sweat testing, nasal transepithelial potential difference measurement, or intestinal current measurement.[16]

Although most patients with CF have the classic triad of lung disease, PI, and a high sweat chloride test result, those with class 4, 5, or 6 mutations may have milder disease with normal pancreatic function, and a growing number of people is recognized as having an intermediate condition that has been named *CFTR-related disorder*.[12] This latter group of patients presents with isolated male infertility, recurrent pancreatitis, chronic sinusitis, or primary sclerosing cholangitis and is then found to have evidence of mild CFTR dysfunction and/or *CFTR* mutations of unclear clinical significance. Individuals with a CFTR-related disorder (generally in 1 organ) should be assessed and followed up by a physician specializing in CF to ensure that any additional symptoms typical of CF that develop are detected.[12,16]

There is an analogous group of infants who are found through NBS to have elevated immunoreactive trypsinogen levels with borderline or normal sweat chloride levels and CF mutations that are not clearly disease causing. The term *CFTR-related metabolic syndrome* (CRMS) has been suggested for use with this group, allowing appropriate follow-up for complications without considering these patients as clearly having CF. These patients should be evaluated at CF centers with expertise and experience with this clinical presentation.[17] Chapter 46, Cystic Fibrosis Newborn Screening and CFTR-Related Metabolic Syndrome, discusses this syndrome in detail.

Clinical Manifestations

Cystic fibrosis is a multisystem disorder that primarily affects the respiratory tract, gastrointestinal tract, sweat glands, and reproductive tract (**Box 45-2**). The appearance of CF-related symptoms occurs throughout life, with great overlap and variability from patient to patient.

Box 45-2

Cystic Fibrosis Is a Multisystem Disorder[a]

- Respiratory tract
  - Sinusitis
  - Nasal polyps (3% require surgery)
  - Chronic bronchitis
    - Bronchiectasis
    - Atelectasis
    - Pneumothorax (1%)
    - Hemoptysis (massive in 2%)
    - Respiratory failure
- Gastrointestinal tract
  - Pancreatic insufficiency (92%)
  - Meconium ileus (21%)
  - Distal intestinal obstruction syndrome (3%)
  - Rectal prolapse (4%)
  - Biliary obstruction, cirrhosis (6%)
- Other
  - Diabetes mellitus (21% of patients aged 14 years or older)
  - Osteoporosis (12% of 18- to 24-year-olds)
- Reproductive tract
  - Congenital bilateral absence of the vas deferens
- Sweat glands
  - Increased chloride content of sweat (99.3%)

[a] Prevalence, when given, is from the Cystic Fibrosis Foundation Patient Registry.[1]

Respiratory Tract Disease

Upper respiratory tract disease, especially chronic sinusitis, is universal in children with CF and often a cause of considerable morbidity. Extensive polyposis may be an additional cause of severe nasal obstruction. The pathogenesis, as in other organ systems, is inspissation of abnormal secretions because of CFTR dysfunction. Some children with CF require repeated surgical procedures for this problem because sinus disease and polyps almost invariably recur. Chronic nasal and sinus obstruction is associated with a high incidence of mouth breathing, and an open-bite malocclusion can occur as an additional morbidity.

The lungs of children with CF are healthy at birth, but airways quickly become infected, inflamed, and obstructed in a self-perpetuating cycle (**Figure 45-4**). Infection rarely spreads beyond the respiratory tract. Chronic airway infection is typically established within the first year after birth and

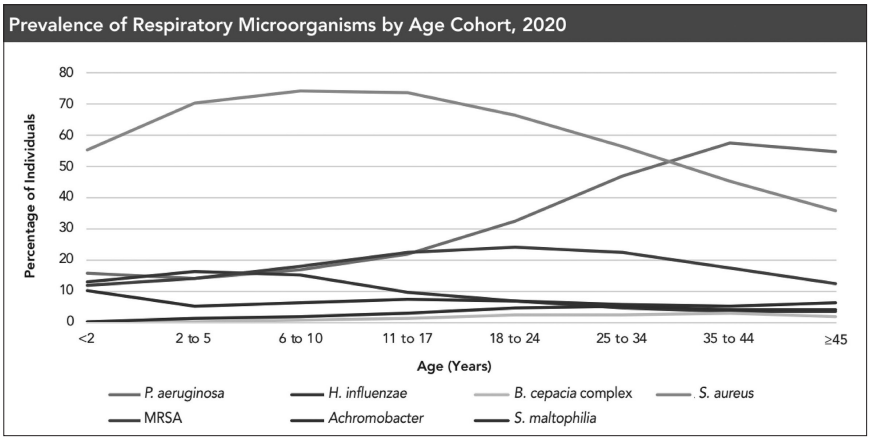


Figure 45-5. Prevalence of respiratory microorganisms by age cohort. Abbreviations: *B. cepacia* complex, *Burkholderia cepacia* complex; *H. influenzae, Haemophilus influenzae;* MRSA, methicillin-resistant *Staphylococcus aureus; P. aeruginosa, Pseudomonas aeruginosa; S. aureus, Staphylococcus aureus; S. maltophilia, Stenotrophomonas maltophilia.*

From Cystic Fibrosis Foundation. *2019 Patient Registry Annual Data Report.* Cystic Fibrosis Foundation; 2020:31. Accessed July 13, 2022. https://www.cff.org/sites/default/files/2021-10/2019-Patient-Registry-Annual-Data-Report.pdf. © 2020 Cystic Fibrosis Foundation.

can be controlled but not eradicated. Chronic bronchitis progressing to obstructive lung disease and bronchiectasis is the hallmark of CF lung disease. Complications of this process include atelectasis due to plugging of segmental and subsegmental bronchi; pneumothorax due to the development of subpleural blebs and cysts, which then rupture; and hemoptysis due to bleeding from hypertrophied bronchial vessels. Pulmonary insufficiency is responsible for most CF-related deaths.

The conventional view of CF microbiology has traditionally focused on a limited suite of opportunistic bacterial pathogens, but it is now appreciated that CF airways (and the gut, as well) typically harbor complex microbial communities that bear on patients' clinical condition and lung disease progression.[18] Although these new insights may alter future clinical treatment of CF, as of the time of this publication most clinical decisions still derive from our understanding of aerobic culture results, which follow a fairly typical course through the life span. Most infants initially harbor *Haemophilus influenzae* and/or *Staphylococcus aureus*; without specific intervention, *P aeruginosa* eventually becomes the predominant organism found in the airways.[1] **Figure 45-5** shows the frequency of different organisms by age. Organisms that play a clinically significant role include the following:

- *H influenzae:* This is typically found in infancy, and less often with increasing age.

- *S aureus:* This is also typically found in infancy but often persists throughout life. Methicillin-resistant *S aureus* is becoming increasingly prevalent in the population with CF as in others; data are conflicting regarding whether its acquisition is associated with worsening lung disease.
- *P aeruginosa:* This becomes increasingly prevalent as patients get older. Initially, *P aeruginosa* grows as a nonmucoid strain that can be cleared by the host or eradicated with aggressive antibiotic therapy.[19] Over time, *P aeruginosa* colonies elaborate an alginate coat and form biofilms.[20] These biofilms, once established, are difficult if not impossible to clear with standard antibiotic therapy. There is a pronounced survival benefit for patients who remain free of *P aeruginosa* infection, so close surveillance for new acquisition of *P aeruginosa* is standard practice, combined with strategies to eradicate early *P aeruginosa* infection (discussed later in this chapter under Pulmonary Therapies: Infection).[19]
- *Stenotrophomonas maltophilia:* This is a relatively resistant organism that has not been associated with acceleration of lung disease.[21]
- *Alcaligenes xylosoxidans:* This is another relatively resistant organism for which the disease course is less clear.
- *Burkholderia cepacia:* This is an uncommon organism that uniquely infects patients with CF and has worrisome implications because it is innately multiresistant, can cause fulminant disease, and is transmissible. Infection with *B cepacia* can cause a rapid decrease in pulmonary function and increased mortality in patients with CF. Occasionally, infection with *B cepacia* can cause an invasive, fatal bacteremia, the so-called cepacia syndrome. *Burkholderia cenocepacia* is particularly transmissible and is associated with a striking deterioration in health, perhaps because of its ability to elicit a more robust inflammatory response from host cells. However, other *B cepacia* strains can also be transmitted from person to person and quickly lead to deterioration, highlighting the need for effective infection control at all CF centers.[22]
- Nontuberculous mycobacteria (also see Chapter 24, Nontuberculous Mycobacteria): *Mycobacterium avium* complex and *Mycobacterium abscessus* are the most common species found in patients with CF, and the prevalence increases from about 10% in children to 30% in adults older than 40 years. It is not always clear whether recovery of these organisms from a patient's sputum indicates true infection or only saprophytic colonization, but patients with persistently positive sputum smears or cultures should be monitored closely for development of worsening disease and treated as described in recommended protocols.[23]
- Fungi: An intense hypersensitivity response to *Aspergillus fumigatus*, known as *allergic bronchopulmonary aspergillosis* (ABPA), is seen in

1% to 15% of patients with CF, the incidence varying with geography. Allergic bronchopulmonary aspergillosis classically manifests as wheezing, pulmonary infiltrates, and central bronchiectasis, but these clues might be obscured by the background of more typical CF lung disease. Diagnostic criteria for ABPA include acute or subacute clinical deterioration, total serum immunoglobulin E concentration greater than 500 IU/mL (1,200 ng/mL), immediate cutaneous reactivity to *Aspergillus*, and either (a) precipitins to *A fumigatus* or immunoglobulin G antibody to *A fumigatus* or (b) abnormalities on chest radiographs or computed tomography scans that have not cleared with standard antibiotic therapy (also, see Chapter 9, Allergic Bronchopulmonary Aspergillosis).[24] There is some speculation that *A fumigatus* may cause progression of lung disease in the absence of ABPA and that other fungi such as *Candida* species and *Scedosporium* may be pathogenic; however, this speculation remains unproved and is an area of controversy and disagreement.[25]

Gastrointestinal Tract

Approximately 21% of infants with CF are born with meconium ileus, an obstructive phenomenon secondary to inspissated material in the small and large bowels. More than 90% of people with CF develop PI, which is usually present at birth but may evolve during the first year after birth. Pancreatic dysfunction is due to obstruction of intrapancreatic ducts with thickened secretions. Typical signs of PI are steatorrhea, flatulence, abdominal bloating, and poor weight gain. Pancreatic insufficiency leads to fat-soluble vitamin deficiency and malnutrition. Abnormal intestinal secretions, malabsorption, and decreased gut motility can lead to distal intestinal obstruction syndrome and/or chronic constipation in older patients.[26] Poor absorption of fat-soluble vitamins (A, D, E, and K) can lead to acrodermatitis, anemia, neuropathy, night blindness, osteoporosis, and bleeding disorders.

Patients with CF are at risk of developing focal biliary cirrhosis due to obstruction of the intrahepatic bile ducts. Clinically apparent cirrhosis is seen in about 5% of patients; it may manifest in infancy and usually is noted by age 15 years.[26]

Reproductive Tract

The vas deferens is exquisitely sensitive to CFTR dysfunction. Virtually all men with classic CF have azoospermia and are infertile due to CBAVD, which can occur in men with only 1 *CFTR* mutation and no other manifestations of CF.[27] Women with CF have cervical mucus abnormalities, but the primary determinant of fertility is their overall health and nutritional status. Results from older studies suggested that pregnancy led to worsening lung disease in women with CF, but results from more recent studies show that women who have adequate nutritional and pulmonary reserve can do quite well with pregnancy, although they are more likely to develop diabetes.[28]

Other Common Manifestations

CF-Related Diabetes

As patients with CF age, the pancreas undergoes autolysis and fatty replacement with loss of insulin-producing islet cells. When a sufficient proportion of islet cells is no longer functional, the patient develops insulin insufficiency and carbohydrate intolerance. This CF-related diabetes (CFRD) is a separate entity encompassing characteristics of both type 1 and type 2 diabetes mellitus. Several factors unique to CF affect glucose metabolism, including elevated energy expenditure, acute and chronic infection, glucagon deficiency, liver dysfunction, decreased intestinal transit time, and increased work of breathing. Clinically apparent CFRD is increasingly common after the first decade of life; the prevalence is more than 30% in adults.[1] The onset of CFRD seems to lead to worsening of both nutritional status and lung disease, and female patients with diabetes have poorer survival than do male patients.[29] Annual screening with fasting blood glucose and oral glucose tolerance tests should be performed in all patients with CF who are aged 10 years or older.[30]

Osteoporosis

Osteoporosis secondary to vitamin D deficiency, chronic systemic inflammation, and intermittent corticosteroid use is increasingly being recognized as a complication of CF. Osteopenia starts in childhood but generally manifests in adulthood. Bone resorption exceeds bone formation even in patients with CF who are well nourished and clinically stable.[31]

Anxiety and Depression

Increasing attention has been paid to the high prevalence of mental health disorders in people with CF, especially anxiety and depression. Although a direct link to CFTR dysfunction has not been ruled out, this anxiety and depression is most likely due to the heavy treatment burden involved in the overall challenge of living with a lifelong chronic disease. Estimates of the prevalence of both anxiety and depression in people with CF and caregivers of children with CF range between 10% and 30%.[32] Depression, in particular, has been associated with decreased ability to maintain daily therapies, worse lung function and quality of life, and decreased survival.[33]

Management

The dramatic improvements in life expectancy and quality of life for people with CF over recent decades have come about largely because of an increased appreciation of the importance of maintaining adequate nutrition and an anticipatory and aggressive approach to controlling chronic airway infection, combined with several new treatment modalities. The benefit of a proactive approach to CF care has been borne out by repeated observations that improved outcomes result from CF center practices associated with increased clinic visits

and clinical monitoring and more proactive use of antibiotics, nutritional interventions, and hospitalization.[34–37]

Furthermore, a historic technological breakthrough has led to the development of a new class of medications, CFTR modulator drugs (discussed later in this section under Pulmonary Therapies: Abnormal CFTR), that appear poised to begin a massive paradigm shift in the treatment and outcomes of CF. Before the introduction of this medication class, all CF treatment was directed at the downstream effects of CFTR dysfunction. Going forward, we will be treating patients in whom that dysfunction has been reversed, so it is not clear how many of the previous standard treatments will be necessary. Patients will still be dealing with the residual consequences of the disease process as it previously manifested, such as bronchiectasis, but not the continuing disease progression resulting from ongoing CFTR dysfunction. However, as of the time of this writing, nearly 10% of the current population with CF have CF mutations that will not benefit from currently available CFTR modulator drugs, and a small percentage of those with eligible mutations are unable to tolerate those therapies for various reasons, so the continued use and refinement of so-called downstream therapies will remain essential for the foreseeable future.

Nutritional Therapies

The benefits of maintaining good nutrition in regard to long-term survival and lung health are well established,[38] making nutritional support an integral component of disease management from early infancy. Pancreatic enzyme therapy should be prescribed for patients with PI either on clinical grounds (steatorrhea, failure to thrive) or as documented by low human fecal elastase-1 levels.[39] The dosage is titrated to minimize fat malabsorption and is standardized according to the lipase activity of the enzyme preparation. The typical dose is between 1,500 and 2,500 U of lipase per kilogram of body weight at each meal and snack. Very high doses (> 6,000 U/kg) have been associated with a rare complication, *fibrosing colonopathy*. Pancreatic enzyme preparations are not completely acid stable, and patients who appear to need relatively high doses will also commonly use a proton pump inhibitor or H_2-receptor antagonist to suppress gastric acidity. The CFF guidelines recommend fat-soluble vitamin supplementation for all patients with PI.[39] Vitamin D deficiency in particular is common. Infants with CF can be safely breastfed, and this form of feeding may confer lifelong benefits.[40] Height, weight, and body mass index should be measured at every CF clinic visit, and patients with a decrease in these parameters should receive nutritional counseling and other interventions. Given the strong correlation between nutritional status and pulmonary function, attention to nutritional well-being should be considered one of the cornerstones of good lung health in patients with CF, and enteral supplements (administered orally or via gastrostomy tube)

should be strongly considered in any patient with less than optimal growth. Patients with CF can and should be expected to maintain a body mass index near the 50th percentile for age. However, success at achieving good weight gain has led to an increasing prevalence of overweight and obesity, especially in patients with pancreatic sufficiency and those on highly effective modulator therapy, so previous blanket encouragement of a high-calorie and high-fat diet needs to be moderated in some patients.[41]

Pulmonary Therapies

Airway infection and inflammation generally begin in the first year after birth, often in the absence of any signs or symptoms. Conventional pulmonary function testing is not sensitive to these early changes, and the average FEV_1 at 5 years of age is 100% predicted. The early institution of a number of preventive and aggressive therapeutic strategies slows the progression of symptomatic lung disease. The effects of treatment beginning in infancy can be seen via magnetic resonance imaging or computed tomography and measurement of lung clearance index (multiple-breath washout), but these are primarily used in research studies rather than in clinical practice.[42] The interventions to counter progression of lung disease can be associated with each of the pathophysiological steps shown in **Figure 45-4**.

Abnormal Gene

The promise of gene therapy, which engendered substantial enthusiasm after identification of the *CFTR* gene in the 1990s, has not yet been borne out, but there continues to be active research into feasible approaches to this modality.[43] Similarly, gene editing tools such as clustered regularly interspaced short palindromic repeat (CRISPR)–based systems are being investigated as a possible approach to making targeted modifications in the genome,[44] but clinical trials have not yet been initiated. However, early-phase trials of novel compounds that deliver messenger RNA that encodes fully functional CFTR protein to the lung epithelial cells are underway, with mixed results as of the time of this publication.

Abnormal CFTR

As noted earlier, the advent of effective and safe CFTR modulator drugs has been a revolutionary breakthrough in CF treatment, allowing the targeting of the primary molecular defect in CF, CFTR dysfunction, as opposed to treating or mitigating the secondary effects such as impaired mucus clearance and recurrent respiratory infections. Modulators can be categorized into 3 types: CFTR correctors, CFTR potentiators, and CFTR amplifiers. The CFTR correctors are small molecular agents that bind to the CFTR protein produced by class 2 mutations (F508del and others) to correct abnormal folding, thus facilitating intracellular processing to improve the probability of a stable CFTR protein reaching the cell membrane. The CFTR potentiators are small molecular agents

that bind to correctly positioned CFTR protein and increase the probability of the CFTR channel being in an open, conformational state, thereby allowing increased ion conductance. This effect is clinically important in patients with gating and conductance defects (class 3 and 4 mutations) but also in conjunction with CFTR correctors by increasing ion conductance in class 2 *CFTR* mutations that have reached the apical cell membrane. The CFTR amplifiers are molecular therapies that it is hoped will increase the amount of CFTR protein made by the cell, but at the time of this writing these are in early clinical trials.

This area is rapidly evolving, so any description of the current state of CFTR modulator therapy will become rapidly outdated, but a brief historical perspective regarding drug development may be of interest.

Ivacaftor: A highly effective potentiator drug, ivacaftor was the first modulator to be developed and approved for clinical use in 2012. It was initially studied in patients aged 12 years or older who had the G551D gating mutation; they had a 10.4% improvement in FEV_1, a 55% decrease in the risk of pulmonary exacerbations, substantial weight gain, reduced pulmonary symptoms, and a decrease in sweat chloride level by 48.1 mmol/L (48.1 mEq/L).[45] It has subsequently been shown to be safe and effective as monotherapy in patients as young as 4 months, with essentially all gating and residual function mutations (classes 3, 4, 5, 6), and (as of 2021) studies are ongoing in infants immediately after diagnosis.

Combination corrector/potentiators: Lumacaftor/ivacaftor was the first combination corrector/potentiator to be developed, approved in 2015 for patients aged 12 years or older with 2 copies of the F508del mutation. This compound was an important first step and proof of principle, but clinical efficacy was much less than that of ivacaftor in patients with gating mutations; pulmonary exacerbations were decreased by one-third, but FEV_1 increased by just 3% predicted, and there was no effect on pulmonary symptoms and mixed results regarding weight gain. As of the time of this writing, it remains the treatment option for children aged 2 to 5 years with 2 copies of the F508del mutation or others who are responsive to the medication for whom the newer triple therapy (discussed next) is not yet approved. Tezacaftor/ivacaftor was approved in 2018 for patients aged 12 years and older with 2 copies of the F508del mutation and as of 2021 is now approved for patients as young as 6 years. Its effectiveness is approximately the same as that of lumacaftor/ivacaftor, with fewer drug interactions, but with the approval in 2021 of the more effective triple modulator therapy for patients as young as 6 years, this medication will likely become archaic.[46]

Highly effective triple combination corrector/potentiator: Elexacaftor/tezacaftor/ivacaftor (ETI) is a triple drug combination consisting of 2 correctors and a potentiator that was approved in 2019 after showing itself

to be highly effective in patients aged 12 years and older with at least 1 F508del mutation or any other *CFTR* gene mutation shown to be responsive on the basis of in vitro data. In this population, ETI increased FEV_1 by about 14% predicted and decreased pulmonary exacerbations by 63% and sweat chloride level by 42 mmol/L (42 mEq/L); it also decreased respiratory symptoms and increased weight gain.[47] This treatment is applicable to about 92% of the population with CF (when patients with at least 1 F508del or 1 of about 180 mutations shown to be sensitive in vitro are included); is, as of 2021, approved for patients as young as 6 years[48]; and will likely dramatically change the face of cystic fibrosis over the next several decades. Furthermore, additional CFTR modulators are undergoing early-phase clinical trial testing as of the time of this writing.

There are several adverse effects of the CFTR modulator drugs, including some that have led to discontinuation in a small percentage of patients. Ivacaftor (and, by extension, all the combinations containing ivacaftor) has been associated with elevated hepatic enzyme levels, and cataracts have been reported in children. Lumacaftor/ivacaftor has been associated with chest discomfort and dyspnea at initiation of the drug, especially in those with advanced lung disease, and worsening of liver disease in patients with preexisting cirrhosis. As a CYP3A4 inducer, it increases metabolism of a host of other drugs that are CYP3A4 substrates, whose levels need close monitoring. These adverse effects of lumacaftor/ivacaftor are seen much less often with tezacaftor/ivacaftor and with ETI. For all CFTR modulators, regular monitoring of liver enzymes is warranted. There have also been some cognitive and mental health adverse effects reported in patients taking ETI, which, as of the time of this writing, have not been well characterized but anecdotally have led to its discontinuation or dose reduction in a small group of patients.

The advent of highly effective modulator therapies has led to a questioning of the ongoing need for the intense treatment of downstream consequences of CFTR dysfunction that has characterized CF treatment up until now. Studies are underway in this regard, but for the time being, most CF physicians recommend continuing treatment, as outlined in the following sections, that focuses on controlling these downstream effects.

Bronchial Obstruction

Airway Clearance Augmentation Techniques

(See also Chapter 55, Airway Clearance Techniques.) Modalities that patients with CF use to augment clearance of tenacious airway secretions include percussion and postural drainage, positive expiratory pressure devices, oscillatory positive expiratory pressure devices, high-frequency chest wall oscillation devices (eg, the Vest [Hill-rom Services, Inc, Chicago, IL), and controlled breathing techniques such as autogenic drainage and active cycle of breathing. The CFF-sponsored guidelines recommend twice daily use of

airway clearance techniques for all patients beginning in infancy.[49] Because there is no clear evidence of the superiority of one technique over the others, convenience, ease of administration, and patient satisfaction are the primary driving forces for choosing a mode of airway clearance. Exercise has many beneficial effects on cardiovascular fitness and sense of well-being. Results from a number of studies show that aerobic and anaerobic exercise improve quality of life in patients with CF and may stabilize lung function to some degree, but exercise should complement and not supplant airway clearance techniques.[50]

Bronchodilators

About 25% of patients with CF have consistent bronchodilator responsiveness, and most have it intermittently. The CFF consensus guideline on pulmonary therapies for patients who have a response on pulmonary function tests recommends the routine use of bronchodilators such as albuterol and salmeterol.[51]

Dornase alfa (Recombinant Human Deoxyribonuclease)

Neutrophils participating in the inflammatory response undergo necrosis, releasing DNA that increases the viscoelasticity and adhesiveness of sputum in patients with CF. Dornase alfa breaks down extracellular DNA, improving the patient's ability to clear mucus. The dose is 2.5 mg once per day, by inhalation. The CFF consensus guidelines recommend its use for patients older than 5 years.[51] It is often used in younger patients, but there is less evidence of benefit in this group.

Hypertonic (7%) Saline

Acting as a hyperosmolar agent, hypertonic saline is thought to draw water into the airways, rehydrating the periciliary layer and improving mucociliary clearance. Twice daily administration as an aerosol has been shown to be beneficial in clinical trials.[52] If hypertonic saline can correct the basic hydration defect in the airways of patients with CF, it might be most efficacious if used early in life, before pulmonary disease becomes established. Results from studies of hypertonic saline use in infants and in 3- to 6-year-olds suggest that this is the case.[53,54]

Infection

Patients who have chronic persistent airway infection with *P aeruginosa* benefit from the use of inhaled tobramycin or aztreonam every other month.[55] The efficacy of inhaling other antibiotics with activity against *P aeruginosa*, methicillin-resistant *S aureus*, and nontuberculous mycobacteria has been suggested but still requires definitive proof. Aerosolized antibiotics achieve high concentration in the airways, so they are potentially effective even when the organism is resistant to levels of antibiotic that might be attainable through systemic administration. However, aerosols do not penetrate into airways that are obstructed, so they do not reach the most involved areas of the lung, and evidence for effectiveness during pulmonary exacerbations is lacking.[56]

The benefit of using prophylactic antibiotics (especially systemic) long-term in children uninfected with *P aeruginosa* is not clear. The CFF recommends against prophylactic use of antistaphylococcal agents because of fears that it increases the likelihood of acquiring *P aeruginosa*, but there is not universal agreement regarding this issue.[57]

At its initial acquisition, *P aeruginosa* can often be eliminated, although the benefit to patients so treated is not entirely clear.[58] Thus, frequent surveillance airway cultures are obtained, and, at initial detection, antibiotics are prescribed to eradicate *P aeruginosa* (even in those without symptoms). The most effective approach to eliminating *P aeruginosa* includes the use of nebulized antibiotics, but the duration of treatment and whether there is advantage to adding systemic antibiotics remain areas of controversy.[19]

Pulmonary Exacerbations and Their Treatment

Intermittent flare-ups of infection in patients with CF are associated with increased inflammation and airway obstruction and are identified by the development of new respiratory signs and symptoms. Increased cough, change in sputum color or quantity, decreased appetite or weight, and change in respiratory rate and auscultatory findings during physical examination are particularly important features (**Box 45-3**). These episodes are called *pulmonary exacerbations* and are treated with discrete courses of systemic antibiotic therapy chosen based on previous cultures of airway secretions. In children, depending on the severity of the exacerbation, it is typical for treatment with oral antibiotics to be attempted initially. If this treatment does not successfully return the patient to baseline status, intravenous antibiotics are used.

Box 45-3

Signs and Symptoms of a Pulmonary Exacerbation[a]

Symptoms
- Cough
- Dyspnea
- Chest tightness
- Hemoptysis
- Increased sputum
- Anorexia

Signs
- New wheezes or crackles
- Weight loss

Laboratory test results
- Decreased FEV_1
- Chest radiograph changes

[a] Note that the presence of even 1 of these findings should prompt treatment and attempts at return to baseline.

There are currently no uniformly accepted defining criteria for what constitutes a pulmonary exacerbation of CF.[37] An aggressive approach to treatment with oral antibiotics—even in patients whose symptoms may be mild or primarily viral in cause—with the addition of intravenous antibiotics when baseline is not promptly reattained leads to better long-term pulmonary outcomes in patients with CF.[59]

Once a pulmonary exacerbation of CF is identified, therapy generally includes systemic antibiotics, increased use of airway clearance techniques, and improved nutrition.

There is a surprising lack of evidence regarding best treatment.[37] Combination antibiotic therapy with 2 or more agents with different modes of action is conventionally used to avoid emergence of resistant strains, and therapy is generally administered for at least 10 to 14 days. Domiciliary treatment with intravenous antibiotics is feasible but may not be as effective as hospital-based therapy.[60]

Inflammation

A number of anti-inflammatory agents are beneficial in patients with CF, but there is some controversy regarding their use.

- Systemic steroids: These can be used in selected patients in the short or long term. They improve airway function when used long-term but are associated with problematic adverse effects such as glucose intolerance and cataracts.[61]
- Inhaled corticosteroids: These are used commonly, particularly in patients with apparent airway reactivity, but their benefit has not been clearly demonstrated.[51]
- Ibuprofen: When administered in high doses (20–30 mg/kg twice daily to a maximum 1,600 mg per dose), ibuprofen leads to long-term benefits in lung function, particularly in children aged between 5 and 13 years. There are concerns regarding gastrointestinal and renal toxicity, but experience has shown these to be unusual.[62]
- Azithromycin: Long-term use of macrolide antibiotics (alternate day azithromycin 250 mg if the patient weighs <40 kg or 500 mg if the patient weighs ≥ 40 kg) is associated with slower decrease in lung function.[63] It is unclear whether macrolides work via an influence on *P aeruginosa* virulence factors or an anti-inflammatory effect, or perhaps by affecting microbiome diversity.[64] Recent concerns have been raised regarding an antagonistic relationship between macrolides and both aerosolized and intravenous tobramycin; a better understanding of how this relationship should be managed is needed.[65]

Tissue Damage

The end result of long-standing infection and inflammation is irreversible bronchiectasis and eventual respiratory failure. At that point, the only remaining option is bilateral lung transplant, which is generally offered when predictive models (which consider current FEV_1, age, sex, lung microbiological characteristics, and rate of FEV_1 decrease, among other factors) suggest that death is likely to be imminent. The 10-year survival after lung transplant is approximately 50%, with bronchiolitis obliterans due to chronic rejection an ongoing problem. Use of nocturnal noninvasive ventilation can improve chest symptoms, sleep-associated hypoventilation, and quality of life in patients with awake hypercapnia who are awaiting transplant.[66]

The Role of the General Pediatrician

Diagnosis

As noted earlier, CF NBS has now been instituted throughout the United States. To counsel the families of patients with positive NBS results appropriately, the general pediatrician must understand the local state screening process and help facilitate it. For more detail, see Chapter 46, Cystic Fibrosis Newborn Screening and CFTR-Related Metabolic Syndrome.

The sensitivity of the CF NBS process is not 100%, so there will always be some patients who have CF diagnosed according to symptoms at a later age. Thus, the pediatrician still has to consider CF in the differential diagnosis in children with chronic or recurrent respiratory symptoms and gastrointestinal complaints.

Follow-up in Patients With CFTR-Related Metabolic Syndrome

Patients with CRMS are particularly important to consider in that they rely primarily on the general pediatrician for follow-up and recognition of symptoms suggestive of a need for intervention. See Chapter 46, Cystic Fibrosis Newborn Screening and CFTR-Related Metabolic Syndrome, for more details in this regard.

Immunizations

Infants and children with CF should receive all recommended immunizations, with special attention to influenza and pneumococcal vaccines. In addition, the American Academy of Pediatrics Section on Pediatric Pulmonology and Sleep Medicine agrees with the CFF recommendation[67] to consider respiratory syncytial virus prophylaxis in all infants with CF younger than 2 years.

Evaluation and Treatment of Apparently Viral Respiratory Tract Infections

As previously noted, aggressive antibiotic treatment of respiratory tract symptoms is a key to attaining better disease outcomes. Children with CF will get as many viral upper respiratory infections as do other children, and these do not immediately call for antimicrobial treatment. However, viral upper respiratory infections are frequent triggers for acute pulmonary exacerbations, which do require antibiotics. When these children are seen in the general pediatric setting for what appears to be even a mild viral respiratory tract infection, it would be advisable to contact the CF center to discuss criteria for antimicrobial treatment, as well as the optimal choice of antibiotic on the basis of previous airway cultures.

Psychosocial Issues

The emphasis on good weight gain that begins early in the course of treatment sometimes leads to behavioral feeding problems that can cause substantial family dysfunction. These are often easily alleviated by appropriate referral to a psychologist with experience in this area. Psychological problems, especially anxiety and depression, are prevalent in children with CF, as well as in their caregivers, and can affect adherence and long-term disease outcomes.[32] These problems should be carefully looked for and, when found, referred for appropriate mental health services. The teenage years for patients with CF, as well as other chronic diseases, can be quite tumultuous, with substantial challenges due to treatment nonadherence and participation in other risk-taking behaviors.[68]

When to Refer

- Any child with an abnormal or borderline abnormal sweat test result should be referred to a CFF-accredited care center for evaluation and treatment.
- The CF center should be consulted if a patient with CF has
  - Persistent cough or congestion (> 1 week)
  - Wheezing or new crackles at chest examination
  - Any new abnormality on chest radiographs
  - Acute dyspnea or hemoptysis
  - Any respiratory infection requiring antibiotics
  - Poor weight gain or weight loss
  - Change in stools: decrease in number, increased steatorrhea
  - Abdominal pain

When to Admit

It is generally ideal for patients with CF, when hospitalized, to be cared for by CF center physicians. There are exceptions; if hospitalization is considered by the primary care pediatrician, the CF center should be contacted to discuss this.

key points

- Cystic fibrosis is a multisystem disease that requires close attention to pulmonary and nutritional parameters.
- Most children with CF in the United States have CF diagnosed by means of NBS. It is important that pediatricians ensure that infants who screen positive are promptly evaluated with a sweat test performed by a laboratory associated with an accredited CF center.
- Patients should be followed up in centers that have experience caring for individuals with CF and can offer expertise in a broad range of areas. A multidisciplinary team including nurses, pharmacists, nutritionists, respiratory therapists, social workers, and others is necessary to achieve the best outcomes. Good communication between the primary care pediatrician and CF care center is key to ensuring optimal care.
- A successful treatment philosophy combines an aggressive approach with high expectations and active participation by patients and family, with the goal of maintaining good (ie, normal) nutrition and respiratory status.

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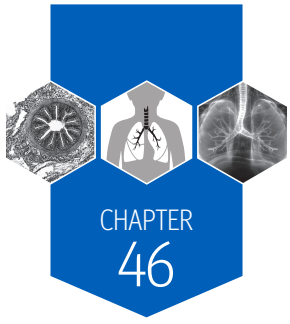
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Cystic Fibrosis Newborn Screening and CFTR-Related Metabolic Syndrome

Danieli B. Salinas, MD, MS
Clement L. Ren, MD, MBA

Cystic Fibrosis Newborn Screening

Background

Cystic fibrosis (CF) is an autosomal recessive genetic condition caused by variants in the gene coding for the CF transmembrane conductance regulator (CFTR).[1] It affects multiple organ systems, but the 2 areas primarily affected are the pancreas and the lungs. In the lungs, loss of CFTR function results in abnormal mucus rheology, impaired innate immunity, and decreased muco-ciliary clearance. These effects result in chronic endobronchial infection, bronchiectasis, and respiratory failure. The pancreatic ducts in people with CF are obstructed, leading to exocrine pancreatic insufficiency (see Chapter 45, Cystic Fibrosis).

Diagnosis of CF was historically based on clinical features, and most commonly infants presented with failure to thrive and profound malnutrition. Establishing a CF diagnosis required performing a sweat chloride test (SCT) in infants and children presenting with clinical features concerning for CF.[2] The principle behind using the SCT as a diagnostic test for CF is based on the fact that CFTR that is present in the sweat duct reabsorbs chloride from sweat while it is being secreted. In the absence of CFTR, excess chloride is secreted, which can be measured using quantitative pilocarpine iontophoresis.[3]

As early as the 1970s it was recognized that earlier diagnosis of CF was associated with better clinical outcomes. The landmark Wisconsin Newborn Screening project, a randomized clinical trial of CF newborn screening (NBS), demonstrated that early diagnosis of CF through NBS was associated with improved nutritional status.[4] Investigators in subsequent epidemiological studies have identified early nutrition as a critical factor in lung function in later life, suggesting that NBS might lead to better lung function in children with CF.[5] These observations led to increasingly widespread implementation

of CF NBS in the United States and throughout the world, and CF NBS was being offered in all 50 states by the end of 2009.

Cystic Fibrosis Newborn Screening Algorithms

Algorithms for CF NBS vary by country and by state. They are also frequently changing, so clinicians should maintain regular contact with their local NBS laboratory to keep current with updates to the algorithm. In the United States, all CF NBS algorithms begin with the measurement of serum immunoreactive trypsinogen (IRT), a pancreatic pro-enzyme that has elevated levels in almost all newborns with CF.[2,5–7] A dried blood spot assay for IRT was first developed in 1979 for use in screening. However, an elevated IRT level is not specific for CF. Some infants without CF, such as those under perinatal stress or of African American descent, can have transiently elevated IRT levels.[8,9] Conversely, IRT levels may actually be lower in infants with CF who present with meconium ileus, although usually in those cases the clinical presentation will have already raised the concern for CF. To improve the predictive value of CF NBS, a second or third tier of testing is performed, the choice of which is state specific.

In the United States, 3 different CF NBS algorithms are used. One approach is to repeat the IRT test 2 to 4 weeks later. In infants without CF, the second IRT test result is usually normal, whereas in infants with CF it is persistently elevated. This approach was used in Colorado, the first state in which CF NBS was performed in 1982, before the discovery of the *CFTR* gene. Another approach is to perform *CFTR* gene variant analysis on the dried blood spot if the IRT level is elevated (**Figure 46-1**).[5] The number of the variants tested ranges from 23 to 338, and the exact composition of the variant panel varies from state to state. If 2 *CFTR* variants are identified, a diagnosis of presumptive CF is assigned, and the infant should be seen as soon as possible at a qualified CF center for a confirmatory SCT and initiation of CF treatment. If 1 variant is detected, the infant is either a CF carrier or has CF with a rare variant not detected on the NBS panel; in this case, an SCT should be performed to rule out CF.

In some states, gene sequencing is performed from the dried blood spot if only 1 variant is detected by the panel. If a second variant is found, a diagnosis of presumed CF is assigned and the infant should be seen as soon as possible at a specialized CF Center for treatment and confirmatory SCT. If no additional variants are identified on sequencing, the infant is considered a CF carrier. In both variant panel testing and sequencing algorithms, if no variants are found the infant is considered screen negative.

The IRT/DNA algorithm allows NBS to be performed from a single blood spot but detects many more carriers than infants with CF. The advantage of sequencing algorithms is a marked reduction in referrals for SCT in infants

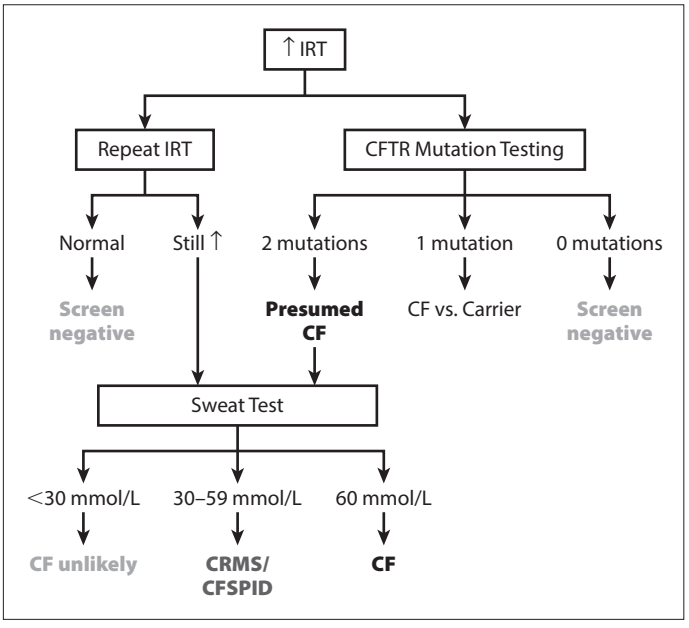


Figure 46-1. Cystic fibrosis newborn screening algorithms. In algorithms using IRT/IRT/DNA, variant panel testing is done only if the second IRT is still elevated. In algorithms using sequencing, CFTR gene sequencing is performed in infants with 1 variant identified on variant panel analysis, and infants with 2 variants identified are presumed to have CF, while those with only 1 variant are classified as carriers.

Abbreviations: CF, cystic fibrosis; CFTR, CF transmembrane conductance regulator; CRMS, CFTR-related metabolic syndrome; CFSPID, CF screen positive, inconclusive diagnosis; IRT, immunoreactive trypsinogen.

with only 1 variant who are carriers. However, sequencing can also result in the identification of a large number of infants with variants of unknown significance or varying clinical consequences.

The IRT/IRT diagnostic algorithm is no longer used in the United States, as all models include DNA analysis (ie, IRT/IRT/DNA or IRT/DNA). Adding DNA analysis to a NBS model increases sensitivity and improves positive predictive value, which leads to fewer false-positive results and shorter time to diagnosis.[10] With this algorithm, IRT testing is repeated 1 to 2 weeks after the initial specimen is obtained. If the IRT level is persistently elevated, then DNA analysis is performed. Although using an IRT/IRT/DNA algorithm can increase the time to diagnosis, the use of this algorithm still allows for CF diagnosis within the first month after birth.

Because IRT levels can fluctuate throughout the year, most states set a cutoff level based on a rolling average of IRT levels (eg, ≥95th percentile over the preceding 30 days). Some NBS algorithms recommend an SCT for infants

with very high IRT levels even if no *CFTR* variants are detected. The algorithm for very high IRT levels can be helpful in detecting infants with rare variants, particularly in populations with high racial and ethnic diversity, who may be missed with a standard DNA variant panel,[11] but it increases the false-positive rate. Results from NBS will be reported as a negative screening result, and no further testing or follow-up is required if the initial IRT value does not meet the state-specific cutoff value. A negative screening result substantially reduces the likelihood of CF but does not rule it out, so SCT and/or genetic testing should be performed in any infant or child who presents with clinical features suggestive of CF.

Initial Management of a Positive CF NBS Test Result

A positive CF NBS test result identifies infants with a high likelihood of having CF, but it is not diagnostic for CF. Any infant with a positive CF NBS test result should undergo an SCT to confirm the diagnosis of CF. In states using the IRT/DNA algorithm, only about 10% of infants who have just 1 CF-causing variant from the screening panel are found to have CF (depending on the variant screening panel and ethnic background of the child); the remaining 90% are CF carriers.[5] Even in cases in which 2 CF-causing variants have been identified, an SCT is indicated because cases of laboratory error or misidentified newborn blood spots have been reported.[7] There are 3 possible outcomes of an SCT:

- Normal (sweat chloride level <30 mmol/L): No further testing or follow-up is required. However, if 2 CF-causing variants have been identified and the SCT indicates a chloride level less than 30 mmol/L, the recommendation of the Cystic Fibrosis Foundation (CFF) is to repeat the SCT and follow up clinically.[7]
- Elevated (sweat chloride level ≥60 mmol/L): This infant meets diagnostic criteria for CF and should undergo appropriate workup and receive therapy as promptly as possible.
- Intermediate (sweat chloride level = 30–59 mmol/L): If 2 CF-causing *CFTR* variants have been identified either through NBS DNA analysis or further genetic testing, then this infant meets diagnostic criteria for CF. If fewer than 2 CF-causing *CFTR* variants are present, then this infant meets diagnostic criteria for CFTR-related metabolic syndrome (CRMS) (see CFTR-Related Metabolic Syndrome later in this chapter).

The clinician and the parents should be informed of a positive NBS result as soon as possible, and referral to an accredited CF center should be made for further evaluation and SCT. Sweat chloride testing should be performed only by using quantitative pilocarpine iontophoresis at an accredited CF care center. The goal of CF NBS is for infants to receive diagnosis and treatment initiated

by 1 month of age. A delay of even 1 or 2 months can have a clinically significant effect on nutrition, and infants with untreated CF are also at risk of developing serious complications such as severe hyponatremic dehydration. Data from the CFF Patient Registry show that there is wide variation in the age at first event (SCT or clinic visit) across the United States and that many infants are seen when they are older than 60 days.[12] Improving the time to first event is the focus of many quality improvement efforts.

In addition to diagnostic testing for CF, the CFF recommends that genetic counseling should be offered to all parents whose infant has an abnormal CF NBS result.[6] Infants with CF diagnosed should be followed up at an accredited CF care center, and their care should follow the guidelines developed by the CFF.[13]

CF NBS Outcomes

Although CF NBS results in improved nutritional outcomes, longitudinal studies have shown that many infants still have abnormal lung function or evidence of structural lung damage.[14] The introduction of highly effective CFTR modulator therapy early in life may be able to affect the natural history of CF lung disease,[15] but for now clinicians must be aware of the need to monitor and treat lung disease in infants with CF diagnosed through NBS.

Although the benefits of CF NBS outweigh its disadvantages, there are some unintended consequences of CF NBS. Both false-negative and false-positive test results can occur. Adding DNA sequencing to NBS and broader access to genetic testing have led to more frequent identification of *CFTR* variants of unknown significance. Uncertainties in diagnosis are recognized as a source of anxiety for parents and a risk for unnecessary medical care of healthy children.[16,17]

CFTR-Related Metabolic Syndrome

Background

An unintended consequence of CF NBS is the identification of infants with a positive CF NBS result but inconclusive diagnostic test results. In the United States, *CRMS* is the term that has been used to describe the condition of these infants.[18] Although the condition is clearly not a metabolic disorder, the *CRMS* label was established to ensure appropriate coding and billing for this group of individuals in the United States. The European Cystic Fibrosis Society has developed an analogous term, *CF screen positive, inconclusive diagnosis* (CFSPID), to classify the condition of these infants.[19] For the purposes of this chapter, we will use the US terminology.

An international consensus conference on CF diagnosis in 2017[20] determined that an infant has CRMS if the infant has no symptoms with a positive CF NBS

test result and either (a) SCT chloride level less than 30 mmol/L and 2 *CFTR* variants, at least 1 of which has unclear phenotypic consequences, or (b) SCT chloride level of 30 to 59 mmol/L and 0 or 1 CF-causing *CFTR* variant. It is important to distinguish CRMS from CFTR-related disorder[21,22] because CRMS is a diagnosis that arises only from CF NBS. In contrast, individuals with CFTR-related disorder present with symptoms with single organ conditions (eg, recurrent pancreatitis) but do not fulfill diagnostic criteria for CF.

The CFF recommends that infants with CRMS be evaluated and followed up by a clinician with expertise and experience in CF care.[18] At the time of this publication, CFF guidelines are in the process of being updated. Updated guidelines from the European Cystic Fibrosis Society in collaboration with international experts outline the following recommendations for short-term and long-term follow-up of these infants[23]:

1. Initial assessment should include clinical evaluation, SCT, extended *CFTR* analysis if the genotype is incomplete, and collection of a stool sample for measurement of fecal elastase-1. Clinical evaluation includes respiratory, abdominal, and nutritional assessment.
2. Offer genetic counseling and parent DNA testing if applicable.
3. Repeat the SCT at 6 months, 1 year, and 2 years. After that, it may be repeated annually if there is a concern about disease progression or the result at 2 years of age is intermediate.
4. Continue annual visits at least until 6 years of age.
5. Continue annual revision of *CFTR* variant classification.
6. Perform respiratory cultures if clinically indicated.
7. Repeat fecal elastase testing if clinically indicated.
8. Primary care physicians should receive annual reports.
9. Perform comprehensive assessment at 6 years, including a repeat SCT, fecal elastase testing, chest radiography (or other modalities of chest imaging), and pulmonary function tests (which may include spirometry and lung clearance index measurement).
10. Discuss results of this comprehensive assessment with parents to decide on future care.
11. In case the child with CRMS is discharged from care at 6 years, that child should be referred back to the CF center for a repeat comprehensive assessment during adolescence or the young adult years.

Prevalence of CRMS

The prevalence of CRMS is difficult to establish because not all cases are reported to national patient registries and there is a high rate of misclassification of infants with CRMS as having CF.[24] Data from the CFF Patient Registry

show that approximately 1 infant receives a diagnosis of CRMS for every 5 cases of CF. Data from studies across the world have shown a prevalence of 1 CRMS case for every 2 to 10 CF cases.[21] In the United States, prevalence may vary by state depending on the NBS protocol and IRT cutoff values. States using an IRT/DNA algorithm and lower IRT cutoff values may identify more CRMS cases because of detection of sequenced variants of unknown significance. States such as California and New York, which use gene sequencing as part of screening, identify even more of such variants (eg, California's ratio is 1.5 CRMS cases per every 1 CF case).[25]

CRMS Outcomes

Data on long-term outcomes in infants with CRMS are limited because CF NBS has only recently become widespread and CRMS has only recently been recognized as a clinical and screening outcome. However, most infants with CRMS will have normal growth and development and will not be reclassified as having CF.[21,26,27] The rate of CRMS to CF reclassification reported so far ranges from 6% to 48%.[24,25,28–33] The discrepancy in CF reclassification rates among studies is due to the different definitions of inconclusive and final CF diagnosis, different interpretations of individual *CFTR* variants (previously variants of unknown significance later classified as causing CF), and different durations of follow-up.[23] The decision to reclassify CRMS to CF is ultimately a clinical decision. However, some of the clinical events that may lead to reclassification include at least one of the following:

- The person develops signs and symptoms suggestive of CF, which may include recurrent isolation of *Pseudomonas aeruginosa* from respiratory cultures.
- The person's *CFTR* variants are reclassified as causing CF.
- Extensive genotyping reveals at least 2 CF-causing variants.
- The SCT result becomes elevated (≥60 mmol/L) at repeat testing.
- Functional assay results (eg, nasal potential difference, intestinal current measurement, or human nasal epithelial cell assays) for CFTR indicate CFTR dysfunction.

The importance of the primary care clinician and their relationship with the CF center cannot be overemphasized. As parents become reassured by their child's lack of symptoms in the first few years after birth, children with CRMS can be lost to follow-up at CF centers, and the responsibility for monitoring the development of symptoms defaults to the primary care clinician.[34] In this era of genetic uncertainty, primary care clinicians should remain aware of the limitations in predicting risk in this population, that *CFTR* variant classifications are constantly changing, and that signs and symptoms may emerge that may or may not be related to CFTR dysfunction. Therefore, primary care

clinicians should rely on CF center expertise and guidance for monitoring children who have received a diagnosis of CRMS. Following are the scenarios that could trigger an immediate re-referral to a CF center:

- One or more episodes of severe dehydration with hyponatremia
- Persistent cough (more than 4 weeks), after exclusion of other causes, such as asthma
- Two episodes of lower respiratory tract infection in a 12 month-period or a total of 3 episodes all together
- Poor growth, after exclusion of other causes
- Signs of malabsorption, after exclusion of other causes
- One or more episodes of pancreatitis
- One or more episodes of severe constipation, distal intestinal obstructive syndrome, and/or small-bowel obstruction
- Findings of air trapping, peri-bronchial thickening, mucous plugging, and/or bronchiectasis in a chest radiograph or computed tomography scan
- Male infertility due to congenital bilateral absence of the vas deferens

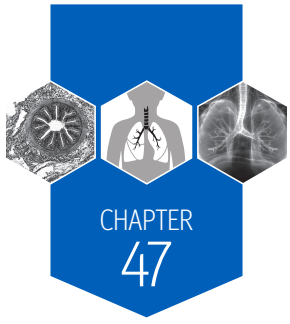
key points

- Early diagnosis of CF through NBS results in improved nutritional outcomes but has not affected the progression of CF lung disease.
- Algorithms for CF NBS that are based on DNA, as applied by all states in the United States, increase the positive predictive value of screening but lead to detection of many more carriers than those with CF.
- Infants with a positive CF NBS result should undergo an SCT to confirm the diagnosis of CF.
- A negative CF NBS result does not rule out CF, and an SCT should be performed in any person presenting with clinical features concerning for CF.
- An unintended consequence of CF NBS is the detection of CRMS in infants who have a positive CF NBS result but are asymptomatic and have inconclusive diagnostic test results.
- The vast majority of infants with CRMS do not develop CF, but a small percentage of them do. Therefore, monitoring and follow-up of infants with CRMS at a CF center is advisable. For those who are not being followed at a CF center, it is important for the primary care clinician to be aware of the scenarios that should trigger re-referral to these centers.

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Primary Ciliary Dyskinesia and Other Genetic Lung Diseases

Madhuri Penugonda, MD
Nico W. Vehse, MD
Thomas W. Ferkol, MD
Bruce K. Rubin, MEngr, MD, MBA, FRCPC, FAAP

Introduction

Several respiratory disorders in children have a genetic predisposition; however, some of these disorders may not manifest until later in life. Recognizing the clinical presentations will aid in early diagnosis. Specific therapies can then be offered, which can decrease the severity of the lung disease or delay the progression. Chronicity of respiratory symptoms is a better indication of a genetic defect than severity. An inherited component should be suspected when chronic lung disease presents with other disease syndromes, such as pancreatic insufficiency, heat intolerance, male sterility, *situs inversus,* and emphysema at a young age. When a genetic disorder is identified or suspected, referral to a genetic counselor should be considered to assist in discussions of prognosis and risk to future pregnancies.

A number of congenital disorders that are not pulmonary in origin nonetheless have significant respiratory complications; these are discussed in the latter part of this chapter.

Primary Ciliary Dyskinesia

Introduction, Terminology, and Epidemiology

Primary ciliary dyskinesia (PCD) is a rare, inherited ciliopathy and the first human disease linked to motile cilia dysfunction. The frequency of primary ciliary dyskinesia has been estimated to be between 1 in 10,000 and 20,000 live births based on the prevalence of *situs inversus totalis* and bronchiectasis in population surveys performed in Norway and Japan.[1,2] A more recent study examining allele frequency of disease-causing variants in genes associated with PCD in populations worldwide estimated a minimum global prevalence

of the disease to be 1:7,500.[3] Although PCD is a rare lung disease, its prevalence in children with repeated respiratory infections was estimated to be as high as 5%.[4]

History

In 1904, the association between *situs inversus* and bronchiectasis was first described.[5] Thirty years later, Kartagener[6] described a clinical syndrome characterized by the triad of *situs inversus totalis,* chronic sinusitis, and bronchiectasis. Afzelius and colleagues[7] found that individuals with chronic sinusitis, bronchiectasis, and *situs inversus* had ultrastructural defects of the ciliary axoneme, and coined the term *immotile cilia syndrome.*[7] Later studies of affected individuals showed that motile cilia had uncoordinated and ineffective beating, and the name was changed to *primary ciliary dyskinesia.*

Motile Cilia Biology

The upper and lower respiratory tracts are lined by a ciliated, pseudostratified columnar epithelium that is critical for mucociliary clearance. Other epithelia are lined by motile cilia, including the ependyma lining the ventricles in the brain and Fallopian tubes. Spermatozoa flagellum has structure and motility fundamentally similar to respiratory cilia.

Each ciliated respiratory epithelial cell contains roughly 200 cilia anatomically and functionally oriented. Motile cilia are tiny (6 mcm in length), hair-like organelles that beat rhythmically, producing a synchronized wave that moves fluid and mucus from the conducting airways, paranasal sinuses, and eustachian tubes. The central fibrillar structure, or axoneme, consists of an array of longitudinal microtubules, organized as 9 microtubular doublets arranged in an outer circle around a central pair, creating the characteristic "9+2" configuration (**Figure 47-1**).[8] The outer doublets of motile cilia have distinct inner and outer arms, consisting of several heavy, intermediate, and light chains.

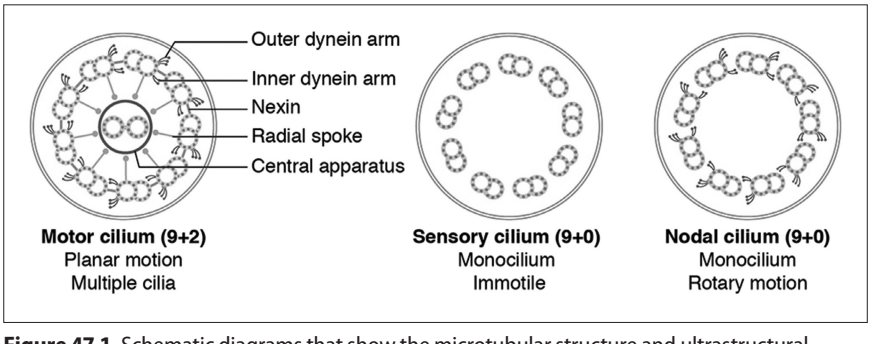


Figure 47-1. Schematic diagrams that show the microtubular structure and ultrastructural elements of normal motile "9+2," nonmotile primary "9+0," and motile nodal "9+0" ciliary axonemes.

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The axonemal dyneins in the outer dynein arm are multiheaded motor proteins that generate force through adenosine triphosphatase activity. The inner dynein arm regulates microtubule sliding and ciliary motion through the dynein regulatory complex.[9] The dynein regulatory complex is located within the nexin link, an elastic element that connects adjacent outer doublets and limits microtubular sliding.[10] The radial spokes connect the central apparatus and outer doublets, and also regulate dynein activity. Normal beat frequency of human motile cilia typically ranges between 8 and 14 beats per second but can be altered by various environmental factors.

There are other cilia in the body. Transiently expressed during embryonic development, nodal cilia are another class of motile cilia with a "9+0" configuration (**Figure 47-1**) that generate leftward flow of extracellular fluid across the nodal surface, activating a signaling cascade that establishes left-right sidedness. In absence of flow, left-right laterality is random, leading to *situs inversus totalis* and heterotaxy.[11,12] Primary (sensory) cilia are non-motile monocilia on the surface of most nondividing cells that have "9+0" microtubule configuration (**Figure 47-1**). They are signaling organelles that sense the extracellular environment and have been linked to a growing number of diseases, termed ciliopathies.[13]

Genetics

Primary ciliary dyskinesia is a genetically heterogeneous disorder without apparent racial or sex predilection.[14] In most cases, it is an autosomal-recessive disease, but X-linked inheritance patterns have been identified.[15,16] To date, more than 50 genes have been linked to motile ciliopathies, and approximately 70% of all patients tested have biallelic pathogenic mutations of these genes.[17] Many of these genes have been linked to specific ultrastructural defects or other ciliary abnormalities. For instance, mutations in *CCNO* and *MCDIAS* lead to chronic respiratory symptoms due to reduction of motile cilia on the airway epithelial surface.[18,19] Pathogenic *GAS2L2* variants have been identified in patients with clinical features consistent with PCD, related to ciliary disorientation.[20]

Genotype-phenotype relationships have emerged in PCD, and respiratory disease severity and progression have been linked to specific mutated genes. Patients with loss-of-function mutations in *CCDC39* and *CCDC40* have been associated with more severe lung disease.[21–23] In contrast, individuals with mutations in *RSPH1* generally have milder respiratory phenotypes compared to other forms of PCD.[24]

Clinical Features

Primary ciliary dyskinesia leads to bronchiectasis similar to other airway diseases, but PCD has 4 cardinal clinical features that differentiate it from other respiratory diseases (**Figure 47-2**).[25]

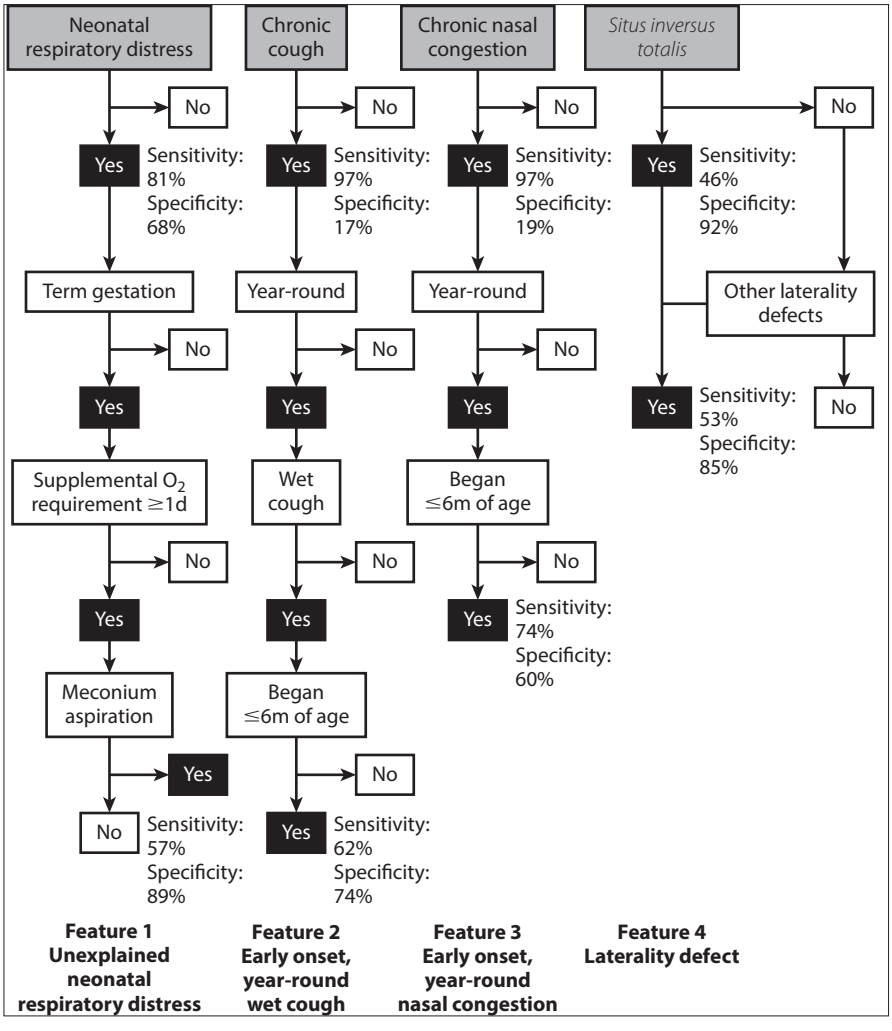


Figure 47-2. Diagram showing the 4 criteria-defined clinical features most predictive of primary ciliary dyskinesia.

Reprinted with permission of the American Thoracic Society. Copyright © 2016 American Thoracic Society. All rights reserved. Leigh MW, Ferkol TW, Davis SD, et al. Clinical features and associated likelihood of primary ciliary dyskinesia in children and adolescents. *Ann Am Thor Soc.* 2016;13(8):1305–1313. *Annals of the American Thoracic Society* is an official journal of the American Thoracic Society.

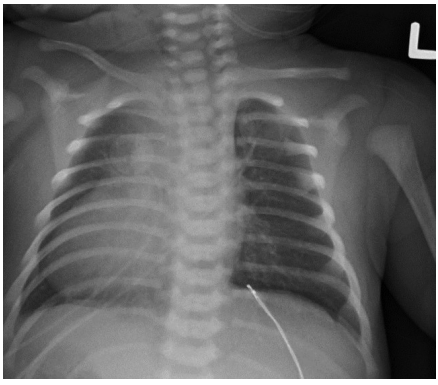


Figure 47-3. Anteroposterior chest radiograph showing *situs inversus totalis* and atelectasis of the morphological left upper lobe in a 1-day-old neonate with primary ciliary dyskinesia.

Most children with PCD present with respiratory distress shortly after term birth without clear explanation, characterized by tachypnea, persistent hypoxemia, and upper and middle lobe atelectasis (**Figure 47-3**). Affected neonates often require supplemental oxygen or positive-pressure ventilator support for more than 24 hours.

Infants with PCD often have daily, nonseasonal nasal congestion and rhinitis that typically begins before 6 months of age.

Affected individuals have chronic, year-round productive (wet) cough that also begins in early infancy. Bronchiectasis involving the morphological right middle lobe and lingula is common. The cough can vary in severity but never completely resolves, even following antibiotic therapy.

Left-right laterality defects occur in approximately half of patients with PCD, usually manifested as *situs inversus totalis* with transposition of the thoracic and abdominal organs (**Figure 47-3**). Conversely, 25% of patients with *situs inversus totalis* will have PCD. As many as 12% of patients with PCD have heterotaxy associated with congenital heart disease, asplenia, or polysplenia.[26]

These 4 criteria can be used to identify at-risk children and direct further diagnostic testing (**Figure 47-2**). If 2 of these features are present, the sensitivity and specificity for PCD are 80% and 72%, respectively. If 3 criteria are present, they are 50% and 96%.[25]Another validated diagnostic predictive tool, PICADAR, has also been created to estimate the probability of a positive diagnosis.[27]

Middle ear disease is a frequent clinical manifestation in PCD, beginning in early infancy, with varying degrees of chronic otitis media with effusion complicated by conductive hearing loss. However, in North America, recurrent and persistent middle ear effusions are common in otherwise healthy infants and toddlers, often requiring tympanostomy tube placement. Thus, this finding has not proved to be useful in identifying children with PCD.[25]

Male and female subfertility are common features in PCD, secondary to sperm dysmotility and ciliary dysfunction in the Fallopian tubes, respectively.[28]

While described in the literature, neonatal hydrocephalus is a rare clinical manifestation of classic forms of PCD.[29]

Patients who have sensory (primary) ciliopathies can have overlapping clinical features with PCD, such as X-linked blindness related to mutations in the retinitis pigmentosa GTPase regulator gene.[30–32]

Diagnostic Testing

While diagnostic approaches for PCD have evolved, clinicians should only perform testing in patients who have a compatible clinical phenotype (see Clinical Features). It is also important for clinicians to understand that there is no single diagnostic test for PCD, and they should thoroughly evaluate suspected patients and not rely on an individual test for diagnosis (**Figure 47-4**).[33]

For more than 4 decades, transmission electron microscopy evaluating the ciliary axoneme for ultrastructural defects has been the conventional diagnostic approach, despite its limitations. Five general ultrastructural phenotypes have been associated with PCD, including outer dynein arm defects, inner and outer dynein arm defects, microtubular disorganization with inner dynein arm defects, radial spokes and central apparatus defects, and normal ultrastructure. Absent inner dynein arms alone are a rare cause of PCD; often they are due to an acquired defect or may be an electron microscopic artifact.[34]

Immunofluorescent staining of ciliary protein markers is a newer method to detect ultrastructural abnormalities in PCD and, in the future, may overcome some of the limitations of transmission electron microscopy.[35]

Nasal nitric oxide (nNO) measurement has been shown to be a useful screening tool for PCD in patients 5 years and older, provided cystic fibrosis (CF) is excluded.[36] However, people who have mutations in some PCD-associated genes can have nondiagnostic nNO values.[37] It is also important to remember that reduced nNO concentrations alone are never sufficient to make the diagnosis of PCD, since people with CF or primary immunodeficiencies (conditions that have clinical features that overlap with PCD) can have reduced levels.[38,39]

High-speed video microscopy has been used as a diagnostic tool, primarily in some European centers, assessing motile ciliary beat patterns and frequency in respiratory epithelia.[40] This approach has not been standardized across centers and still needs to be validated against other diagnostics.

Ciliary beat analyses using standard bright-field microscopy can be misleading, since they can be caused by acquired ciliary defects, and should *never* be used as a screen or diagnostic tool for PCD.

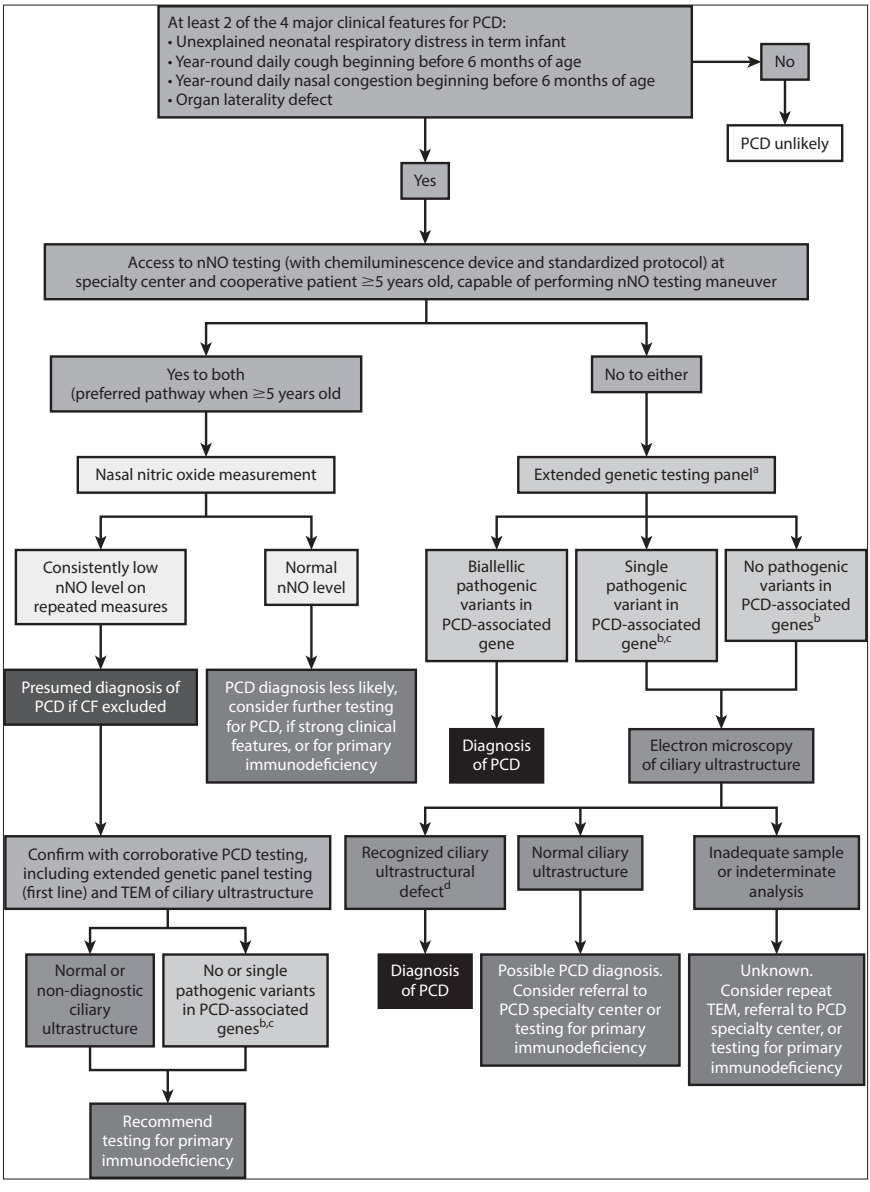


Figure 47-4. Revised diagnostic algorithm for primary ciliary dyskinesia.
[a]Genetic panels testing for mutations in >12 disease-associated PCD genes, including deletion/duplication analysis.
[b]In genes associated with autosomal recessive trait.
[c]In presence of variants of unknown significance.
[d]Known disease-associated TEM ultrastructural defects include outer dynein arm defects, outer dynein arm plus inner dynein arm (IDA) defects, IDA defect with microtubular disorganization, and absent central pair, identified using established criteria.
CF = cystic fibrosis; nNO = nasal nitric oxide; PCD = primary ciliary dyskinesia; TEM = transmission electron microscopy.
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Shapiro AJ, Davis SD, Leigh MW, Knowles MR, Lavergne V, Ferkol T. Limitations of nasal nitric oxide testing in primary ciliary dyskinesia. *Am J Respir Crit Care Med.* 2020;202(3):476-477. *The American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society.

Finally, as more primary PCD genes have been discovered, genetic testing has become the first-line diagnostic tool in North America.[33]

Differential Diagnosis

The early clinical features of PCD distinguish it from other, more common pediatric respiratory diseases, such as asthma.

Cystic Fibrosis

Because CF and PCD can have similar clinical phenotypes, including chronic sinusitis and bronchiectasis, sweat chloride measurement or testing for mutant CF transmembrane conductance regulator (*CFTR*) alleles is indicated. Indeed, CF must be excluded, since these patients can also have reduced nasal nitric oxide levels, though often not as low as patients with PCD.[38]

Primary Immunodeficiencies

Because immunological defects can lead to chronic suppurative infections involving the lungs, middle ear, and paranasal sinuses, evaluation for possible primary immunodeficiency should be considered, including complete blood cell counts with leukocyte differential, lymphocyte subpopulation analyses, serum quantitative immunoglobulin and complement concentrations, neutrophil killing assays, and serological responses to specific immunizations.

Protracted Bacterial Bronchitis

Characterized by a persistent, isolated wet cough lasting for more than 4 weeks, protracted bacterial bronchitis is a recently described clinical condition that has features similar to PCD in young children. However, the cough caused by protracted bacterial bronchitis should resolve following treatment with systemic antibiotics.

Infants and children with recurrent protracted bacterial bronchitis should be tested for CF, immunodeficiencies, and possibly PCD.[41]

Management

Individuals with PCD should be regularly evaluated in a specialized center with spirometry, surveillance respiratory cultures, chest imaging, and audiological testing performed according to the PCD Foundation guidelines.[42] A list of certified centers can be found on the PCD Foundation website (see Family and Patient Resources at the end of this chapter).

No therapies have been shown to correct ciliary dysfunction.

Because patients with PCD are dependent on cough to mobilize infected secretions from the lower respiratory tract, airway clearance maneuvers are key. Patients are encouraged to cough and participate in vigorous aerobic exercises to clear secretions. Cough suppressants should be avoided.

Preventive counseling should include advice regarding avoidance of airborne irritants and pollutants, such as tobacco smoke.

Individuals with PCD should receive scheduled immunizations against pertussis, measles, influenza, *Streptococcus pneumoniae,* and *Hemophilus influenzae* type b.

Antibiotic therapy for respiratory exacerbations or superinfections is important for symptomatic relief and to prevent irreversible airway damage. Some people with PCD benefit from use of azithromycin thrice weekly, which reduces the rate of respiratory exacerbations.[43] Other preventive antibiotic therapies may be considered on a case-by-case basis. In contrast to CF, no studies have shown that eradication of *Pseudomonas aeruginosa* impacts later disease progression or clinical outcomes.

While inhaled β-adrenergic bronchodilators increase ciliary beat frequency in normal epithelial cells, there are no data showing that they correct or reduce cilia dysfunction in PCD.

Inhaled topical corticosteroids, other anti-inflammatory agents, and nebulized hypertonic saline are often prescribed, but little has been published that clearly demonstrates their efficacy in primary ciliary dyskinesia.

The inhaled mucolytic agent dornase alfa should be used with caution, since a larger, multicenter study in non-cystic fibrosis bronchiectasis found worsening lung function in the treatment group as compared to controls.[44]

Evidence concerning the benefits of tympanostomy with ventilation tube placement is mixed. Tympanostomy placement may improve hearing but is often complicated by otorrhea and persistent membrane perforation.[45] Hearing aids should be used when necessary.

Rhinosinusitis is common in PCD, and functional endoscopic sinus surgery and daily nasal saline irrigation may relieve severe nasosinal symptoms that have not responded to antibiotic therapy. However, it is unclear whether this intervention improves long-term clinical outcomes or decreases episodes of symptomatic sinusitis.[46]

Historically, lobectomy was performed in patients with persistent, localized bronchiectasis or atelectasis, usually involving the right middle lobe, but there is no evidence demonstrating any clinical benefits.

Heart-lung and bilateral lung transplantation has been performed in patients with end-stage lung disease, though *situs inversus totalis* could potentially present technical challenges for the surgeon.

Prognosis

Primary ciliary dyskinesia can be compatible with a normal or near-normal life span. However, progression of lung disease is variable and some patients die early. Two studies indicated that early, aggressive airway therapy with airway clearance and antibiotics can slow progression of lung disease.[47,48]

Other Genetic Lung Diseases

Mounier-Kuhn Syndrome

Mounier-Kuhn syndrome is a rare congenital disorder characterized by tracheobronchomegaly. Prevalence estimates are 0.4% to 1.6% with an age range from 18 months to 86 years based on published case reports.[49]

Pathogenesis

The disease is caused by a congenital deficiency (absence or atrophy) of large airway smooth muscle and elastic fibers.[50] This leads to enlargement of the trachea and segmental bronchi, resulting in impaired mucociliary clearance and retention of airway secretions. It has been associated with Ehlers-Danlos syndrome, cutis laxa, and Kenny-Caffey syndrome.[51] Mounier-Kuhn syndrome is generally diagnosed in the third to fifth decade of life and is more common in men.[49] A familial form has been described, but no specific gene has been identified.[50]

Clinical Features

Patients commonly present with chronic cough, purulent sputum, dyspnea, and recurrent pneumonia. Hemoptysis, nail clubbing, pneumothoraces, bronchiectasis, emphysema, pulmonary fibrosis, and respiratory failure may be present. It is unclear if tracheobronchomegaly is progressive, but it is often misdiagnosed as asthma, tuberculosis infection, or chronic obstructive pulmonary disease.[49]

Diagnosis

Pulmonary function tests may be normal or show airflow limitation with some bronchial hyperreactivity. The trachea size will exceed the size of the vertebral column on chest radiograph. Dynamic CT scan of the chest is diagnostic and will show dilation of the trachea and bronchi[49] (**Figure 47-5**).

Management

Treatment is supportive with antibiotics, vaccinations against influenza and pneumococcal infections, chest physiotherapy, pulmonary rehabilitation, oxygen, and noninvasive positive-pressure ventilation (NPPV) for chronic hypercapnic respiratory failure. Stenting of the trachea has been used but has a high complication rate. Bronchodilators and corticosteroids may be helpful for bronchial hyperreactivity. Surgical tracheobronchoplasty is used in select patients and lung transplant for end-stage lung disease.[52]

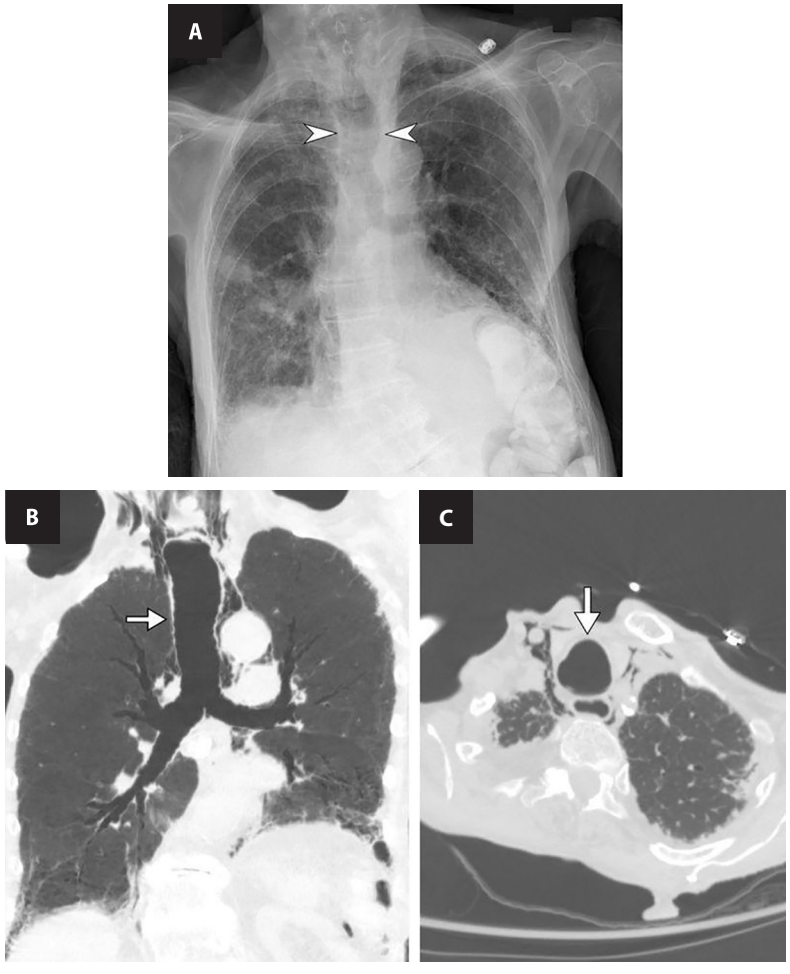


Figure 47-5. Tracheobronchomegaly in Mounier-Kuhn syndrome. **A.** Chest radiograph showing large trachea. **B.** & **C.** Computerized tomography showing tracheal size.

Reprinted with permission from Simkins A, Abishek M, Cherian SV, Trujillo DO, Estrada-Y-Martin RM. Mounier-Kuhn syndrome. *BMJ Postgrad Med J*. 2017;93(1104):642.

Williams-Campbell Syndrome

Williams-Campbell syndrome is a rare congenital disorder characterized by diffuse bronchomalacia. It was initially described in 1960 as a rare form of bronchiectasis.[53] Familial cases have been reported, but no specific gene has been identified.[53]

Pathogenesis

Williams-Campbell syndrome is caused by a congenital defect or absence of cartilage in the second to seventh divisions of bronchi. This leads to airway

instability with airway collapse, retention of secretions, and ultimately bronchiectasis.[53] There is no evidence that the cartilage defect occurs outside the lungs. Trachea and central bronchi caliber are normal. It has been associated with other congenital anomalies such as polysplenia, malrotation of the abdominal viscera, congenital cardiac disease, and bronchial isomerism.[54]

Clinical Features

Patients often present early with recurrent pneumonia, chronic productive cough, wheeze, and nail clubbing.

Diagnosis

Williams-Campbell syndrome is diagnosed by an appropriate clinical history, radiographic evidence of expiratory airway collapse, and exclusion of other common causes of congenital and acquired bronchiectasis. Pulmonary function tests may suggest an obstructive or restrictive defect.[53,54] A CT scan of the chest is diagnostic and will show extensive peripheral bronchiectasis.[55] A CT bronchoscopy with 3D reconstruction of the bronchial tree is a better option and may show absences of cartilage ring impressions in the bronchial wall.[55]

Management

Treatment is supportive with chest physiotherapy, airway clearance, and antibiotics for suppurative infections and oxygen and NPPV for chronic respiratory failure. Surgical resection of affected lobes has shown no benefit. Lung transplant is for end-stage lung disease.

Pulmonary Lymphangioleiomyomatosis

Pulmonary lymphangioleiomyomatosis (LAM) is a rare multisystem disorder that mainly affects postpubertal females.[56] There have been rare cases in prepubertal girls and in boys.[56] It occurs sporadically or in patients with tuberous sclerosis complex. Lymphangiomatosis is often confused with LAM, but lymphangiomatosis is associated with abnormal proliferation of lymphatic tissue and preservation of the lung parenchyma.[57]

Pathogenesis

The disease is characterized by proliferation of neoplastic cells resembling smooth muscle cells within the lung, kidney, and lymphatics. Within the lung, there is cyst formation in the parenchyma resulting in destruction and risk of pneumothoraces. With disease progression, blood vessels can also become affected, leading to impaired diffusion, hemosiderosis, and hemoptysis. Additionally, lymphatics may become involved, leading to chylothorax. Female hormones may contribute to the disease pathogenesis. It is largely limited to postpubertal, premenopausal females with reports of exacerbations

with pregnancy, menstruation, and estrogen use.[58] It has also been associated with the neurocutaneous syndrome tuberous sclerosis, suggesting a genetic component. There are 2 forms of LAM: tuberous sclerosis complex (TSC)-associated LAM and a sporadic type. Hamartin and tuberin proteins, which are encoded on *TSC1* gene and *TSC2* gene, respectively, are absent.[58,59] Patients with TSC should be screened for LAM at the age of 18 years with a computed tomography (CT) scan of the chest.[59]

Clinical Features

Presenting symptoms vary and include dyspnea, chronic dry cough, wheeze, hemoptysis, pneumothorax, cyanosis, cor pulmonale, chylous pleural effusions and respiratory failure.

Diagnosis

Pulmonary function tests show variable patterns from normal to obstructive, restrictive, and mixed.[58] Diffusion capacity for carbon monoxide is generally decreased. Chest radiographs may show normal lung tissue to reticulonodular interstitial infiltrate to end-stage honeycombing. Additionally, pneumothorax and pleural effusions may be seen on radiographs. A high-resolution CT scan of the chest shows diffuse, thin-walled cysts, which are classic signs of LAM. Diagnosis can often be determined based on classic CT appearance and associated findings of LAM. If diagnosis remains uncertain, histologic diagnosis from lung biopsy or transbronchial biopsy may be necessary and is the gold standard.

Management

Treatment is symptomatic, primarily reversing complications such as pneumothorax, ascites, and hemorrhage. General pulmonary support includes supplemental oxygen where appropriate, prophylactic vaccination, and pulmonary rehabilitation. Scuba diving should be avoided, but air travel is safe for most patients with LAM because the risk of a pneumothorax is low. Pleurodesis for recurrent pneumothoraces and thoracic duct ligation for chylothorax may be needed. There have been some studies using hormonal therapy with variable results.[58] In individual cases, progesterone may be tried, as some case reports and retrospective studies have shown some reduction in the rate of lung function decline. Currently, sirolimus, a US Food & Drug Administration–approved mTOR inhibitor, has shown improvements in lung function and quality of life.[60] A potential prognostic biomarker in LAM may be serum VEGF-D, which decreases with sirolimus. Lung transplant may be an option in end-stage lung disease; however, there are some reports of recurrence after lung transplant. Survival is about 10 years, with most children eventually succumbing to progressive respiratory failure.[58]

Alpha-1 Antitrypsin Deficiency

Alpha-1 antitrypsin (AAT) deficiency is an autosomal recessive disorder, with genetic origin from Western/Northern European regions, that was first recognized in 1963. It is mainly a disease of adults characterized by severe emphysema, but it can rarely show manifestations in children, who mostly present with liver disease.[61] Prevalence is 1 in 2,500 in the general North American population.

Pathogenesis

Alpha-1 antitrypsin is a 394-amino acid glycoprotein that inhibits the activity of certain proteolytic enzymes. It is a serine protease inhibitor encoded by *SERPINA 1* gene (also known as *protease inhibitor [PI]*) that is located on the long arm of chromosome 14 and is mainly synthesized by hepatocytes. More than 100 alleles have been identified. M alleles are most common and are associated with normal AAT serum protein levels. ZZ, SS and SZ genotypes have decreased AAT levels and develop pulmonary or hepatic symptoms. MS or MZ genotypes also have decreased levels but rarely develop clinical symptoms.[61] Normal lung homeostasis and repair requires a balance between protease inhibitors and proteolytic enzymes. Neutrophil elastase is the main protease in the lung, where it degrades elastin, collagen, proteoglycan, and other proteins in the alveolar wall. If left unchecked, this process can lead to alveolar destruction. Alpha-1 antitrypsin is the main antineutrophil elastase and prevents degradation of the lung architecture. An imbalance between protease inhibitors and proteolytic enzymes can lead to lung damage such as that seen in emphysema. Smoking is an independent risk factor for emphysema, though in individuals who are deficient in AAT, it can hasten the development of disease secondary to the accumulation of lung inflammatory cells, release of proteases from inflammatory cells, and release of smoke-associated oxidants that inhibit antitrypsin.[62] Together, these further contribute to protease-antiprotease imbalance and, ultimately, lung damage.[62]

Clinical Features

Most people with AAT deficiency do not present with respiratory symptoms until the third or fourth decade of life, or a decade earlier in those who smoke.[62] There are a few rare cases of emphysema in children with severe AAT deficiency.[61,62] However, pulmonary function abnormalities, complaints of wheezing, and diagnosis of asthma are not uncommon in the second decade of life, especially if firsthand or secondhand smoking is present.[62] Children may have wheezing, chronic cough, or dyspnea on exertion. Liver disease, such as jaundice, hepatitis, and cirrhosis, is associated with lung disease in children. In adults, AAT deficiency usually presents as progressive dyspnea and panacinar emphysema.

Physical examination findings are usually normal, though growth restriction, digital clubbing, and signs of chronic obstructive pulmonary disease, such as dyspnea, tachypnea, hyperexpansion, or barrel chest, may be present with advanced lung disease.

Chest radiographs may show hyperinflation with bibasilar hyperlucency. High-resolution chest CT is more sensitive than plain radiography and may demonstrate emphysema and bronchiectasis.

Findings of pulmonary function testing may be normal, though as the disease progresses, evidence of chronic obstructive pulmonary disease develops with an obstructive pattern on spirometry, air trapping on lung volume measurements, and diffusion impairment.

Diagnosis

Alpha-1 antitrypsin deficiency should be considered in cases of prolonged neonatal jaundice, liver disease in any age group, and adults with emphysema, bronchitis, and late-onset asthma. The differential diagnosis should include asthma, CF, and immunodeficiencies. Serum AAT levels can be measured and the risk of disease predicted from the relative deficiency, as 100% of individuals with no detectable AAT develop emphysema and 60% to 85% of those with severe deficiency develop disease.[63] Alpha-1 antitrypsin is an acute phase reactant, and levels may be falsely elevated with any acute or chronic inflammation, such as infection, stress, or pregnancy. Currently, there is no routinely available method for prenatal diagnosis, but protein phenotyping and genotyping are available to confirm the diagnosis, aid in genetic counseling for families, and predict the disease course.[61]

Management

The clinical course of the lung disease in AAT deficiency is variable, suggesting a prominent role for environmental or genetic modifiers.[63] Tobacco smoke exposure seems to be the most important risk factor. Therefore, avoiding smoke exposure is paramount in prevention of lung disease in patients known to be AAT deficient. Augmentation therapy, which consists of weekly intravenous infusions of AAT, is proving to be safe and effective at raising AAT levels, may inhibit the progression of lung disease, and should be considered in consultation with a pulmonary specialist.[64] Supportive therapies include early antibiotics for bacterial infections, bronchodilators, nutritional support, and oxygen as needed for hypoxemia. Patients should receive routine vaccinations (yearly influenza and lifetime pneumococcal vaccinations). Surgical options, such as bullectomy and, ultimately, lung transplant, may be needed in cases of severe disease. Novel therapies under investigation include gene transfer techniques, induced pluripotent stem cells, chemical chaperones, hepatocyte transplantation, and autophagy inducers.

Pulmonary Complications of Other Congenital Disorders

Achondroplasia

Achondroplasia is the most common form of short-limbed dwarfism. It is classified as a chondrodysplasia and is autosomal dominant. It is caused by mutations in the fibroblast growth factor receptor- type 3 (*FGFR3*), which is on chromosome 4. The average adult height is 131 cm (51.5 inches) for males and 123 cm (48.5 inches) for females. The prevalence is 1 in 25,000 to 30,000. Cognitive function is normal in most, but motor delays are common.

Clinical Features

The major features of achondroplasia are hypotonia, macrocephaly with frontal bossing, midface retrusion, short stature with rhizomelic disproportion, and small thoracic cavity. The large head and abnormality at the craniocervical junction contribute to significant mortality in the first year after birth. The risk for sudden death is 2% to 5%, with the major cause of death being spinal cord compression. Central apnea may result from vertebral artery compression at the craniocervical junction, and obstructive apnea may result from midface hypoplasia.[65]

Respiratory difficulty is commonly seen in achondroplasia due to restrictive lung disease secondary to small chest cavity. Patients also have central and obstructive sleep apnea. Untreated sleep apnea can cause serious developmental consequences and cor pulmonale.[66,67] Tracheobronchomalacia has also been seen.

Diagnosis

Diagnosis is established by clinical and radiographic assessment plus genetic testing.[65] Diagnosis can be suspected based on fetal ultrasonography. A polysomnogram is a necessary part of standard assessment.

Management

Caregivers must be aware of the risk of craniocervical compression, which, in extreme form, may result in atlantoaxial dislocation. Endotracheal intubation is difficult because of the midface hypoplasia and the necessity of avoiding extension of the head (backward). Fiberoptic bronchoscopy assistance may be the safest way to intubate, particularly during infancy and early childhood. Referral to pulmonology and neurology specialists in the first year is important to diagnose respiratory disorders as described and assess the craniocervical area of the spinal column. Treatment of obstructive sleep apnea may be tonsillectomy and adenoidectomy with hospitalization for postoperative complications. Noninvasive positive-pressure ventilation (continuous positive airway pressure/bilevel positive airway pressure) treatment may be needed.

Arthrogryposis Multiplex Congenita

The defining feature of arthrogryposis multiplex congenita (AMC) is multiple contractures that are present at birth.

Pathogenesis

During embryogenesis, decreased fetal movement causes extra connective tissue to develop around joints, which results in fixation of the joint, leading to contractures and contributing to decreased chest wall movement. Decreased fetal movement may result from multiple fetal disorders or maternal issues. The earlier in pregnancy that the fetal movement is reduced, the more severe the joint abnormalities. Although a genetic cause may be identified in 30% of cases, most cases are of undetermined etiology.

Clinical Features

The deformities are present at birth, and the condition is not progressive. The condition that causes AMC (eg, muscular dystrophy) may progress.

Classic arthrogryposis is also known as amyoplasia with symmetrical involvement of limb deformity and normal intelligence. The pulmonary complications tend to be related to the size and shape of the chest wall, which may result in a restrictive defect. Williams et al[68] reported significant pulmonary findings in children with distal arthrogryposis type 5 (DA5). Although this report is from Salt Lake City, UT (altitude 7,000 feet) and refers to DA5, the conclusions apply to children at other altitudes, including sea level and other variants of DA. These conclusions include pulmonary function tests that show severe restrictive pulmonary defect (forced vital capacity 30% predicted; total lung capacity 51% predicted) and reduction of maximal inspiratory and expiratory pressures. Arterial blood gases document alveolar hypoventilation. Restrictive chest disease is a component of DA5. This implies involvement of the skeletal and respiratory muscles. Pulmonary evaluation of children with distal arthrogryposis is warranted due to these findings. Additional respiratory complications include tracheal and laryngeal clefts or stenosis. The respiratory muscles as well as the diaphragm may be weak. Scoliosis is common and contributes to restrictive lung disease. Early-onset respiratory failure has a poor prognosis for long-term survival.

Management

The respiratory manifestations may be severe and require assisted ventilation. Endotracheal intubation may be difficult because those affected tend to have a small, immobile jaw. Also, the airway may be compromised so that a tracheostomy may be necessary. Physical therapy might improve overall joint function, and experimental surgeries, such as vertical expandable prosthetic titanium rib, have been explored with some improvement in thoracic growth.[69]

Down Syndrome

Trisomy 21, which results in Down syndrome, is the most common chromosomal abnormality, affecting 1 in every 600 to 800 live births. Pulmonary complications of Down syndrome are multiple, and pneumonia is the most common indication for hospital admission. Despite being common, the pulmonary features are often underappreciated.[70] There are several categories of pulmonary problems, as shown in **Box 47-1.**

Sleep-Disordered Breathing

Sleep-disordered breathing (SDB) is common in Down syndrome during infancy and occurs in older children with Down syndrome. It is reported to be as high as 30% to 75% compared with 2% to 3% in the general population. In infancy, the most usual cause is related to laryngotracheomalacia. The most common cause after infancy is secondary to adenoidal and tonsillar hypertrophy, and upper airway obstruction may result from the small size of the midface, small nasal airways, micrognathia, increased collapsibility of the oropharynx and nasopharynx, and enlargement of the tongue. Obesity is often a contributing factor. The symptoms of sleep apnea include snoring, restless sleep, difficulty awakening, and daytime sleepiness with behavioral changes, including school problems. Evaluation of SDB, including polysomnography (PSG), should be considered in infancy and later because early recognition and management will reduce the likelihood of developing pulmonary hypertension.

Box 47-1

Pulmonary Complications of Down Syndrome

Sleep-disordered breathing
- Large tongue
- Lax pharynx
- Adenotonsillar hypertrophy
- Obesity

Airway abnormalities
- Laryngomalacia
- Tracheomalacia
- Bronchomalacia
- Tracheal bronchus

Parenchymal lung disease
- Subpleural cysts
- Interstitial lung disease

Pneumonia
- Immune deficiency
- Aspiration

Pulmonary Vascular Problems
- Pulmonary artery hypertension
- Pulmonary hemorrhage
- Pulmonary edema

Asthma

Sleep-disordered breathing is so common among children with Down syndrome that the American Academy of Pediatrics recommends referral to a specialist as early as the first year for evaluation.[71] Parents are often unaware of problems even though 97% of children with Down syndrome who snore have SDB confirmed by PSG. Therefore, the American Academy of Pediatrics recommends routine PSG for all patients with Down syndrome by age 4 years.[72]

Airway Abnormalities

Laryngomalacia and tracheomalacia are common in those with Down syndrome and should be evaluated with flexible bronchoscopy. Large tonsils and adenoids, lingual tonsils, large tongue, and lax pharyngeal tissue all contribute to the potential for upper airway obstruction. This can lead to otitis media (50%–70% at 3–5 years of age) and alveolar hypoventilation with resulting hypoxemia, which may lead to pulmonary hypertension. Subglottic stenosis and tracheal stenosis are also common. Tracheal bronchus, also known as a pig bronchus, where the right upper lobe bronchus originates from the trachea above the carina, is not uncommon. Tracheal bronchus should be considered if there is persistent right upper lobe infection or consolidation.

Parenchymal Lung Disease

Pathologists have long been aware of the presence of subpleural cysts in patients with Down syndrome. The cysts are not visible on chest radiographs but are prominently visible on CT scan. They are seen in 20% to 36% of children with Down syndrome and are more common in children with Down syndrome who have congenital heart disease. The presence of cysts confers an increased risk for pneumothorax.

Children with Down syndrome studied at autopsy have shown a decrease in the number of alveoli with increase in alveolar size. The number of alveoli is decreased by 58% to 83% regardless of the presence of heart disease. In addition, pulmonary hypoplasia, pulmonary lymphangiectasia, and interstitial lung disease occur more in children with Down syndrome than in children who do not have Down syndrome.

Pneumonia

Pneumonia is the most common cause for hospital admission among children with trisomy 21, and, of these patients, 10% require admission to the pediatric intensive care unit. The presence of congenital heart defect (CHD) does not influence admission rates to the hospital, but those with CHD seem to have more severe illness with more pediatric intensive care unit admissions and

longer length of stay.[73] The causes of recurrent pneumonia are multiple and include pharyngeal incoordination with aspiration as well as immune deficiency. Airway abnormalities include laryngomalacia and tracheomalacia, and tracheal bronchus may be found on CT scan or bronchoscopy.

Pulmonary Vascular Problems

Pulmonary vascular problems of children and adolescents with Down syndrome include pulmonary hypertension, pulmonary edema, and pulmonary hemorrhage. Congenital heart defects are common, with various abnormalities occurring in 43% of 482 children with trisomy 21 in the review by Weijerman et al.[74] They reported atrioventricular septal defect (includes atrioventricular canal) in 54% of cases, ventricular septal defect in 33.3%, and patent ductus arteriosus in 5.8%. Their incidence of primary pulmonary hypertension was 5.2%, considerably higher than that seen in the general population. Pulmonary hypertension in children with Down syndrome has various etiologies, including polycythemia (35%), asphyxia (12%), hemangioendothelioma (6%), and unknown (47%). Children with Down syndrome who have a large left-to-right shunt typically develop pulmonary artery hypertension (PAH). Although some die in the first few months, others do not develop PAH despite having a large shunt.

Pulmonary artery hypertension also develops in children with Down syndrome who have SDB with resultant hypoxia. The problem of PAH may even occur in Down syndrome without any obvious reason for its occurrence.

Chronic pulmonary hemorrhage is not an uncommon complication of Down syndrome. It is a complication of children who have large left-to-right shunt, increased pulmonary venous pressure from mitral valve dysfunction, or pulmonary venous obstruction. Even in the absence of cardiac abnormalities, it occurs with recurrent pneumonia or aspiration. The clinical features vary from frank hemoptysis to a drop in hemoglobin with minimal symptoms.

Pulmonary edema is also common and is especially seen following relief of upper airway obstruction either intraoperatively or postoperatively. Noncardiogenic pulmonary edema is also seen associated with acute lung injury in children with Down syndrome with pneumonia and postoperatively following cardiac surgery. High-altitude pulmonary edema is more common in children with Down syndrome than in children who do not have Down syndrome.[70]

Asthma

Most studies concerning asthma in children with Down syndrome have reported a lower incidence of asthma than in the general population. There is an increased risk for severe respiratory syncytial virus infection, including bronchiolitis, but the long-term risk for recurrent wheezing is decreased.

Hermansky-Pudlak Syndrome

Hermansky-Pudlak syndrome (HPS) is a rare group of autosomal recessive disorders caused by defects in the biogenesis and function of lysosome-related organelles, including macrophages and type II pneumocytes. The genetic mutation has been identified, with HPS type 1 mutation being the most common and severe.[75]

Clinical Features

Patients with HPS have tyrosinase-positive oculocutaneous albinism with related ocular findings, bleeding caused by poor platelet aggregation, pulmonary fibrosis, granulomatous enteropathic disease, and renal failure.[76] Pulmonary fibrosis usually manifests in the third and fourth decades of life, but onset of pulmonary fibrosis has been described in children as young as 3 years old. The most common symptoms are dyspnea and exercise intolerance.[76]

Diagnosis

Pulmonary function testing may demonstrate a restrictive defect with reduced total lung capacity and impaired diffusion capacity consistent with pulmonary fibrosis. High-resolution chest CT scans are abnormal in most patients (up to 85%), with ground-glass opacities, loss of lung volume, subpleural honeycombing, and traction bronchiectasis[75] (**Figure 47-6**). Diagnosis can be made by careful ophthalmologic examination and confirming tyrosinase-positive oculocutaneous albinism via hair bulb analysis. Although genetic testing can help determine HPS subtype, it is expensive and not widely implemented and some HPS patients have no identified genetic mutations, suggesting additional HPS genes are yet to be discovered.

Management

Therapy is generally supportive with the goal being to reduce bleeding risks and improve pulmonary quality of life. Lung transplant may be the only option. Two antifibrotic drugs, pirfenidone and nintedanib, are being studied

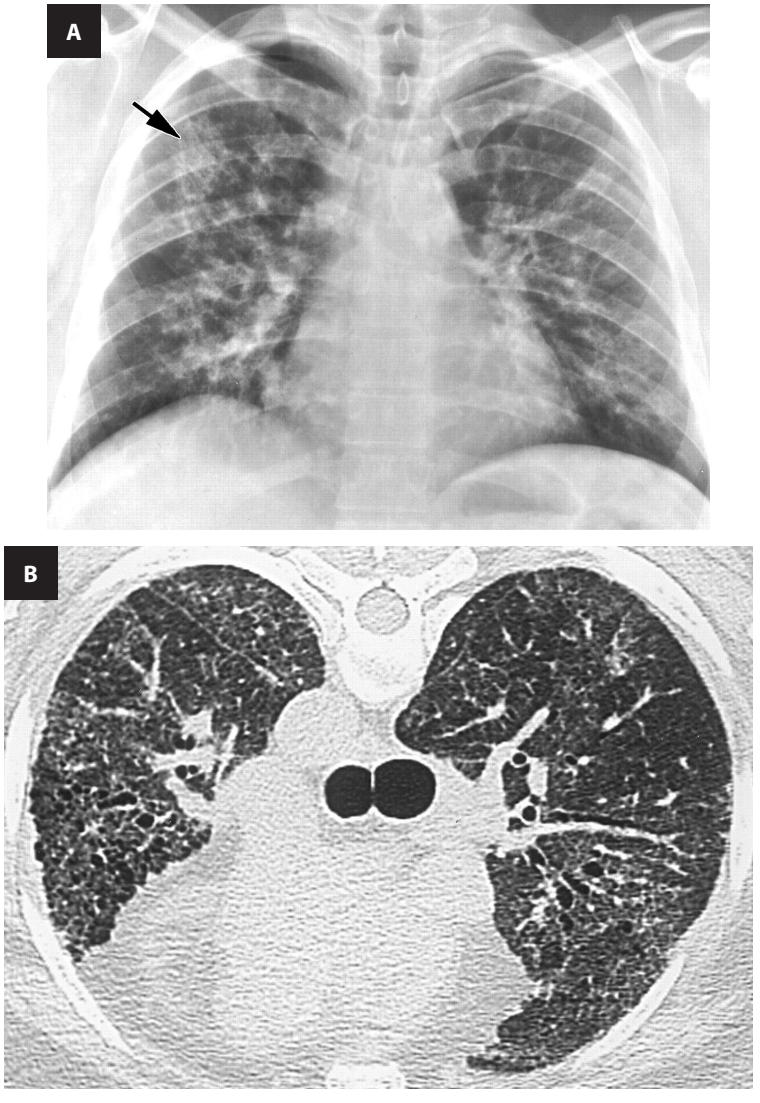


Figure 47-6. Radiographic findings in Hermansky-Pudlak syndrome. **A.** Posteroanterior chest radiograph shows patchy areas of interstitial infiltrates (arrow). **B.** High-resolution computed tomography scan shows ground-glass opacities, bronchiectasis, peribronchovascular thickening, septal lines, and reticulation.

Reprinted from Avila NA, Brantly M, Premkumar A, Huizing M, Dwyer A, Gahl WA. Hermansky-Pudlak syndrome: radiography and CT of the chest compared with pulmonary function tests and genetic studies. *AJR Am J Roentgenol*. 2002;179(4):887–892. Copyright © 2002 American Roentgen Ray Society.

for HPS pulmonary fibrosis. Initial results have been disappointing. Current clinical trials are studying better biomarkers for disease progression. Patients generally survive to 40 or 50 years and die of complications from organ damage.[75] There is high mortality related to pulmonary complications. Patients should be referred to a pulmonologist as soon as respiratory symptoms develop.

Mucopolysaccharidosis

Mucopolysaccharidoses (MPS) are a group of inherited progressive lysosomal storage diseases with multisystem involvement caused by an enzyme deficiency that degrades glycosaminoglycans.[77] There are 7 types, which are inherited as autosomal recessive disorders except for MPS type II (Hunter syndrome), which is an X-linked disorder.

Clinical Features

The spectrum and severity of disease manifestations vary between the different MPS types. Some clinical features include coarse facial features, respiratory and cardiac disease, hepatosplenomegaly, skeletal and joint abnormalities, short stature, spinal cord compression, cognitive impairment, and hearing and vision loss.[78] Respiratory manifestations occur in all MPS types. Otolaryngological manifestations present early with chronic rhinorrhea, chronic otitis media with effusions, hearing loss, and enlarged tonsils and adenoids. Upper airway manifestations include macroglossia, retroglossia, pharyngeal narrowing, stridor, and laryngomalacia. Lower airway manifestations include subglottic stenosis, tracheobronchomalacia, recurrent pneumonia, and bronchitis. Restrictive lung disease results from pectus carinatum and kyphoscoliosis, which alter the chest wall structure, and hepatosplenomegaly causes diaphragm excursion compromise.[77] Sleep-disordered breathing is present in 80% of MPS patients with obstructive and central sleep apnea, hypopnea, and sleep disturbances.[78] Cardiorespiratory failure and death occur from progressive airway obstruction and respiratory insufficiency.

Diagnosis

Clinical evaluation should include urine analysis for excess levels of glycosaminoglycans and enzyme assays. Guidelines from the International Consensus Panel on the Management and Treatment of Mucopolysaccharidosis I recommend patients undergo pulmonary function testing at the time of diagnosis and every 6 to 12 months thereafter.[79] Spirometry and plethysmography with diffusion capacity show restrictive, obstructive, or mixed patterns and can help assess disease progression and response to enzyme replacement therapy. Reduced vital capacity can be a good predictor of sleep-disordered breathing severity. Impulse oscillometry and maximum voluntary ventilation may be an alternative test in those patients with impaired cognition who are cooperative. A six-minute walk test can be used to assess

exercise tolerance. Flexible bronchoscopy may be used to assess dynamic airway changes. Imaging studies, such as soft tissue neck radiographs for pharyngeal narrowing, may be helpful. Routine PSG is suggested yearly in severe forms of MPS type I and every 3 to 5 years in MPS type II.[77]

Management

Respiratory dysfunction poorly correlates with clinical appearance, so anticipation of respiratory problems and management at early stages is important to maximize treatment outcome.[78] Treatment includes vaccinations, airway clearance, nasal decongestants, adenotonsillectomy, inhaled corticosteroids, anticholinergic bronchodilator agents, hematopoietic stem cell transplant, enzyme replacement therapy, spinal cord decompression surgery, and NPPV. In severe forms, tracheostomy with assisted ventilation may be required. Patients with MPS are at high risk for anesthetic complications, with intraoperative and perioperative mortality as high as 20%.[77] A multidisciplinary treatment approach is needed for patients with MPS, with a referral to a pulmonologist early for evaluation, lung function testing, and preoperative respiratory assessments.

Pseudohypoaldosteronism

Pseudohypoaldosteronism (PHA) is a hereditary salt-wasting disorder characterized by renal unresponsiveness or resistance to aldosterone.

Pathogenesis

Pseudohypoaldosteronism has been classified into a type I and type II. Pseudohypoaldosteronism type I has been described to have 2 forms, with either renal or multi-target organ disorder (MTOD).[80] The severe form of PHA type I, which involves other organs, including the lung, is inherited as an autosomal recessive trait and causes severe salt loss secondary to a mutation in the epithelial sodium channel.[81] This defect leads to defective sodium transport in organs such as the kidney, lung, colon, and sweat and salivary glands. Pulmonary symptoms are common in MTOD PHA type I, where increased airway sodium chloride concentration impairs bacterial killing and raises the airway fluid layer, leading to airway clearance impairment.

Clinical Features

Neonatal respiratory distress syndrome at birth is possible due to failure of lung fluid absorption in MTOD PHA type I.[82]

Patients with MTOD PHA type I have clinical signs and symptoms similar to those with CF, including recurrent pneumonia secondary to impaired airway clearance and bacterial killing.[80] They may have periods of dyspnea, fever, tachypnea, and increased work of breathing with crackles auscultated on examination. These individuals also have severe salt-wasting episodes and are prone to periods of dehydration. Pseudohypoaldosteronism is recognized as a

cause of a false-positive sweat test, where sweat sodium and chloride values are elevated secondary to defective electrolyte transport.[80] Chest radiography can demonstrate thickened airways caused by failure to absorb liquid from the airway surface.[83] This can also appear similar to radiographic findings in early CF, although no bronchiectasis has been reported to date.

Diagnosis

The diagnosis of PHA is clinical, with the identification of elevated urinary sodium.

Management

Treatment is similar to CF, with aggressive management of dehydration and electrolyte imbalance as well as early antibiotics for pulmonary infections. Patients can develop *Pseudomonas aeruginosa* colonization, and this should be considered when choosing antibiotic treatments. Supplemental oxygen may be needed during times of active infection. Patients are treated with dietary modification with high-sodium, low-potassium foods. Other therapies, such as diuretics, potassium-binding resins, and alkalinizing agents, may be indicated. Prognosis is guarded, with potential mortality in infancy due to the severe metabolic/electrolyte derangements. Additionally, MTOD PHA type I does not improve with advancing age. Treatment and monitoring are lifelong.

key points

Primary Ciliary Dyskinesia

- Primary ciliary dyskinesia has 4 cardinal clinical features: neonatal respiratory distress in full-term infants, left-right laterality defects, persistent nonseasonal rhinitis that begins early in life, and daily productive (wet) cough that develops in infancy.
- Laterality defects, including *situs inversus totalis* and heterotaxy, occur in roughly half of affected individuals.
- Diagnostic testing should be considered only in those patients who have a compatible clinical phenotype.
- Diagnostic testing has evolved and includes nasal nitric oxide measurements, high-speed videomicroscopy (outside North America), transmission electron microscopy, and genetic testing.
- Nevertheless, there is no single test that will diagnose all cases of PCD.
- The cornerstones of therapy are daily routine airway clearance maneuvers, aerobic exercise, scheduled immunizations, avoidance of airborne exposures, and antibiotic therapy during respiratory exacerbations.
- Despite advances in understanding of the genetics and pathogenesis of PCD, well-tested, disease-specific treatments are still lacking.

(continued)

key points (*continued*)

Mounier-Kuhn Syndrome

- Mounier-Kuhn syndrome is a rare congenital disease that causes tracheobronchomegaly.
- Patients clinically present with recurrent pneumonia, bronchiectasis, pneumothoraces, hemoptysis, emphysema, pulmonary fibrosis, and respiratory failure.
- Treatment is supportive care with chest physiotherapy, antibiotics, and positive end-expiratory pressure.
- Referral to a pulmonologist should be considered early when the diagnosis is suspected to confirm and closely manage lung disease.

Williams-Campbell Syndrome

- Williams-Campbell syndrome is a rare congenital disorder that causes diffuse bronchomalacia. Trachea and central bronchi caliber are normal.
- Patients present with recurrent pneumonias, chronic productive cough, wheeze, and nail clubbing.
- Treatment is supportive with airway clearance and antibiotics.
- Referral to a pulmonologist should be considered early when the diagnosis is suspected to confirm and closely manage lung disease.

Pulmonary Lymphangioleiomyomatosis

- Pulmonary lymphangioleiomyomatosis is a rare condition affecting postpubertal females.
- Neoplastic cells proliferate in the lung, kidney, and lymphatics causing airway narrowing, impaired diffusion, cyst formation, and chylothorax in the respiratory system.
- Symptoms vary and may include chronic dry cough, wheeze, hemoptysis, cyanosis, cor pulmonale, and respiratory failure.
- Treatment is supportive.
- Referral to a pulmonologist should be considered early when the diagnosis is suspected to confirm and closely manage lung disease.

Alpha-1 Antitrypsin Deficiency

- Alpha-1 antitrypsin deficiency is an autosomal dominant inherited disorder caused by the imbalance of protease-antiprotease enzymes in the lung.
- Clinically, patients present with symptoms later in life, with rare cases of emphysema in children.
- Smoke exposure is an independent risk factor for emphysema in these patients.
- Treatment is supportive with avoidance of tobacco exposure, early antibiotics, bronchodilators, oxygen as needed, and nutrition.
- Genetic counseling is advisable when the diagnosis is suspected.
- Referral to a pulmonologist should be considered when the diagnosis is confirmed to closely monitor and manage progression of lung disease.

key points (*continued*)

Achondroplasia

- The first year after birth is important in the prevention of complications related to craniocervical compression.
- Obstructive sleep apnea is common, and symptoms of snoring and other sleep-disordered breathing should be evaluated by a sleep specialist.

Arthrogryposis Multiplex Congenita

- Pulmonary complications result from restrictive lung disease and airway anomalies.
- Pulmonary management is supportive and may require assisted ventilation.

Down Syndrome

- Stay up to date on AAP policy on Health Supervision for Children With Down Syndrome
- Airway and pulmonary complications of Down syndrome may be underappreciated.
- Sleep-disordered breathing is common in Down syndrome. Infants and children should be evaluated by a sleep specialist.
- Pneumonia is the most common cause for admission, and 10% of patients with pneumonia require intensive care unit admission.

Hermansky-Pudlak Syndrome

- Treatment is supportive.
- Referral to a pulmonologist should be considered when the diagnosis is confirmed to closely monitor and manage progression of lung disease.

Mucopolysaccharidosis

- Airway problems are the most problematic symptoms of MPS and have the most potential for morbidity and mortality.
- Sleep-disordered breathing is present in 80% of patients with MPS.
- The airway abnormalities in severe MPS types may require tracheostomy.

Pseudohypoaldosteronism

- Clinical features are similar to CF with recurrent pneumonias, airway clearance impairment, and *Pseudomonas aeruginosa* colonization, but no bronchiectasis.
- Patients may have false-positive sweat test results.
- Treatment is rehydration, early antibiotics, oxygen as needed, airway clearance, and dietary modification.
- Referral to a pulmonologist should be considered when the diagnosis is confirmed to closely monitor and manage progression of lung disease.

Family and Patient Resources

- PCD Foundation. www.pcdfoundation.org
- PCD Family Support Group UK. www.pcdsupport.org.uk
- Genetic Disorders of Mucociliary Clearance Consortium. www.rarediseasesnetwork.org/cms/gdmcc

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PART 10

Lung Disease Associated With Systemic Disorders

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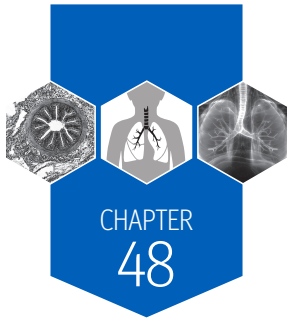
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Respiratory Considerations in Children With Cardiac Disease

Yehudit Pollack, MD
Sankaran Krishnan, MD, MPH

Introduction

The heart and the lungs are intrinsically connected, functioning as a coupled unit with a shared circulatory system. Severe lung disease and abnormalities in the pulmonary vascular bed can cause cardiac alterations, and, conversely, changes in blood flow and pressures in the great vessels and pulmonary vascular bed can cause significant airway and lung changes.

Respiratory symptoms are often the initial, and sometimes the only, manifestation of cardiac disease, especially in a neonate or infant. Congestive heart failure commonly presents with tachypnea, which, if left untreated, can progress to dyspnea with intercostal and subcostal retractions. Tachypnea is initially likely due to increased pulmonary venous pressure or volume. Later in the clinical course, bronchial compression, due to either enlarged pulmonary arteries or enlarged left atrium, may result in hyperinflation and atelectasis. In some patients, the clinical picture is dominated by pulmonary symptoms due to pulmonary edema, including chest discomfort, dyspnea, wheezing, and cough, leading to the term cardiac asthma. Vascular anomalies that affect the major vessels can cause symptoms of airway compression, including stridor, wheezing, and dysphagia, which can lead to acute respiratory presentations.[1]

This chapter examines the interactions between the cardiac and pulmonary systems and, more specifically, discusses the pathophysiology and clinical manifestations attributable to the respiratory system that are often present in children with congenital heart diseases.

Physiology/Pathophysiology

Distribution of Pulmonary Blood Flow

Pulmonary blood flow depends on the interaction between cardiac output and pulmonary vascular resistance. Alterations in pulmonary vascular resistance occur due to passive and active changes to pulmonary vessel caliber. Gravity-dependent and gravity-independent factors may alter distribution of pulmonary blood flow. Gravity-dependent variations in pulmonary blood flow occur due to the net differences in 3 intrapulmonary pressures: intra-alveolar pulmonary capillary pressure, alveolar pressure, and venous pressure. Gravity-independent determinants of passive pulmonary blood flow are affected by changes in lung volumes causing changes in pulmonary vessel caliber.

Active changes in pulmonary vascular resistance due to changing caliber of the resistance vessels in the pulmonary vascular bed lead to changes in pulmonary blood flow. A variety of physiological and pharmacologic stimuli can alter pulmonary resistance. The most important of these factors, alveolar hypoxia, causes localized pulmonary vasoconstriction, referred to as *hypoxic pulmonary vasoconstriction*. Regional alveolar hypoxia causes localized increased vascular resistance and shunts blood toward normal lung, which improves ventilation/perfusion ($\dot{V}/\dot{Q}$) mismatch. Increased pulmonary blood flow in children with congenital heart defects (left-to-right shunts) and in children with arteriovenous malformations may lead to irreversible changes in the pulmonary vascular bed and progressive pulmonary vascular disease.

Alterations in Respiratory Physiology in Congenital Heart Disease

Congenital Heart Disease With Increased Pulmonary Blood Flow

Increased pulmonary blood flow is the physiological sequela of congenital cardiac lesions associated with left-to-right cardiac shunts. These left-to-right shunts are most commonly seen in acyanotic defects (ventricular septal defect, patent ductus arteriosus, atrioventricular canal defects, atrial septal defect). However, certain cyanotic defects may have increased pulmonary blood flow as well as right-to-left shunt (truncus arteriosus, transposition of great arteries, total anomalous pulmonary venous return, single ventricle with unrestricted pulmonary blood flow). The respiratory derangements seen in these patients are secondary to a combination of excessive pulmonary blood volume and increased pulmonary vascular pressures. Systemic arteriovenous malformations are noncardiac congenital defects that are associated with increased pulmonary blood flow and pulmonary hypertension. Increased pulmonary blood volume results in perfusion in excess of ventilation and a $\dot{V}/\dot{Q}$ inequality. When alveolar ventilation is inadequate for pulmonary blood flow, partial pressure of oxygen falls and hypoxia occurs. Increased pulmonary blood flow increases pulmonary arteriolar, capillary, and venous pressures, leading to increased extravascular fluid. Increased pulmonary blood volume

also causes increased lung weight, which further alters pulmonary mechanics. Increased lung weight and hypertensive pulmonary arteries lead to decreased lung compliance. This, along with alveolar atelectasis due to cardiomegaly, causes loss of lung volume, a reduction in lung compliance, and a decreased tidal volume, with a compensatory increase in respiratory frequency.

During spontaneous respiration, the hypertensive pulmonary arteries in patients with left-to-right shunts, in combination with less compliant pulmonary parenchyma, result in a restrictive effect on the lungs, which, in turn, requires more respiratory effort to produce effective lung inflation. A secondary effect of this reduction in pulmonary compliance is the need for increased airway pressure to generate adequate lung volume in patients on mechanical ventilation.

Congenital Heart Disease With Decreased Pulmonary Blood Flow

Right-to-left shunts due to cyanotic heart disease are associated with decreased pulmonary blood flow and have the opposite effects on respiratory mechanics when compared with lesions with increased pulmonary blood flow. Cyanosis in certain cyanotic defects (pulmonary atresia, critical pulmonary stenosis, tetralogy of Fallot, single ventricle with pulmonary stenosis) results from a combination of obstruction to pulmonary blood flow and an intracardiac defect that permits right-to-left shunting. Decreased pulmonary flow results in a decreased lung weight, improved lung compliance, and alterations in $\dot{V}/\dot{Q}$ matching.[2] Physiological dead space increases due to ventilation of under-perfused lung. The extent of the V/Q mismatch directly correlates with the level of hypoxia.[3] The increase in dead space leads to compensatory mechanisms, which include an increase in minute ventilation and a reduction in arterial carbon dioxide. The magnitude of the increase in minute ventilation correlates inversely with the magnitude of the reduction in partial pressure of oxygen. Thus, the acutely hypoxic newborn with decreased pulmonary blood flow typically has effortless tachypnea and cyanosis both due to increased physiological dead space and stimulation of hypoxic pulmonary drive.[4]

In contrast, it is well known that chronic hypoxia as seen in children with palliated or uncorrected cyanotic heart disease blunts the respiratory responses to acute hypoxia. These findings may explain the further oxygen desaturation seen during sleep in some of these patients.[4,5] Loss of normal compensatory responses to hypoxic stimuli may also account for the devastating effects of pulmonary infection in these patients.

Airway Compression With Congenital Heart Disease

Vascular compression of the airway in children is usually caused either by congenital anomalies of the great vessels (vascular rings, vascular slings) or enlargement of otherwise normal structures, such as the aorta, pulmonary artery, or cardiac chambers. (See Chapter 14, Congenital Lung Abnormalities.) Both large and small airway obstruction can occur in patients with increased

pulmonary blood flow. Small airway obstruction results from either intrinsic narrowing of the airways due to fluid collecting in the lumen or extrinsic obstruction from either interstitial edema or dilatation of the pulmonary vessels.[2,6]

The diagnosis of vascular ring is established when there is total encirclement of the trachea and esophagus by vascular structures originating from the aortic arch, including the arterial duct or ligament. Incomplete rings or non-circumferential anomalies, termed slings, can also cause airway compression.[7]

The most common causes of obstructing vascular lesions include

- Double aortic arch.
- Right aortic arch with aberrant retro-esophageal left subclavian artery arising from the descending aorta. This anomaly is due to embryonic left arterial duct and presence of left arterial ligament after birth.
- Pulmonary artery sling, where the left pulmonary artery arises from the right pulmonary artery and courses posteriorly and leftward between the trachea and esophagus, compressing the distal trachea and right bronchus.
- Innominate artery compression, which is caused by more distal attachment of the innominate artery along the aortic arch and can compress the trachea as the artery crosses anteriorly.

Increased pulmonary blood flow combined with pulmonary arterial hypertension (PAH) causes dilatation of the pulmonary arteries and the left atrium, which predisposes to large airway compression and, consequently, air trapping[8] or atelectasis. The latter is most commonly observed in the left lower lobe, followed by the left upper lobe bronchus as the left main bronchus is entrapped and compressed between an enlarged, hypertensive left pulmonary artery and the left atrium.

Large airway obstruction results in restriction to airflow, primarily during expiration. When obstruction is severe, inspiration may also be compromised. When gas trapping occurs, chest radiographs demonstrate increased lung volumes, and studies of respiratory mechanics show abnormalities of expiratory flow and increased airway resistance. A rare variant of tetralogy of Fallot, tetralogy of Fallot with absent pulmonary valve, produces airway obstruction of both large and small airways by hugely dilated pulmonary arteries, leading to lobar collapse, bronchial obstruction with air trapping, and often severe distress.

A combination of imaging techniques is usually required for a full assessment of airway compression in a child with congenital heart disease.[6,7] Historically, chest radiography and barium esophagram were performed to evaluate children suspected of having extrinsic airway compression (**Figure 48-1** and **Figure 48-2**). Multi-slice computed tomography or magnetic resonance angiography can delineate precise anatomic details of the vascular anomaly as well

as the relationship of the vascular structures to the airway and the airway caliber. Bronchoscopy may also be helpful in identifying the location and degree of airway compression.

Often the abnormalities of pulmonary function and respiratory mechanics can be reversed with surgical correction of the vascular anomalies and other cardiac causes of airway compression. However, long-standing extrinsic airway compression may lead to tracheobronchomalacia, which may persist even after correction of the cardiac defect. Therapy should be directed at reversing the underlying cardiac lesion, because surgical interventions aimed at the airway, such as aortopexy and airway stent placement, involve risk and may be unsuccessful or offer only temporary relief.

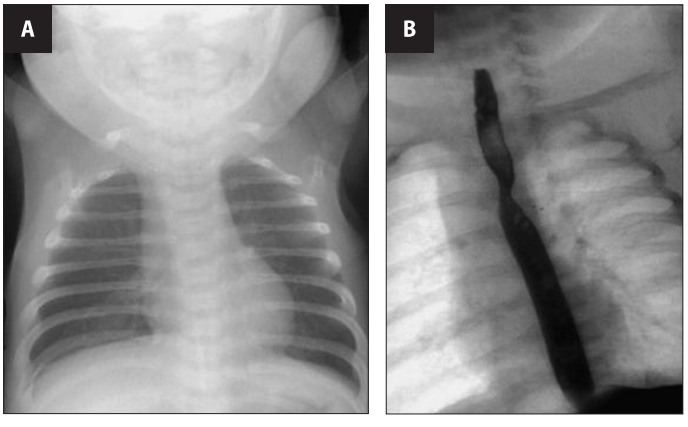


Figure 48-1. A. Anteroposterior radiograph of the chest in a child with a double aortic arch. **B.** Esophagram showing compression of the upper thoracic esophagus by the double aortic arch.

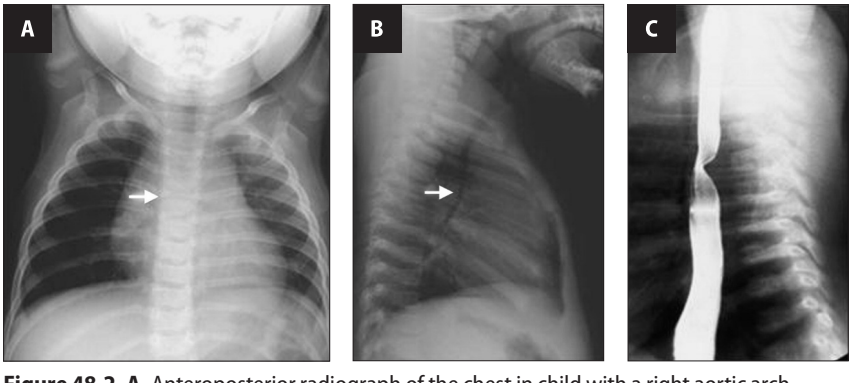


Figure 48-2. A. Anteroposterior radiograph of the chest in child with a right aortic arch. Note displacement of the trachea toward the left indicating a right aortic arch. **B.** Lateral radiograph of the chest demonstrating narrowing and anterior displacement of the trachea by the aberrant left subclavian artery, which passes behind it. **C.** Esophagram showing posterior impression of the esophagus by the aberrant left subclavian artery.

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Eisenmenger Syndrome and Pulmonary Vascular Disease

One of the most common causes of pulmonary vascular disease is as the result of prolonged left-to-right shunting. This usually follows a period of large left-to-right shunt resulting in high pulmonary blood flow, but it may rarely occur in patients who never have manifested clinical features associated with a large left-to-right shunt, namely tachypnea, tachycardia, poor feeding, and failure to thrive. Paradoxically, clinical signs of congestive heart failure improve with increasing pulmonary vascular resistance. This is followed by the appearance of cyanosis and progressively oligemic lung fields. Although now rare due to early diagnosis and treatment of congenital heart disease, Eisenmenger syndrome results when an unrestricted and large left-to-right shunt leads to irreversible pulmonary vascular disease and subsequent right-to-left shunt.[9]

Pulmonary vascular disease may also develop due to congenital heart defects causing increased pulmonary venous pressure, such as congenital mitral stenosis, cor triatriatum, and pulmonary venous stenosis. Lastly, certain cyanotic congenital cardiac defects are associated with pulmonary hypertension and, if uncorrected, with pulmonary vascular disease. These include transposition of great arteries, pulmonary atresia with ventricular septal defect and unrestricted flow through aortopulmonary collaterals, and truncus arteriosus.

Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is defined as an elevated mean pulmonary arterial pressure of greater than 20 mm Hg, with a normal pulmonary artery wedge pressure (PAWP <15 mm Hg) and increased pulmonary vascular resistance (PVR >3 WU) in children older than 3 months.[10–15] Pulmonary arterial hypertension may occur in the absence of congenital heart disease and was previously classified according to the presence (secondary) or absence (primary) of an identifiable underlying cause. Pulmonary arterial hypertension is now classified based on underlying risk factors and associated conditions. In 2018, the 6th World Symposium on Pulmonary Hypertension updated the existing classification of pulmonary hypertension to include many of the etiologies of pediatric pulmonary hypertension, as shown in **Box 48-1**.[11] Persistent pulmonary hypertension of the newborn (PPHN) and pulmonary hypertension secondary to lung disease are briefly discussed in the following text.

Box 48-1

Classification of Pulmonary Hypertension

(Group 1) Pulmonary Arterial Hypertension (PAH)

- (1.1) Idiopathic PAH
- (1.2) Heritable PAH
- (1.3) Drug- and toxin-induced PAH
- (1.4) Pulmonary arterial hypertension associated with the following:
  - (1.4.1) Connective tissue disease
  - (1.4.2) HIV infection
  - (1.4.3) Portal hypertension
  - (1.4.4) Congenital heart disease
  - (1.4.5) Schistosomiasis
- (1.5) Pulmonary arterial hypertension long-term responders to calcium channel blockers
- (1.6) Pulmonary arterial hypertension with overt features of venous/capillaries involvement
- (1.7) Persistent pulmonary hypertension of the newborn syndrome

(Group 2) Pulmonary Hypertension Due to Left Heart Disease

- (2.1) Pulmonary hypertension due to heart failure with preserved left ventricular ejection fraction
- (2.2) Pulmonary hypertension due to heart failure with reduced left ventricular ejection fraction
- (2.3 Valvular heart disease
- (2.4) Congenital/acquired cardiovascular conditions leading to post-capillary pulmonary hypertension

(Group 3) Pulmonary Hypertension Due to Lung Diseases and/or Hypoxemia

- (3.1) Obstructive lung disease
- (3.2) Restrictive lung disease
- (3.3) Other lung disease with mixed restrictive/obstructive pattern
- (3.4) Hypoxia without lung disease
- (3.5) Developmental lung disorders

(Group 4) Pulmonary Hypertension Due to Pulmonary Artery Obstructions

- (4.1) Chronic thromboembolic pulmonary hypertension
- (4.2) Other pulmonary artery obstructions

(Group 5) Pulmonary Hypertension With Unclear and/or Multifactorial Mechanisms

- (5.1) Hematologic disorders
- (5.2) Systemic and metabolic disorders
- (5.3) Others
- (5.4) Complex congenital heart disease

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Persistent Pulmonary Hypertension of the Newborn

Persistent pulmonary hypertension of the newborn, the most common cause of transient PAH, is often associated with conditions such as meconium aspiration, pneumonia, and sepsis. Persistent pulmonary hypertension of the newborn is characterized by increased pulmonary vascular resistance, right-to-left shunting at the atrial or the ductal level, and severe hypoxemia. Persistent pulmonary hypertension of the newborn is typically transient and resolves with appropriate treatment; however, it can be fatal in a small percentage of children.

Pulmonary Hypertension Due to Lung Diseases and/or Hypoxia

The major causes of pulmonary hypertension associated with pulmonary disease are obstructive pulmonary diseases such as bronchopulmonary dysplasia[13,14] and cystic fibrosis, restrictive pathologies including interstitial lung disease, and obstructive sleep apnea. The pathophysiology varies, but the common factors include chronic hypoxia with resulting vasoconstriction and muscular arteriolar hypertrophy. The hypertrophy is initially reversible if the underlying condition, especially the hypoxia, is remediable. Nocturnal hypoxia due to underlying lung disease or untreated obstructive sleep apnea may also cause pulmonary hypertension.

Clinical Features

Signs and symptoms may appear late in the clinical course of patients with pulmonary hypertension and are often nonspecific. Infants may present with sweating, tiring with feeding, and failure to thrive, while older patients may experience fatigue, exertional dyspnea, and chest pain. If infants have a patent foramen ovale, they may also present with cyanosis either at rest or with exercise because of a concomitant right-to-left shunt. In infants and children without the atrial level shunt to alleviate right atrial pressure and maintain cardiac output or act as a "pop-off," syncope can be a presenting symptom, and, in these cases, the prognosis is worse.

Typically, the pulmonic component of the second heart sound is accentuated. A right ventricular heave with or without chest wall distortion may be noted as a result of right ventricular hypertrophy or dysfunction. Tricuspid regurgitation is common, with a holosystolic murmur at the left lower sternal border. Clinical signs of right heart failure, such as hepatomegaly, peripheral edema, and cyanosis, are rare in infants but can be observed in older children and adults. Digital clubbing may be seen in patients with persistent hypoxemia.

Diagnosis and Evaluation

In addition to a comprehensive history and physical examination, diagnostic studies will need to be performed to assess for both cardiac and pulmonary function and potential underlying etiologies. Electrocardiographic findings may be normal early in disease or have evidence of cor pulmonale, with right axis deviation with right ventricular hypertrophy, which may be seen later in the disease process.[10–15] Initially, chest radiograph findings may be normal or later demonstrate cardiomegaly with increased pulmonary vascular markings. Severe pulmonary hypertension is characterized by an enlarged main pulmonary artery segment and diminished pulmonary vascularity.[10–14]

Echocardiography should be used to confirm a clinical suspicion of pulmonary hypertension and evaluate right ventricular function. An indirect estimate of right ventricular pressure is obtained by the tricuspid regurgitation jet velocity. The peak velocity of the tricuspid regurgitation jet is proportional to the right ventricular to right atrial pressure difference. In addition, there are other indirect observations suggestive of pulmonary hypertension, such as flattening or posterior bowing of the interventricular septum and right ventricular hypertrophy and gradients across ventricular or arterial shunts. Echocardiography is useful as a noninvasive screening tool but can miss pulmonary hypertension, even when severe, and often can underestimate pulmonary artery pressures. Cardiac catheterization remains the gold standard in determining the presence and severity of pulmonary hypertension.[10,14]

Catheterization with acute vasoreactivity testing should be performed to test the potential reversibility of pulmonary vascular disease. Though cardiac catheterization is regarded as the gold standard, presence of sedation, hypoventilation, and hypoxia may change the pulmonary vascular resistance. Lastly, cardiac catheterization in the presence of advanced pulmonary vascular disease may be associated with a higher risk of morbidity and mortality and should only be performed in centers with expertise in management of pulmonary hypertension. Interval repeat echocardiograms and catheterizations should be performed to monitor the clinical course and response to therapies.

Chest computed tomography, lung perfusion scan, magnetic resonance imaging, cardiopulmonary exercise testing, and polysomnography may be helpful in evaluating the underlying pathogenesis and monitoring response to therapy of PAH. Brain natriuretic peptide or N-terminal pro b-type natriuretic peptide are biomarkers measured at baseline and follow-up to assess cardiac disease severity and treatment response, with elevated levels correlating with a poor prognosis in pulmonary hypertension. The 6-minute walk distance test can be

used to monitor exercise tolerance in older children. This test can assess overall distance walked, how this distance compares to predicted normal distance, and the presence of exercise-induced oxygen desaturations. Serial walk tests can also monitor the patient's disease progression and response to therapy.

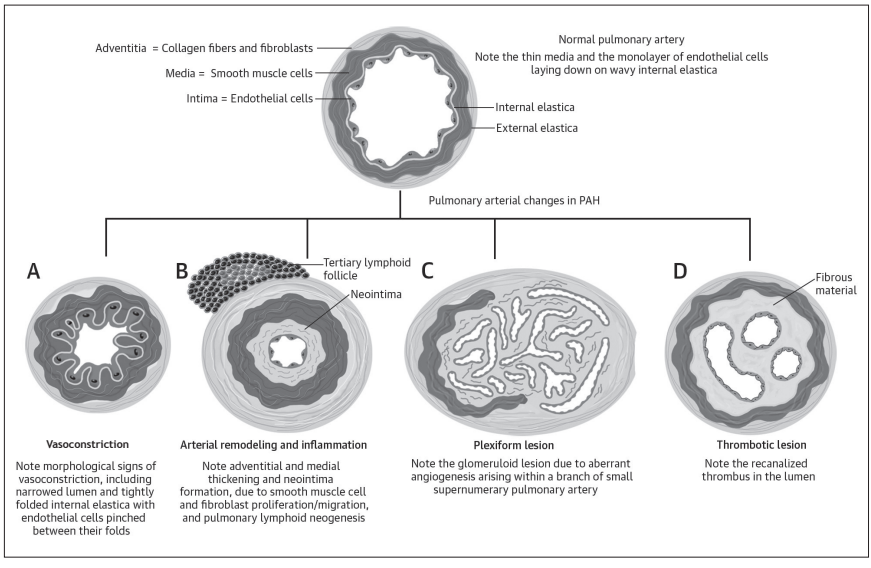


Figure 48-3. Vascular changes in pulmonary hypertension.

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Evaluation of pulmonary vascular structure in lung biopsy specimens can provide important information, especially in preoperative patients. The Heath-Edwards Classification describes 6 grades of changes seen in patients with pulmonary hypertension.[16] These changes range from medial hypertrophy in grade I to formation of angiomatoid lesions and fibrinoid necrosis in grade VI, which convert the lung to a stiff mesh-like organ (**Figure 48-3**).

It is believed that pulmonary vascular changes of grades I and II severity are reversible, whereas more advanced changes indicate that pulmonary vascular disease will persist or worsen following correction of the underlying lesion. However, in practice, biopsy is rarely performed exclusively to assess the pulmonary vasculature, in part due to the nonuniform nature of pulmonary vascular disease and in part due to lack of widespread expertise in preparing and interpreting pulmonary vascular changes. Lung biopsy is often useful in the diagnosis and clinical management of underlying pulmonary pathologies associated with pulmonary hypertension including, but not limited to, childhood interstitial lung disease.[17]

Surgical Treatment of Pulmonary Hypertension

The recognition and management of pulmonary hypertension is important both preoperatively and postoperatively. In most cases, early repair of the underlying cardiac lesion will prevent development of pulmonary vascular disease; however, in some cases, pulmonary hypertension may persist and progress to irreversible pulmonary vascular disease despite appropriate and timely interventions. This process seems to be accelerated at high altitudes and in patients with Down syndrome. The timing and selection of patients for surgical repair is of utmost importance, as intervention may be futile and counterproductive if advanced vascular disease is present. The availability of medical therapy increases the possibility for surgical repair of defects in children who previously would not have been candidates for surgery.

Medical Treatment of Pulmonary Hypertension

General health care maintenance measures include recommendations for limitation of physical activity, prevention of pregnancy, and aggressive treatment of infections.[12,13] Decisions regarding selection, initiation, and modification of pulmonary hypertension–specific therapy should be made based on disease severity, drug tolerance (and availability/cost), and consultation with pulmonary hypertension specialists[12–14] (**Figure 48-4**). Supportive medical therapies, such as diuretics and digoxin, are options for patients with right heart failure but should be used cautiously. Oxygen can act as a pulmonary vasodilator, and supplemental oxygen may be used in patients with daytime or nocturnal hypoxemia. Oral anticoagulation with warfarin may be cautiously used, particularly in patients with underlying hypercoagulability, but benefits must be weighed against bleeding risk, such as hemoptysis.

Inhaled nitric oxide dilates the pulmonary vasculature by increasing cyclic guanosine monophosphate (cGMP) levels, resulting in smooth muscle relaxation. Inhaled nitric oxide can be used in the acute management of pulmonary hypertension. Four classes of drugs are used as part of targeted pulmonary vasodilator therapy, including (1) phosphodiesterase inhibitors, (2) endothelin receptor antagonists, (3) prostacyclin analogues, and (4) calcium channel blockers.

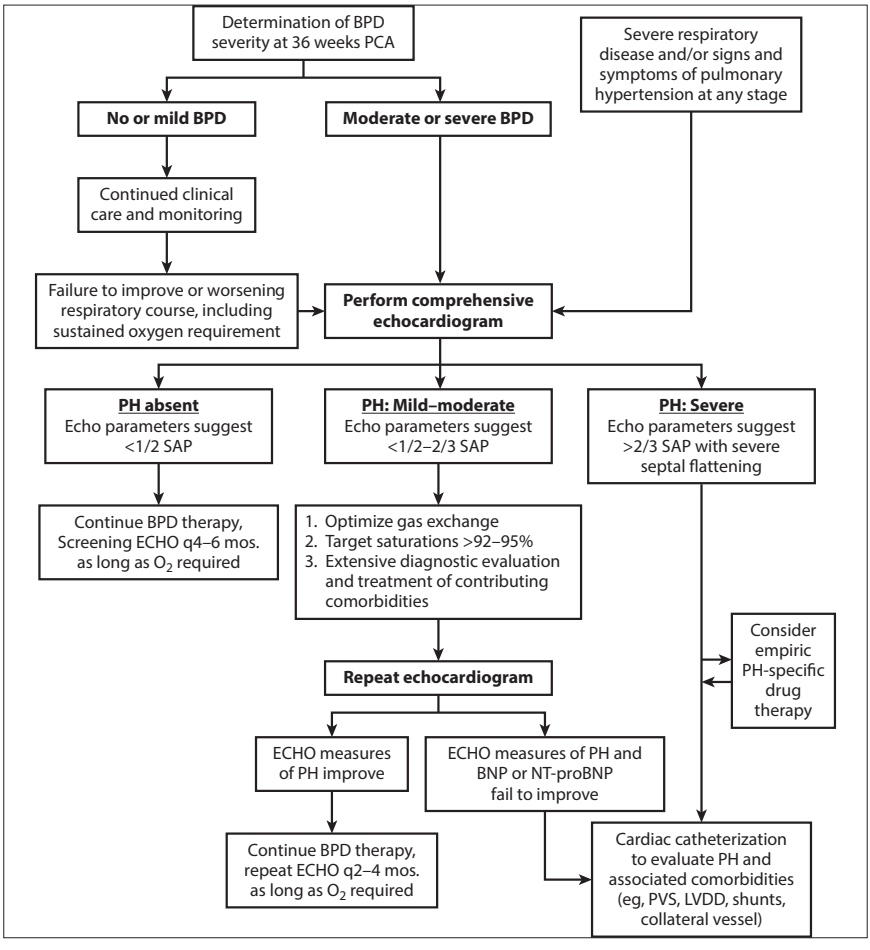


Figure 48-4. Management of pulmonary hypertension in infants with bronchopulmonary dysplasia (BPD) . Abbreviations: ECHO, echocardiogram; LVDD, left ventricular diastolic dysfunction; O_2, oxygen; SAP, systemic arterial pressure

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Phosphodiesterase Inhibitors

Phosphodiesterase type-5 inhibitors (sildenafil, tadalafil) cause vasodilation by preventing the breakdown of cGMP.[18] Tadalafil has a longer duration of action, with dosing once daily as opposed to 3 times daily with sildenafil; however, pediatric data are limited.

Endothelin-1 Receptor Antagonists

Endothelin-1 receptor antagonists (bosentan, ambrisentan, macitentan) lower pulmonary vascular resistance by blocking the receptor for endothelin-1, a potent vasoconstrictor.[19]

Prostacyclin Analogues

Prostacyclin analogs (epoprostenol, treprostinil, iloprost) stimulate cyclic adenosine monophosphate, resulting in vasodilation, inhibition of platelet aggregation, and anti-inflammatory effects.[12,13] Limited by a short half-life, they are typically administered intravenously or subcutaneously or inhaled, with limited data on pediatric use of oral treprostinil.

Calcium Channel Blockers

Calcium channel blockers (nifedipine, diltiazem, amlodipine), which inhibit calcium influx in vascular smooth muscle, are indicated for patients who demonstrate vasoreactivity to inhaled nitric oxide on catheterization. These patients form a unique subset of patients with PAH who have a significantly better long-term prognosis and have been recently subclassified as Group 1.5 (see **Box 48-1**).

Infants with pulmonary hypertension and bronchopulmonary dysplasia should have outpatient follow-up with the multidisciplinary pulmonary hypertension team for ongoing treatment of their chronic lung disease and pulmonary hypertension at intervals of 3 to 4 months with use of echocardiography, biomarkers, hemodynamic studies, and sleep studies when indicated during follow-up, depending on disease severity and clinical progress.[12,13] Surgical options may be considered in severe cases unresponsive to medical treatments. An atrial septostomy creates a right-to-left atrial shunt to improve cardiac output while a Potts shunt, created from the descending aorta to the left pulmonary artery, helps reduce right ventricular pressure and increase systemic blood flow. The option of last resort is lung or heart-lung transplantation.

Prognosis

The prognosis for children with pulmonary hypertension varies depending on the underlying etiology and associated comorbidities. Overall prognosis has improved in the era of targeted vasodilator therapy. Despite advancements in diagnosis and management of pediatric pulmonary hypertension, the estimated 5-year survival rate is only 75%.[11–15]

Viral Respiratory Infections in Children With Congenital Heart Disease

Children with congenital heart disease represent a high-risk group for viral respiratory infections. The complex risk factors include altered cardiorespiratory status at baseline, altered pulmonary mechanics, potential cyanosis with or without pulmonary hypertension, and $\dot{V}/\dot{Q}$ mismatch. All these factors exacerbate the adverse effects of respiratory disease and blunt normal compensatory mechanisms. A review of respiratory infections in children younger than 24 months with significant congenital heart disease demonstrated a 10.4% incidence of hospitalization.[20] Risk factors for hospitalization (in order of decreasing odds ratio) include presence of 22q11 deletion syndrome, weight below the 10th percentile for age, previous respiratory infections, incomplete prophylaxis against respiratory syncytial virus (RSV), recent cardiopulmonary bypass, trisomy 21, and siblings younger than 11 years. In the first report of children with congenital heart disease and RSV, a 37% mortality was noted, with a 73% mortality in patients with pulmonary hypertension.[21] More recent studies have noted an improvement in survival, with mortality rates of approximately 2% to 3%.[22,23] Morbidity remains high, with about 30% requiring intensive care unit admission and prolonged mechanical ventilation. Improved outcomes have been attributed to early repair of hemodynamically significant lesions and, more recently, use of palivizumab for RSV immunoprophylaxis. A large, multicenter, international clinical trial of immunoprophylaxis in infants with congenital heart disease demonstrated a reduction in hospitalization by 45% when compared with the placebo group.[24] The investigators concluded that monthly palivizumab prophylaxis is safe and effective in children with serious congenital heart disease. Current American Academy of Pediatrics (AAP) guidelines[25] recommend that monthly palivizumab prophylaxis is indicated for infants 12 months of age and younger with hemodynamically significant CHD, including infants with acyanotic heart disease who are receiving medication to control congestive heart failure and will require cardiac surgical procedures and infants with moderate to severe PAH. The AAP does not recommend palivizumab for children with hemodynamically insignificant CHD, those with surgically repaired CHD who are not receiving medication for heart failure, those with cardiomyopathy who are not taking medical therapy, or children in their second year after birth.[25] Other anti-RSV antibodies, subunit, live-attenuated and recombinant virus, and polypeptide vaccines are in clinical trials and have the potential for increasing protection in this vulnerable patient population.[26]

The only antiviral agent approved for treatment of RSV infection is ribavirin.[27] It is expensive and cumbersome to deliver in a spontaneously breathing patient and has potential health risks for caregivers; therefore, its use is

restricted to the highest-risk patients. Moreover, studies have documented marginal benefit, if any, for most patients. Nevertheless, the AAP recommends that ribavirin may be considered for use in highly selected situations involving documented RSV bronchiolitis with severe disease or in those who are at risk for severe disease (eg, immunocompromised or hemodynamically significant cardiopulmonary disease).[28] Other respiratory infections, even if trivial, should be treated symptomatically with close follow-up and early hospitalization if indicated in this patient population.

key points

- The cardiac and respiratory systems function as one unit, and pulmonary manifestations occur in most patients with congenital heart disease.
- Pulmonary blood flow is dependent on both cardiac output and pulmonary vascular resistance.
- Increased pulmonary blood flow and pulmonary hypertension are seen in many forms of congenital heart disease with left-to-right shunts and are a cause of impairment of lung mechanics.
- Irreversible pulmonary vascular disease may be the end result of severe pulmonary hypertension and carries a high mortality and morbidity.
- Treatment of pulmonary hypertension requires a multidisciplinary approach. Newer treatment strategies for pulmonary hypertension, such as prostacyclin analogues, endothelial receptor antagonists, and phosphodiesterase inhibitors, have shown good short-term results.
- Infections with respiratory viruses, especially RSV, can be devastating in children with congenital heart disease; appropriate prophylaxis with palivizumab is important in this patient population to reduce morbidity and mortality.

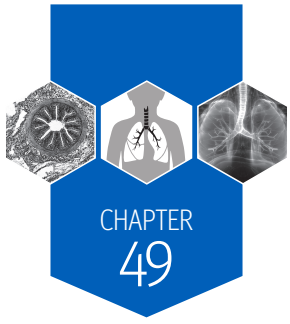
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Lung Disease Associated With Endocrine Disorders

Michael J. Light, MD
Martin Draznin, MD

The endocrine system comprises about 8 major glands; their impact on the respiratory system is a function of the level of hormone output, be it normal, increased, or decreased. These effects are more evident in the adult literature, some of which may be extrapolated to the pediatric population.

Endocrine disorders may lead to pulmonary disease (**Table 49-1**). Thyroid disorders may affect pulmonary function at the level of respiratory drive; parathyroid disorders may lead either to tetany with attendant laryngospasm or to muscle weakness from hypercalcemia. Diabetes has considerable effect on lung structure and function, although pituitary, adrenal, and reproductive disorders have little effect on lung function.[1]

Table 49-1. Examples of Pulmonary Effects of Endocrine Disorders

Endocrine Disorder	Pulmonary Effect	Clinical Significance
Hypothyroidism	Diminished respiratory drive	Usually subclinical, reversible with treatment
	Pleural or pericardial effusion	Usually subclinical and reversible, can be severe
Hyperthyroidism	Increased respiratory drive	Usually subclinical, reversible with treatment
Thiourea drugs for hyperthyroidism	Diffuse alveolar hemorrhage	Life-threatening, prolonged supportive care needed
Hypercalcemia due to hyperparathyroidism	Pulmonary calcinosis with respiratory failure	Can be severe, symptoms reversible, lung changes partly reversible
Hypocalcemia	Stridor due to tetany	Reversible with therapy
Growth hormone deficiency	Diminished lung volumes and respiratory pressures	Treatable with appropriate dose of growth hormone for appropriate duration
Acromegaly, gigantism	Obstructive sleep apnea syndrome	Treatable
Diabetes	Restrictive lung disease Vascular disease Autonomic nerve function Oxidative stress	All are subclinical, may be present at diagnosis, might manifest at high altitude, in presence of chronic lung disease. Possible increase in infection.

Thyroid Disorders

In hypothyroidism, the respiratory drive is reduced,[2] but this may not be evident clinically because children with hypothyroidism tend to be less active compared to children with a thyroid that functions normally. There may be clinical signs of subcutaneous myxedema or pleural or pericardial effusion. In most cases, the physical signs are more evident than the clinical effects, which tend to be minor.

Increase in thyroid hormones results in increased central respiratory drive and responsivity to carbon dioxide with a direct relationship. There may be an increase in respiratory rate and shortness of breath, particularly on exercise.[3] The clinical effect may be minor because the finding of hyperthyroidism typically is associated with the recommendation to limit exercise until the thyroid hormone levels are more normal.

Alterations of pulmonary function may be temporary but will improve as treatment improves the clinical picture. The changes may be a consequence of myopathic weakening of respiratory muscles.

An important complication of the treatment of hyperthyroidism with the thiouracil class of agents has been reported. It involves diffuse alveolar hemorrhage due to antineutrophil cytoplasmic antibody-positive vasculitis.[4]

Parathyroid Disorders

Hypercalcemia due to primary hyperparathyroidism is uncommon in infants and children. In one case report, a 2-month-old infant with pulmonary calcinosis due to hyperparathyroidism presented with respiratory distress and failure to thrive.[5] Chest radiograph and radionuclide scanning demonstrated calcium deposits within lung tissue. The respiratory distress resolved when calcium levels were normalized, yet the pulmonary calcinosis did not fully resolve. Reversible respiratory muscle weakness due to the hypercalcemia would be an expected finding; anatomical changes, though, are less likely. A more severe case of pulmonary calcification from hyperparathyroidism was reported in which respiratory failure ensued requiring 40 days of ventilator support.[6] The severity was such that the patient had only partial clearing of the lung abnormalities over a 1-year period.

The respiratory disorder one would expect to be associated with hypocalcemia would be tetany leading to increased respiratory muscle tone and stridor due to vocal cord spasm. The lungs in children with vitamin D-dependent rickets seem to be affected most by chest wall deformity, as reported in a series of 30 infants and children from Iran.[7] In the oldest 3 children, the findings were mild. However, in the rest, lobar or segmental atelectasis and compression atelectasis under the costochondral junctions, where the *rachitic rosary* is

seen, was described. The deformity of the chest wall and resultant restrictive defect together with malnutrition results in diminished reserve and, in some cases, interstitial pneumonitis.[7] Treatment for chronic hypocalcemic states is routinely monitored for induction of nephrocalcinosis; it may be prudent to assess pulmonary changes.

Pituitary

Excess of growth hormone (somatotropin), results in acromegaly, which is called gigantism if it occurs before puberty. Growth hormone derives from the pituitary. Both acromegaly and gigantism are rare. In children, there is abnormally tall stature with abnormal growth of face, hands, and feet. After the growth plates have fused, there is not the increase in height seen in acromegaly.

The major respiratory effect seen is obstructive sleep apnea syndrome. There may also be shortness of breath, particularly on exertion.[8]

Growth hormone deficiency may result in diminished lung volume and respiratory strength.

Cushing syndrome is a consequence of considerable exposure to exogenous or endogenous corticosteroids. There is no adult or pediatric literature to suggest that the myopathy associated with this results in clinically evident changes.[9]

Diabetes Mellitus

Children with diabetes are encouraged to be physically active. In those with type 2 diabetes, increased activity helps reduce insulin resistance and weight, which directly assists in the diabetes management. In children with type 1 diabetes, exercise and physical activity are encouraged to achieve fitness and maintain cardiovascular health. There have been numerous reports of compromise of lung function due to diabetes. One study from the Netherlands, done in anticipation of safety and efficacy trials for an inhaled form of insulin, showed increased airway resistance in the treated group and no correlation with duration of disease or age of the children.[10] The concern was that the studies had been small and that more systematic studies might be helpful, but the conclusion is that the lung is definitely a target organ for damage from diabetes, with both microvascular and other tissue changes being likely. An Italian study of children with type 1 diabetes found forced vital capacity, forced expiratory volume in the first second of inspiration, and transfer factor for carbon monoxide to be diminished compared with age-matched controls.[11] Of interest was that changes in these indices were noted at the time of diagnosis in the subset studied from onset and that, counter to expectations, the duration of diabetes and level of blood glucose control or presence of

associated complications did not correlate with the degree of the changes. Again, the subjects had no clinical complaints.

A more recent review summarizes changes in pulmonary physiology from the standpoint of lung mechanics, gas exchange, autonomic function, and a newer area of interest: the pulmonary effects of oxidative stress.[12] The interesting idea that some of the changes could occur years before diabetes is diagnosed, as is true in adult type 2 diabetes, is important in children because the incidence of type 2 diabetes in youth is increasing rapidly; children are reported to accrue the other complications at a more rapid rate than adults. This larger review again notes that the changes are subclinical until unmasked by intercurrent illness, high altitude, aging, or onset of primary lung disease. Obesity, which is a nearly universal finding in type 2 diabetes when diagnosed in children and adolescents, also affects pulmonary function. (See Chapter 43, Asthma and Other Respiratory Disorders Associated With Obesity.)

When to Refer

The disorders of lung function that have been outlined are uncommon accompaniments of less-than-common conditions, with the exception of diabetes mellitus and hypothyroidism. It would not seem cost effective to investigate each case of dyspnea for an underlying endocrine disease. However, there are many examples of when a combined evaluation by a pediatric endocrinologist and pulmonologist would be valuable. Although rickets is less common in more well-developed countries, it is important to evaluate a patient with stridor but no fever, without an anatomical airway disorder, for tetany by clinical examination. The changes from diabetes may not be preventable if indeed they occur prior to diagnosis, even in type 1 diabetes, and monitoring of lung function with the help of a pediatric pulmonologist is appropriate.

When to Admit

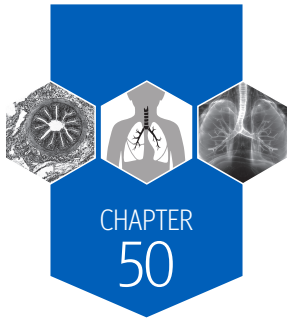
The need to hospitalize flows from the level of lung function and the necessity to treat the underlying endocrine disorder on an inpatient basis. The changes from lung calcification seen in hyperparathyroidism are the most severe, while the changes from diabetes seem to be subclinical in children.

key points

- Although not always clinically evident, endocrine disorders potentially have an effect on lung function and physiology.
- Hyperthyroidism and hypothyroidism can lead to reduced exercise tolerance, which normalizes with treatment.
- Pulmonary hemorrhage may be a complication of treatment of hyperthyroidism with thiouracil agents.
- Hypocalcemia is a nonpulmonary cause of stridor in infants.
- Diabetes can cause early changes in lung structure and function; therefore, lung function monitoring in diabetes should be studied further to assess its value to patients.

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Pulmonary Complications of Gastrointestinal Diseases

Edward W. Fong, MD

Introduction

The interactions between the body's organ systems can be very complex, and what starts out as a minor problem in a seemingly unrelated organ system may blossom into a major morbidity in another. The interaction of the gastrointestinal (GI) system does have a role in causing morbidity in the pulmonary system, although the extent of this role is controversial. Aspiration syndromes, a related topic, are discussed in Chapter 41, Acute Aspiration and Chronic Aspiration-Related Lung Disease.

Gastroesophageal Reflux

Pathogenesis

Despite a strong association between gastroesophageal reflux (GER) and chronic respiratory disease, the mechanism by which GER precipitates or exacerbates respiratory illness remains incompletely understood. Gastroesophageal reflux is usually caused by transient lower esophageal sphincter relaxation with retrograde movement of gastric contents into the esophagus. Other mechanisms include low-resting lower esophageal sphincter pressure; increased intragastric pressure; increased intra-abdominal pressure due to coughing, which can raise the gastroesophageal pressure gradient and increase the risk of reflux; and the presence of a hiatal hernia.

Clinical Manifestations

The most common respiratory manifestations of GER include wheezing and nighttime coughing (**Box 50-1**). Presenting symptoms can be divided into typical esophageal symptoms (such as heartburn and regurgitation) and atypical/extraesophageal symptoms (which include chronic coughing, hoarseness, wheezing, and poorly controlled asthma).[1,2] Presenting symptoms may also be age-dependent (discussed in the following sections).

Box 50-1

Clinical Findings in Gastroesophageal Reflux

Frequent
- Cough (nocturnal)
- Gagging
- Emesis
- Feeding resistance
- Wheezing
- Recurrent bronchitis/pneumonia

Infrequent
- Apnea
- Brief resolved unexplained event (previously acute life-threatening event)
- Failure to thrive
- Stridor
- Abnormal head, neck, and thorax positioning (Sandifer syndrome)

Rare
- Hoarseness
- Hematemesis
- Anemia
- Pulmonary fibrosis

Newborns and Infants

Gastroesophageal reflux is commonly seen in newborns and infants and is usually not thought to be pathologic (indicating an underlying abnormality). Regurgitation is present in 50% to 70% of all newborns and infants, peaks at age 4 months, and typically resolves by 1 year of age (physiologic GER). There is a weak association with the later development of GER disease (GERD, defined as GER causing troublesome symptoms or complications).[2] Newborns, infants, and children with an absent or blunted cough reflex may present with silent aspiration, where they aspirate but do not have a normal reaction (coughing/choking/sputtering) indicating that they have done so, and have findings of increased respiratory mucus, chronic wheezing, recurrent bronchitis, or recurrent pneumonia. Others with an active cough reflex may present with associated coughing (especially with meals) or just an isolated chronic cough. A small group of newborns and infants may develop other symptoms including feeding refusal, irritability, hematemesis, anemia, and failure to thrive. They may also present with Sandifer syndrome, an abnormal hyperextension of the neck from torticollis, but this is neither sensitive nor specific for the presence of reflux.

Preschool-Aged Children

Preschool-aged children with GERD may present with intermittent regurgitation and, less commonly, with respiratory complications. Sandifer syndrome also has been described in children with developmental delay with more severe GERD. Young children with GERD and swallowing difficulty may present with only decreased food intake without other complaints.

Older Children and Adolescents

After preschool age, more classic symptoms of esophagitis develop. These include chronic heartburn, nausea, dysphagia, odynophagia, epigastric pain, and water brash (“angry burps”). Complications of GERD may be seen,

including esophagitis, strictures, Barrett esophagus, and hoarseness due to reflux laryngitis.

Pulmonary Disorders Associated With GER

Apnea

Patients may experience episodes of apnea that may be categorized as central, obstructive, or mixed (where it may start out as obstructive and progress to central). These events may occur while awake or asleep and may be associated with either subclinical or overt regurgitation. The pathophysiology of the event is thought to occur with the reflux/emesis causing stimulation of the vagal nerve (causing centrally controlled/mediated cessation of breathing), laryngospasm (causing obstruction where the patient has respiratory effort but little to no air movement), or both. Often, vigorous stimulation is required to resolve the apnea.

Apparent Life-threatening Events

In patients 1 year or older who experience an apparent life-threatening event (ALTE) (episodes where a combination of all or some of the following occurs: altered muscle tone, cessation of breathing, color change, and choking/gagging requiring vigorous stimulation to resolve), recurrent regurgitation or emesis is common. However, investigations in patients with ALTEs have not demonstrated a convincing relationship between GER and apnea or bradycardia. In patients with frequent ALTE episodes in which the role of GER is uncertain, esophageal pH or impedance monitoring with simultaneous measurement of respiration and chest wall movement may be useful to determine if there is a temporal association of acid or nonacid reflux with ALTE.

Brief, Resolved, Unexplained Event

In 2016, the American Academy of Pediatrics published a clinical practice guideline[3] that recommended the replacement of the term ALTE with the term *brief resolved unexplained event* (BRUE) for newborns and infants <1 year that have experienced a sudden, brief, and now-resolved episode of 1 or more of the following: (1) cyanosis or pallor; (2) absent, decreased, or irregular breathing; (3) marked change in tone (hypertonia or hypotonia); or (4) altered level of responsiveness.[4] The American Academy of Pediatrics stratified these newborns and infants into 2 categories—lower- and higher-risk BRUE—and focused on the evaluation and management of lower-risk BRUE, defined as (1) age younger than 60 days, (2) gestational age 32 weeks or greater and postconceptional age 45 weeks or greater, (3) no cardiopulmonary resuscitation required by trained medical provider, (4) BRUE duration less than 1 minute, and (5) first BRUE (no repeat events, regardless of time interval) as well as having no concerning historical features (eg, sudden death in a relative) and no concerning physical examination findings (eg, unexplained bruising).[3] There are currently no recommendations for newborns and infants who do

not meet these criteria and are considered higher risk.[4] One of the hallmark differences between ALTE and BRUE is that if a newborn or infant has choking and gagging associated with an event, which typically indicates common diagnoses such as GER, their presence suggests the event was not a BRUE; rather, it indicates that there is an explanation for the event: GER. Further, the clinical practice guideline made grade C, moderate recommendations for both the diagnosis and treatment of lower risk BRUE: "Clinicians should not obtain investigations for GER (eg, upper gastrointestinal series, pH probe, endoscopy, barium contrast study, nuclear scintigraphy, and ultrasonography) in infants presenting with a lower-risk BRUE; clinicians should not prescribe acid suppression therapy for infants presenting with a lower-risk BRUE."[3]

Asthma

Symptoms of GER are common in asthma. Its prevalence is estimated to range between 34% and 89%. Esophageal pH or impedance monitoring should be considered in children with nocturnal asthma whose symptoms occur more than once a week; in children with radiographic evidence of recurrent pneumonia or who require either continuous oral corticosteroids, high-dose inhaled corticosteroids, or frequent bursts of oral corticosteroids (>2 per year); or in children with persistent asthma unable to wean their medical management despite the absence of GER symptoms. If esophageal or pH impedance monitoring demonstrates an increased frequency or duration of esophageal acid exposure or nonacid reflux, a trial of prolonged medical therapy for GER should be considered.

Diagnosis

Establishing the diagnosis of GER may prove challenging. For most infants with vomiting and for older children with regurgitation and heartburn, a history and physical examination are sufficient to reliably diagnose GER, recognize its complications, and initiate empiric medical management.

Empiric Medical Therapy

A trial of time-limited medical therapy of 4 to 8 weeks may be useful to determine if GER is causing specific symptoms. Empiric therapy initially with H_2 blocker and potentially progressing to proton pump inhibitor (PPI) is widely used but has not been validated for any symptom presentation in pediatric patients.

Upper Gastrointestinal Series

The upper gastrointestinal series study is used to evaluate for anatomical or physiological abnormalities of the upper GI tract. These tests are neither sensitive nor specific in the diagnosis of GER. Since these tests only capture a particular time, a negative test does not necessarily mean that the patient does not have aspiration or GER.

Gastroesophageal Scintigraphy

Gastroesophageal scintigraphy, also referred to as a milk scan, is a radionuclide study that involves the ingestion of technetium-labeled food or formula followed by scanning to detect the distribution of the isotope in the stomach, esophagus, and lungs. This study can document aspiration and GER and assess gastric emptying time. If the isotope is seen in the lungs, this is indicative of some type of aspiration event (either "from above" during the swallowing phase of the study or "from below" from a reflux episode that is then aspirated). Unlike esophageal pH monitoring, scintigraphy can detect postprandial reflux of both acidic and nonacidic gastric contents and measure gastric emptying time. Radiation exposure is minimal (using technetium-99m), and the test is noninvasive.

24-Hour Esophageal pH Probe and Impedance Monitoring

This is considered the gold-standard test for the diagnosis of GER. The test is performed by the gastroenterologist and can be done in either the inpatient or the outpatient setting. The probe is placed through the nasal cavity and, using fluoroscopy, the tip is positioned at approximately 87% of the distance from the nasal alae to the lower esophageal sphincter. Activities, meals, position, and symptoms are recorded while the probe remains in place. Acid reflux is defined as a decrease in pH to less than or equal to 4. The frequency, overall time of esophageal exposure to acid, and longest reflux episode are recorded. It should be remembered that asymptomatic episodes of acid reflux can occur in healthy infants and children, so the interpretation of the pH probe should be put in context with the patient's clinical course.

Esophageal pH monitoring has the drawback of not detecting nonacidic reflux, which can also cause lung disease. Multichannel intraluminal impedance with pH monitoring has been increasingly used for its ability to detect anterograde and retrograde passage of acid, nonacid, and gaseous material. Studies have demonstrated that, in contrast to adults, infants with GER have a much greater proportion of nonacid reflux than acid reflux, so this makes it a useful test for assessing reflux in this population.[5]

Endoscopy and Biopsy

Endoscopy with biopsies allows the advantage of directly visualizing lesions or anatomical anomalies. It can assess the presence and severity of esophagitis, strictures, and Barrett esophagus as well as exclude other disorders such as Crohn disease and eosinophilic or infectious esophagitis. A normal appearance of the esophagus, however, does not exclude histopathological esophagitis since subtle mucosal changes, such as erythema and pallor, may be observed in the absence of esophagitis.

Treatment of GERD

Conservative Measures

The first line of therapy is non-medicinal. Smaller, more frequent meals as well as dietary modifications (such as formulas composed of medium-chain triglycerides, whey hydrolysate, or soy, or having a low osmolality) represent a simple, first-step approach. Positioning maneuvers, such as keeping the child in the 30- to 45-degree position for at least 30 minutes after feeding and placing the child horizontally in the prone position, are other noninvasive interventions available to treat GERD. Children should not sit at 90 degrees after feeding, however, as studies have shown that GERD worsens when sitting up after meals. This is due to increased intra-abdominal pressure generated from bending at the waist. Milk-thickening agents do not improve acid reflux index scores but do decrease the number of episodes of vomiting.

Medical Therapy

The second line of therapy for the treatment of GERD involves medication. Cryoprotective agents, histamine-2 (H_2) receptor blockers, PPIs, and prokinetic agents are all used in the control of GERD.

Antacids work by neutralizing gastric acid and provide quick, short-term relief of intermittent symptoms in older children. It has been shown that, if given in high doses, aluminum hydroxide is as effective as cimetidine (an H_2 blocker) for the treatment of peptic esophagitis in children aged 2 to 42 months, though its use is limited by toxicity at high levels.[6] Gaviscon, an over-the-counter antacid preparation of alginic acid, does not contain aluminum and may, therefore, be of some benefit in infants.

H_2 blockers work by inhibiting the histamine receptor of the parietal cells that affect acid production. They have been shown to be safe and effective in treating children with GERD and are often the first-line medical treatments for GERD. It should be noted, though, that ranitidine was removed from the US marketplace on April 1, 2020, by the US Food & Drug Administration (FDA) due to it containing N-Ntirosodimethylamine (NDMA), which is a probable human carcinogen. On April 16, 2020, the FDA alerted patients that nizatidine oral solution had been voluntarily recalled due to the possibility that it may contain unacceptable levels of NDMA. To date, the FDA has not found NDMA to be contained in famotidine or cimetidine. In April 2021, Sanofi may have inadvertently caused confusion in the marketplace with the release of its brand Zantac-360, whose active ingredient is famotidine, whereas the brand Zantac, whose active ingredient was ranitidine, had been previously removed from the marketplace by the FDA.

Proton pump inhibitors are the mainstay of medical treatment of GERD. The PPIs effectively inhibit acid production by shutting down the proton pump. Compared to H_2 blockers, PPIs decrease acid production and have longer

duration of action. Because of limited experience with the use of these agents in children, PPIs are usually used after a therapeutic failure of H_2 blockers.

Adult studies have shown that PPI therapy, particularly with long-term or high-dose administration, is associated with several potential adverse effects, including enteric infections (eg, *Clostridium difficile*) and community-acquired pneumonia.[7,8] Due to this risk, an initial trial of 4 to 8 weeks should be used to determine effectiveness of the therapy with discontinuation if there is minimal to no change in symptoms.

Prokinetic agents act to increase lower esophageal sphincter pressures and decrease gastric emptying time. The number of reflux episodes, however, remain largely unchanged in patients on these agents because of transient relaxation of the lower esophageal sphincter. Metoclopramide is the most commonly used prokinetic agent. It functions as a cholinergic agonist and dopamine antagonist. When used at the recommended doses, the risk for more serious side effects, such as tardive dyskinesia, is low. The antibiotic erythromycin stimulates the motilin receptor on intestinal smooth muscle cells and decreases gastric emptying time. While its use in this manner is not approved by the FDA, it remains useful as an off-label prokinetic agent. Baclofen has been found to decrease transient lower esophageal sphincter relaxation and to increase postprandial lower esophageal sphincter pressure, which may reduce the number of reflux events.[9]

The surface agents sodium alginate and sucralfate both protect the esophageal and stomach mucosa from the damaging effects of gastric acid by forming a surface gel. There is not sufficient evidence regarding the safety and efficacy of surface agents in the treatment of GERD in children.

Surgery

Surgery is the treatment of choice in children who fail maximal medical therapy. Nissen fundoplication is the most common surgical procedure. Both open and laparoscopic techniques appear to be equally effective. Success rates vary by study but are around 75%. The most common complications include breakdown of the fundoplication, small bowel obstruction, infection, pneumonia, perforation, and esophageal stricture. Mortality varies from 0% to 4.7%. Reoperation rates vary from 3% to 18%.[10]

Inflammatory Bowel Disease

Bronchopulmonary manifestations of inflammatory bowel disease (IBD) rarely have been described in children, with only isolated cases reported in the literature.[11–14] The pulmonary involvement in IBD may include airway inflammation involving both the pulmonary parenchyma and small and large airways.

Pulmonary Parenchymal Disease

The most common lung parenchymal involvement that has been described in IBD is bronchiolitis obliterans with organizing pneumonia and interstitial lung disease. Pulmonary function testing in patients with airway involvement usually reveals an obstructive respiratory pattern. Munck et al[14] showed that 26 children with acute or quiescent Crohn disease all had normal chest radiographs. Even though no significant differences were found between acute and quiescent Crohn disease for pulmonary volumes and expiratory flows, carbon monoxide diffusing capacity was significantly decreased during the active phase of the disease when compared with values measured during remission (15%–53% vs 19%–81% predicted). Decreased diffusing capacity of the lungs for carbon monoxide levels may, therefore, indicate an early interstitial disease process.[15] Although pediatric reports are sparse, isolated or diffuse lung granulomas have also been noted to be associated with IBD. (See Chapter 26, Respiratory Disorders Associated With Systemic Inflammatory Disease.) Pulmonary infiltrates in the setting of immunosuppression present a diagnostic dilemma as it is not clear if these abnormalities are caused by the underlying disease process or secondary to the patient's immunosuppression. Krishnan et al[12] reported 3 children with Crohn disease who presented with lung lesions that were unresponsive to antimicrobial therapies but quickly responded to infliximab therapy. Although an empiric trial of medication may help with diagnosis, a definitive diagnosis usually requires a lung biopsy. It should also be kept in mind that patients being treated for IBD with antitumor necrosis factor are at increased risk for pulmonary tuberculosis and histoplasmosis as well as other serious opportunistic infections.[16]

Airway Inflammation

Bronchial involvement is the most common, but inflammation of the trachea and bronchioles can also occur in IBD. Patients with bronchial involvement due to IBD may have bronchiolitis, unexplained chronic bronchitis, or bronchiectasis. The pathogenesis of the pulmonary disease associated with IBD is not known. A common systemic mechanism affecting both the bronchial and colonic epithelium may be responsible. It has been reported that the incidence of respiratory changes is greater in ulcerative colitis than in Crohn disease.[17] Mansi et al[17] showed that bronchial hyperresponsiveness occurs in 71% of children and adolescents with Crohn disease even in the absence of clinical, radiologic, and functional evidence of airway disease. This indicates that bronchial hyperresponsiveness may be the only manifestation of subclinical airway inflammation, which, in turn, is most likely responsible for the development of the various pulmonary manifestations in Crohn disease.[18]

Histologic similarities between the inflammatory infiltrate of the airways and that of the colon suggest that the bronchial disease may result from a common abnormality in immune regulation that affects both the bowel and the bronchial tree.[19]

Diagnosis and Treatment

Drug-induced lung disease and superimposed bacterial infection should be considered in patients with IBD who have lung involvement. If drug toxicity is suspected, the offending drug should be discontinued, at least temporarily, to help with the causality determination. However, if there is no alternative IBD treatment, continuation of the drug, depending on the type/severity of the lung involvement versus the severity of the IBD, should be considered. In patients with signs of airway disease and chronic purulent sputum production, superimposed bacterial infection must be ruled out. When drug toxicity and bacterial infection have been ruled out, traditional therapies for IBD, including mesalamine and other immunosuppressive agents, may be effective depending on the type of pulmonary complications.

Alpha-1 Antitrypsin Deficiency

Alpha-1 antitrypsin (AAT) deficiency is one of the most common inherited disorders among white individuals. Alpha-1 antitrypsin deficiency is inherited in families in an autosomal codominant pattern, and this condition can cause cirrhosis, usually in childhood, and chronic obstructive pulmonary disease, which usually does not present until adulthood. Pulmonary symptoms typically begin in the third to fourth decade of life, but children as young as 18 months can have respiratory manifestations.[20–23]

Diagnosis

Initially, a serum AAT level is performed if this disease is suspected. If the level is low, then a confirmatory genetic test is obtained. Occasionally, in patients with both the clinical manifestations and a family history of AAT deficiency, the genetic testing is performed outright. At least 100 alleles of AAT have been identified, all of which are categorized into 4 basic groups.[24]

1. **Normal—**There are normal levels and functioning of AAT; genotype is MM.
2. **Deficient—**Plasma AAT levels are less than 35% of the average normal level. The most common deficient allele associated with emphysema is the Z allele, which is carried by 2% to 3% of the white population in the United States. This genotype is MZ.

3. **Null—**No detectable AAT levels in plasma; these individuals have the rarest and most severe form of the disease. This genotype is designated as a null mutation.
4. **Dysfunctional—**Normal quantity of AAT protein, but it does not function properly.

Population studies suggest a minimum plasma threshold of 11 μmol/L (corresponding to 57 mg/dL using nephelometry) is required for proper functioning. Below this level there is insufficient AAT to protect the lung, leading to a risk of developing emphysema.

Clinical Manifestations

Symptoms include asthma, which is more severe in individuals with protease inhibitor with MZ mutation; bronchitis; panacinar emphysema, occurring primarily in the lung bases; chronic obstructive lung disease; and bronchiectasis.[25] Pulmonary disease is very rare in children.

Treatment

Treatment focuses on controlling and slowing the progression of the clinical symptoms of lung and liver disease. Weekly or monthly intravenous infusion of purified human AAT can normalize plasma and lung AAT levels, inhibit protease activity, and diminish airway reactivity. However, it has no effect on intracellular aggregation of the protein in hepatocytes. Lung and liver transplantation are end-stage measures for terminal organ dysfunction.

Pulmonary Involvement in Liver Disease

Hepatic disease may cause or be associated with pulmonary disorders without a clearly understood etiology[26] (**Table 50-1**). Acute hepatic disease associated with lung complications can result from infections, medications, and toxins. Chronic hepatic disease can also cause pulmonary disorders through mechanisms resulting in cirrhosis and liver failure, which can lead to chronic pulmonary infection. Systemic disorders, such as AAT deficiency, chronic granulomatous disease of childhood, cystic fibrosis, hereditary hemorrhagic telangiectasia, Langerhans cell histiocytosis, and sarcoidosis can also be associated with hepatopulmonary syndrome.

Hepatopulmonary syndrome consists of liver disease (most commonly cirrhosis), abnormal pulmonary vascular tone, and arterial hypoxemia. The disease mechanisms include the imbalance of vasoactive substances caused by the diseased liver, which leads to pulmonary vascular dilatation and

subsequent ventilation/perfusion mismatch, hypoxemia, and loss of hypoxic pulmonary vasoconstriction. As the hepatic damage progresses, the alveolar-capillary disequilibrium worsens and leads to intrapulmonary venoarterial shunting, with limitation of oxygen diffusion and, ultimately, severe respiratory failure. Portopulmonary anastomoses and pulmonary arterial hypertension may also occur.[27,28] Liver transplantation for hepatopulmonary syndrome in children may be appropriate even in the absence of cirrhosis.[29]

Table 50-1. Pulmonary Disorders Associated With Hepatic Disorders

Hepatic Disease	Pulmonary Disorder
Infections	Hilar adenopathy Pneumonia Tracheobronchitis Pleural effusions
Primary sclerosing cholangitis	Bronchitis Bronchiectasis
Chronic active hepatitis	Pneumonia Atelectasis Interstitial pneumonitis Interstitial fibrosis Fibrosing alveolitis Pleural effusion Pulmonary hypertension Pulmonary hemorrhage
Cirrhosis (alcoholic, postnecrotic, cryptogenic)	Pneumonia Pleural effusion Pulmonary angiodysplasia Pleural vasodilatation Pulmonary hypertension
Primary biliary cirrhosis	Hyperreactive airway disease Interstitial pneumonitis Interstitial fibrosis Fibrosing alveolitis Pulmonary hypertension

Pulmonary Involvement in Pancreatic Disease

Pulmonary disorders associated with acute and chronic pancreatitis are listed in **Box 50-2**.[30]

Clinical Manifestations

Pleural Effusion

Although pleuropulmonary complications of pancreatitis have been most commonly described in adults (most often due to alcoholism, trauma, or cholelithiasis), pleural effusions have also been reported in children with pancreatitis. Most pleural effusions are left-sided; however, right-sided and bilateral effusions have also been reported.[30] Pleural effusions usually occur shortly after the onset of acute pancreatitis and are characterized by small, serous, serosanguineous, or hemorrhagic exudates with high amylase levels. Fluid resorption correlates with the resolution of intra-abdominal etiology. Chronic pancreatic disease, such as a pseudocyst, abscess, or pancreatopleural fistula, may also result in chronic pleural effusions. The etiology and pathogenesis of the fluid have not been defined. Transdiaphragmatic lymphatic blockade, pancreatopleural fistulae, and disruption of the pancreatic duct or pseudocysts have been speculated.[30,31] Treatment of pancreatic pleural effusion is usually conservative but may require thoracentesis when symptomatic.

Box 50-2

Pulmonary Disorders Associated With Pancreatitis

Acute Pancreatitis
- Pleural effusion
- Hemidiaphragm elevation
- Atelectasis: left lower lobe
- Pneumonia: left lower lobe
- Pulmonary embolism
- Pulmonary infarction
- Acute respiratory distress syndrome
- Pulmonary edema
- Cystic fibrosis transmembrane conductance regulator (CFTR) mutation

Chronic Pancreatitis
- Pancreatopleural fistula
- Pancreatobronchopleural fistula
- Recurrent pleural effusion
- Recurrent lobar pneumonia
- CFTR mutation

Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is the most serious complication of pancreatitis. The mechanism of pancreatitis-induced ARDS is complex and has not been fully elucidated. It is thought to occur secondary to the release of active enzymes and vasoactive substances from the pancreas, including leukotrienes and pancreatic elastase. These chemical mediators increase vascular permeability and decrease pulmonary surfactant production, which promotes the development of ARDS.[31]

Atelectasis

Macrophages and mast cells secrete phospholipid A2 (sPLA2; lecithinase) which hydrolyzes lecithin, the main component of the phospholipids in surfactant. Secreted phospholipases A2 (sPLA2) routinely assists in the catabolism of surfactant, which assists in maintaining the correct balance of the complex proteolipid mixture, which is essential in maintaining alveolar opening. However, sPLA2 is also a pro-inflammatory substance. Thus, inflammation and cell injury may result in recruiting more macrophages and mast cells to the area, causing an imbalance in the amount of sPLA2 being secreted and, therefore, too much catabolism of surfactant. The loss of surfactant increases alveolar surface tension, resulting in atelectasis.

Diagnosis and Therapy

Because pancreatitis-associated acute lung injury has a wide spectrum of presentation, the diagnosis of pancreatic pulmonary complications relies on a thorough history, physical examination, and radiographic and laboratory studies.

Therapy consists of supportive measures including antibiotics for pneumonia; thoracentesis or chest tube drainage for an effusion causing respiratory distress; chest physical therapy for atelectasis (if tolerated); anticoagulants for pulmonary emboli; and lung protective ventilation strategies for patients who require mechanical ventilation.

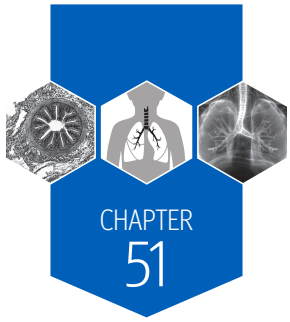
key points

- Because the pulmonary and GI systems are interconnected, disorders that are primarily GI in etiology can cause serious sequelae in the pulmonary system.
- The role of GERD in asthma is controversial, but treatment of GERD may improve a patient's asthma control.
- Inflammatory bowel disease may directly affect the lung parenchyma or indirectly cause serious opportunistic infections of the lung parenchyma secondary to the immunosuppression used to treat IBD.
- Alpha-1 antitrypsin deficiency rarely causes pulmonary disease in children but should be considered if there is a family history of early-onset (< 45 years old) emphysema.

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Pulmonary Complications of Sickle Cell Disease

Robyn T. Cohen, MD, MPH

Introduction

Sickle cell disease (SCD) affects approximately 100,000 individuals in the United States and is the most common inherited disorder among African Americans.[1] Because a large number of people with SCD are from vulnerable populations (including communities of color and largely uninsured and underinsured individuals), striking disparities exist in research and clinical care for SCD in comparison to other inherited diseases, such as cystic fibrosis.[2] There have been advances in recent decades regarding diagnosis, preventive management, and treatment for SCD—all of which have led to improved survival for children[3]—however, the median life expectancy is in the fifth decade.[4,5] The pulmonary complications of SCD are numerous and have been associated with an increased risk of early death.[6–9] One autopsy study of patients with SCD with sudden death showed that 71% of patients had significant pulmonary pathology at the time of death.[10]

Acute Chest Syndrome

Acute chest syndrome (ACS) is a clinical syndrome consisting of fever, cough, tachypnea, chest pain, wheezing, and/or hypoxemia plus a new segmental pulmonary infiltrate on chest radiograph in individuals with SCD (sickle cell anemia [HbSS], HbSC, HbSβ-thalassemia).[11] Acute chest syndrome is a leading cause of hospitalization and early death in individuals with SCD.[5,12] There were 24,000 pediatric hospitalizations for ACS in the United States in 2018.[12]

CASE REPORT 51-1

A.J. is a 7-year-old boy with sickle cell anemia (HbSS), steady-state hemoglobin (Hb) of 85 g/L (8.5 g/dL), and 3 to 4 admissions for painful episodes per year. He was admitted with a 2-day history of nasal congestion and cough, and a 1-day history of head and back pain not controlled with oral pain medications. On admission, he was febrile to 38.2°C (100.7°F), with a heart rate of 140 beats per minute, respiratory rate of 24 breaths per minute, and an oxygen saturation of 96% on room air. His Hb at admission was 79 g/L (7.9 g/dL). His chest radiograph at admission was clear. He was started on intravenous (IV) morphine and ketorolac, IV ampicillin/sulbactam, and IV fluids, and received an incentive spirometer, which he used sporadically during his first hospital day. On his second hospital day, A.J. became increasingly tachypneic with wheezing, intercostal retractions, and oxygen desaturation, and required 2 L/minute of oxygen by nasal cannula to maintain an oxygen saturation above 92%. Repeat Hb was 52 g/L (5.2 g/dL). A repeat chest radiograph showed right upper lobe and left lower lobe opacities. Azithromycin and albuterol were added, and he received a packed red blood cell transfusion. By hospital day 3, his Hb was 70 g/L (7.0 g/dL), his oxygen requirement had decreased to 1 L/minute, and he was able to use the incentive spirometer more consistently. By hospital day 5, A.J. was no longer febrile, he did not require supplemental oxygen, his pain was well controlled on oral analgesia, and he was discharged home.

Pathophysiology

The National Acute Chest Syndrome Study Group reviewed 671 episodes of ACS in 538 adults and children.[13] Community-acquired infection was the most common identifiable cause (most commonly chlamydia, mycoplasma, and respiratory syncytial virus), followed by fat embolism in association with severe vaso-occlusive pain episode. Viral infections were a common etiology in children younger than 10 years. Pulmonary infarction was presumed to be the cause of ACS in 16% of cases in which no cause could be identified.[13]

Infection, atelectasis from splinting or hypoventilation, pulmonary fat embolism, and in situ vaso-occlusion leads to ventilation-perfusion mismatch with localized and generalized hypoxemia. Decreased oxygen content contributes to polymerization of hemoglobin (Hb) and sickling of erythrocytes. Combined with the elevated leukocyte counts seen in SCD in general[14] and in ACS specifically,[13] as well as increased expression of adhesion molecules and inflammatory mediators (such as vascular cell adhesion molecule-1, secretory phospholipase A2, and others), there is a vicious cycle of adherence of sickled red blood cells to each other, leukocytes, platelets, and the vascular endothelium; increased transit time; more extensive polymerization of sickled erythrocytes; and obstruction of microvascular flow.[15,16] In addition to pulmonary vaso-occlusion, decreased production and increased

consumption of the potent pulmonary vasodilator nitric oxide leads to increased pulmonary vasoactivity.[16,17]

Clinical Features

Acute chest syndrome often occurs during the first few days of a hospitalization for a vaso-occlusive pain episode or after a surgical procedure, but patients can also present with ACS in the absence of a pain episode. Episodes can range from mild and self-limiting to severe, rapidly progressive, and life-threatening.[18–20] The main predictors of an impending severe episode include multilobar disease, severe hypoxia, sudden rapid drop in Hb, and thrombocytopenia.[20] Severe rapidly progressive ACS is seen more commonly in adults than in children with SCD. Children with asthma or a history of ACS (particularly prior to 4 years of age) are at increased risk for future ACS episodes.[21]

In 2 large clinical studies of ACS, fever and cough were the most common presenting symptoms, with tachypnea, crackles, and wheeze as the most common physical findings among younger children. Chest and rib pain were more commonly seen in adolescents and adults.[13,22] Varying degrees of hypoxemia can be seen with ACS, although the best way to measure oxyhemoglobin saturation has been controversial—particularly in the setting of illness and severe anemia.[23–25] If there is any question about the accuracy of pulse oximetry or routine blood gas analysis in a particular clinical situation, blood gas analysis with co-oximetry should be the method of choice, because all forms of Hb, including the COHb produced during hemolysis, are accounted for.[26]

Chest radiographic findings may include segmental, lobar, or multilobar consolidation but may also lag behind the clinical presentation. Lower-lobe involvement is the most common finding at all ages, though young children are more likely to have middle- and/or upper-lobe involvement than adults.[22,27] Pleural effusions—both at presentation and developing during the course of the hospitalization—are more often seen in adolescents and adults.[27] Hb concentration is typically decreased from steady-state value, and mean white blood cell count at presentation is often greater than 20×10^9/L (20,000 cells/μL).

Acute chest syndrome can progress to respiratory failure requiring mechanical ventilation (22% of adults vs 10% of children and adolescents in one study) and to death (9% of adults vs < 1% of children and 2% of adolescents).[13,28] Infants younger than 1 year have the highest risk of mortality from ACS in the pediatric age group.[28]

Management

One of the main goals of overall treatment of SCD should be prevention of ACS. Prophylactic penicillin and vaccination against *Streptococcus pneumoniae, Hemophilus influenzae,* and seasonal influenza have a role in the improved survival among children with SCD because of a reduced frequency of pulmonary infection. Incentive spirometry has been shown to reduce the incidence of ACS among patients hospitalized with chest and back pain and a clear chest radiograph.[29,30]

Both the 2014 NIH Expert Panel Report *Evidence-Based Management of Sickle Cell Disease*[31] and the 2015 British Thoracic Society Guidelines for the Management of Acute Chest Syndrome in Sickle Cell Disease[19] recommend a chest radiograph and measurement of oxygen saturation for all patients with respiratory symptoms, regardless of the presence of fever, to evaluate for possible ACS.

Treatment of ACS is primarily supportive. The immediate goals of treatment of an episode of ACS include prevention of alveolar collapse, maintenance of gas exchange, and prevention of further lung injury.[32] Careful pain management is essential, with a careful balance to control chest wall pain[33] and avoid the associated rapid, shallow breathing without promoting the hypoventilation associated with overuse of narcotic agents or IV diphenhydramine.[19,34] Incentive spirometry devices should be used to prevent atelectasis.[35] Supplemental oxygen should be administered to patients with oxygen saturation below 95% (or with more than a 3% decrease from their baseline oxygen saturation as measured by pulse oximetry [Spo_2]).[19,31] Epidemiologic data suggest that broad-spectrum antibiotics, including a macrolide, should be initiated.[13,19,36] Given the prevalence of airway lability among patients with SCD[37] and the frequency of wheezing associated with ACS,[13] bronchodilators have become common empiric therapy for patients with comorbid asthma or who are acutely wheezing as part of their clinical presentation. Strict monitoring of oral and IV fluid intake and urine output is important once ACS develops to avoid worsening pulmonary edema that develops from the increased vascular permeability from damaged lung tissue.[19] Red blood cell transfusion early in the course of ACS serves 2 purposes: to increase oxygen carrying capacity and to reduce the percentage of sickled erythrocytes. This can be accomplished by either simple red blood cell transfusion[19,38] (with phenotypically matched, sickle negative, leukocyte-depleted packed red blood cells with extended crossmatching, and only when Hb is less than 90 g/L [9 g/dL])[35] or by exchange transfusion, which does not have the associated risks of iron overload or hyperviscosity but carries the risk for the development of catheter-associated deep venous thrombosis.[39] The use of steroids to treat ACS remains controversial. Although one clinical trial showed a beneficial effect from IV dexamethasone in children with ACS,[40] other studies have shown an increased risk of readmission and pain

following the use of systemic corticosteroids.[41,42] The risk to benefit ratio of systemic steroids in ACS management deserves further evaluation in the era of more widespread use of hydroxyurea (HU).

Because recurrent vaso-occlusive and ACS episodes are associated with progressive cardiopulmonary morbidity and mortality, preventive strategies must be considered. Given the proportion of ACS episodes that are associated with infection in children, pneumococcal vaccination, influenza vaccination, and prophylactic penicillin administration are standard of care in children with SCD.[31] Hydroxyurea, which increases the concentration of fetal hemoglobin, thus causing a decrease in the proportion of sickle hemoglobin (HbS) and reducing erythrocyte polymerization, has been shown to reduce the incidence of new ACS episodes in adults with frequent pain crises.[43] Infants and young children in the Pediatric Hydroxyurea Phase 3 clinical (BABY-HUG) trial randomized to receive HU had fewer episodes of ACS in the 2-year trial compared to those randomized to receive placebo,[44] and early initiation of HU is becoming increasingly widespread for patients with sickle cell anemia.[45] Chronic transfusions have also been shown to reduce the incidence of ACS in children[46,47]; hematologists should be involved in the decision to implement chronic transfusions for patients with SCD. Given the prevalence of viral-induced wheeze and the frequency of wheeze as a presenting symptom of ACS in young children, a trial of preventive inhaled corticosteroids may benefit some children—particularly in the setting of a history of eczema or a positive family history of asthma.[48,49]

Asthma and Airway Disease

The pathophysiology, clinical features, and management of asthma in the general pediatric population are discussed in detail in Chapter 12, Asthma. This section discusses asthma as it relates specifically to SCD.

Asthma is the most common chronic disease in childhood, with African Americans disproportionally affected.[50] Because SCD is the most common inherited genetic disorder among African Americans, a certain number of children will be affected with both SCD and asthma. While many children with SCD have episodic wheeze, it has not been conclusively demonstrated that true asthma occurs at a higher frequency among children with SCD compared to children without SCD. Several studies have reported an association between asthma and increased risk of acute chest syndrome,[12,21] as well as an increased risk of mortality.[7] Questions still remain regarding the extent to which asthma exists as a comorbid condition with SCD and acts synergistically to worsen SCD outcomes, how SCD pathogenesis contributes to an obstructive pulmonary process in children that causes clinical features similar to asthma, and how to determine which individuals with SCD and isolated features of asthma warrant preventive asthma therapy.

Pathophysiology

While the causal direction of airway disease and SCD pathogenesis has not been conclusively determined, experimental animal models have demonstrated exaggerated inflammatory responses to ovalbumin challenge and house dust mite sensitization.[51–53] Sickle cell mouse studies have shown that compared to wild-type mice, SCD mice developed elevated serum levels of immunoglobulin E and inflammatory cytokines[51] and others showing elevated bronchoalveolar lavage leukocytosis and eosinophilia in response to allergen challenge.[52] One group showed that these inflammatory responses were associated with increased airway responsiveness to methacholine,[53] while another did not.[52] In contrast to these animal data, Knight-Madden and colleagues noted that while a Jamaican cohort of children with SCD had increased Th2 cytokines compared to age- and race-matched control children, a cohort of children with SCD from the United Kingdom had *decreased* Th2 cytokines compared to controls.[54]

Mechanisms for airway disease other than allergic inflammation have been proposed. Individuals with anemia have increased cardiac output and dilation of the pulmonary vasculature. Studies of adults and children with SCD have demonstrated associations between increased pulmonary capillary blood volumes and multiple indicators of lower airway obstruction.[55,56] One study of children receiving chronic transfusions showed increased pulmonary capillary blood volume, increased respiratory system resistance, and decreased forced vital capacity (FVC) and forced expiratory volume in the first second of expiration (FEV_1) posttransfusion compared to pre-transfusion,[57] suggesting that increased pulmonary capillary blood volume may result in anatomical (rather than inflammatory) lower airway obstruction.

Clinical Features

Physician-diagnosed asthma seems to have a strong contributory effect toward the incidence of ACS in children with SCD.[49] Among 291 children with HbSS in a prospective cohort that began in infancy, those with a comorbid diagnosis of asthma were younger at the time of their first episode of ACS, had twice as many episodes of ACS, and had more frequent pain crises than the children without asthma.[58] Among 80 children with SCD in Jamaica, asthma and atopy were more common among those with a history of recurrent ACS ($\geq$4 episodes) compared to those with 1 or fewer episodes of ACS (53% vs 12%, $P < .001$).[59]

Determining which children with SCD have asthma is difficult. Many children with SCD and ACS present with wheezing on physical examination.[22] However, whether these children at steady state have partially reversible airway obstruction or reproducible symptoms in response to known triggers (in other words, meet clinical criteria for asthma) is not always clear. Children

with SCD may be more prone to airway obstruction and airway hyperresponsiveness.[37,60] In one study of 187 children with sickle cell anemia, 11% of children without asthma met American Thoracic Society (ATS) criteria for lower airway obstruction.[49] In the largest research cohort study of 99 school-age children with sickle cell anemia, 55% had airway hyperresponsiveness to methacholine.[37] In one study of pulmonary function of 20 infants and toddlers (aged 3–30 months) with SCD, the majority of children had evidence of lower airway obstruction and hyperinflation; 6 of those infants also had a history of intermittent bronchospasm.[61]

Management

Management of chronic, persistent asthma in children with SCD should follow guidelines established by the National Asthma Education and Prevention Program.[62] Use of systemic steroids for asthma exacerbations in patients with SCD is a controversial topic,[63] given the observed increased risk of pain episodes following courses of systemic corticosteroids given for ACS.[41,42] That said, undertreated status asthmaticus can be life-threatening, and, therefore, systemic corticosteroids should be used in cases of moderate-severe acute exacerbations.[62] Many clinicians employ a prolonged taper following a course of oral steroids, but there are no data to support this recommendation. Furthermore, most studies that demonstrated a risk of pain following systemic corticosteroid administration were conducted in children with ACS, not status asthmaticus, and before the more widespread use of HU in children.

To date, there are no published studies on the effect of improved asthma management on sickle cell outcomes. One promising phase 2 trial showed that administration of inhaled steroids to adults without asthma who were experiencing respiratory symptoms was associated with reduced daily pain and lower soluble vascular cell adhesion molecule-1 (s-VCAM-1) levels compared to those who did not receive inhaled steroids, suggesting a beneficial effect of anti-inflammatory therapy on SCD pathogenesis.[64] The consequences of asthma exacerbations, including ventilation/perfusion mismatch and local pulmonary tissue hypoxia, on patients with sickle cell are serious. The use of evidence-based asthma guidelines[62] in the treatment of children with both SCD and asthma is crucial. Referral to a pediatric pulmonologist should be made for all children with SCD and signs or symptoms of asthma.

Sleep-Disordered Breathing

Pathophysiology

Children with SCD are at increased risk of nocturnal desaturation compared with children without SCD.[65–67] This observation historically has been attributed to upper airway obstruction from compensatory adenotonsillar hypertrophy after splenic infarction or resection.[68,69] This explanation is contradicted

by a study in which 20 of 32 research subjects had nocturnal desaturation on an overnight oximetry study (defined as Spo_2 <92% for ≥5% of total sleep time); 12 of those 20 had no evidence of obstruction on a full, in-laboratory sleep study.[66] Two additional convenience clinic sample studies reported several patients with nocturnal hypoxemia in the absence of obstructive sleep apnea (OSA).[65,70] Some authors suggest that abnormalities in gas exchange associated with severe anemia (specifically, a rightward shift of the oxyhemoglobin dissociation curve and decreased oxyhemoglobin affinity [**Figure 51-1**]) are a cause of nocturnal desaturation, given the finding that nocturnal desaturation is most commonly seen in SCD patients with low daytime Spo_2.[23,65,66]

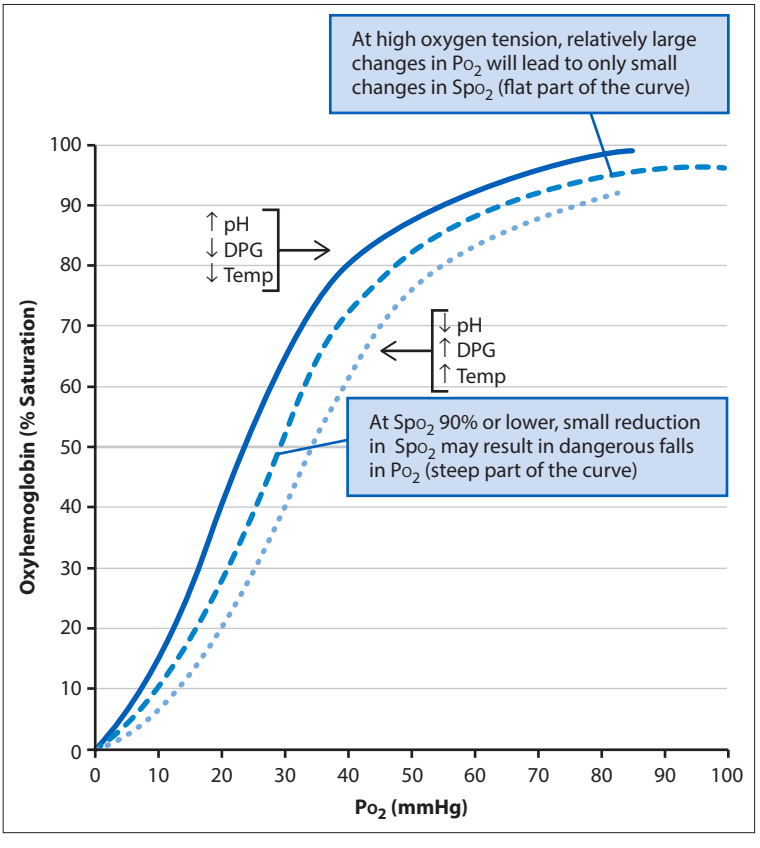


Figure 51-1. Oxyhemoglobin dissociation curve. The rightward shift, as seen in sickle cell disease, indicates that oxyhemoglobin saturation at a given arterial oxygen pressure is lower in patients with sickle cell disease because of decreased oxygen affinity of HbS, increased 2,3-diphosphoglycerate in sickled erythrocytes, and hypoventilation due to pain or opioid use, and as an adaptation to severe anemia to prevent tissue hypoxia.

From Krishnan S. Oximetry and capnography. In: Stokes DC, Dozor AJ, et al, eds. *Pediatric Pulmonology, Asthma, and Sleep Medicine: A Quick Reference Guide.* American Academy of Pediatrics; 2018:63–67.

Clinical Features

In the largest observational cohort study of 243 unselected pediatric research subjects with sickle cell anemia (aged 4–18 years), the prevalence of OSA (with an obstructive apnea hypopnea index [OAHI] of ≥1 event per hour) was 41%; 10% of children had an OAHI 5 or higher, consistent with moderate OSA.[71] While significant risk factors for OSA in this cohort included habitual snoring and a resting daytime oxygen saturation of less than 96% on room air, 20% of children with moderate OSA did not have caretaker-reported habitual snoring and only 32% had caretaker-witnessed apneas, suggesting that inquiring about common OSA symptoms in the general population may be insufficient for determining which children with SCD warrant a sleep study. In the same cohort, the presence of OSA (with an OAHI ≥2 events per hour) was associated with more than twice the odds of severe nocturnal enuresis.[72]

Data are conflicting about the association between sleep-disordered breathing (SDB) and SCD morbidity in children. In one study of 95 children with SCD and no history of stroke, nocturnal desaturation (but not obstructive events) was an independent risk factor for central nervous system events (seizure, stroke, or transient ischemic attack),[73] but these results have not been replicated. In the same cohort, nocturnal desaturation was highly associated with rates of pain (every increase of Sao_2 percentage point was associated with 0.83 fewer days of pain per year, $P < .001$).[67] In contrast, recent longitudinal prospective data from 140 children with sickle cell anemia did not show any association between nocturnal oxygen desaturation or higher OAHI and increased rates of pain or ACS.[74] No studies have looked at the consequences of SDB or nocturnal desaturation in adults with SCD.

Management

All children with SCD should be screened for clinical signs and symptoms of SDB. If a history of snoring, disturbed sleep, poor school performance, daytime somnolence, or hyperactivity is elicited, or if daytime oxyhemoglobin saturation (Spo_2) is 94% or less or tonsillar enlargement is detected on physical examination, patients should be referred for nocturnal polysomnography (PSG). In contrast to the children without SCD, in whom adenotonsillectomy is often curative, children with SCD frequently have residual PSG abnormalities following adenotonsillectomy.[75] Positive airway pressure therapy could be considered.[76] Children with SCD and abnormal sleep studies who undergo adenotonsillectomy should have follow-up PSG 3 to 6 months postoperatively to assess the potential need for positive airway pressure.[76,77] In addition, 3 small case series describe improvement in OSA as well as daytime and nocturnal hypoxemia in response to treatment with HU.[78–80]

Lung Function in Sickle Cell Disease

Overview

Our understanding of the natural history of lung function in individuals with SCD is limited for several reasons. One reason is that while there are a small number of studies that follow lung function among children or among adults longitudinally, there are no large prospective studies of lung function among individuals with SCD across the life span from childhood through adulthood. A second reason is that lung function is interpreted differently across different studies, with some studies using lower limit of normal criteria to determine normal lung function vs obstructive, restrictive, or mixed ventilatory defects; other studies classify individuals using arbitrary cutoffs (such as an $FEV_1/FVC < 0.70$ or 0.80) to distinguish normal vs obstruction. Despite these limitations, a few general patterns have emerged in the literature.

Clinical Features

Children with SCD have reduced lung function compared to otherwise healthy age- and gender-matched Black controls, but most children with SCD have lung function in the normal range.[60,81] The most common abnormality seen in children is obstruction, occurring in about 15% to 20% of children with SCD. A restrictive defect is less common, occurring in 7% to 9% of children.[60,81] Retrospective chart review studies of children suggested that history of ACS may be associated with lung function abnormalities, but the largest prospective research cohort study in children with HbSS found that a history of ACS was not associated with lung function abnormalities in children, and that the presence of abnormal lung function (obstruction or restriction) did not predict future ACS or pain episodes in children.[60] Data from several studies suggest that restriction is common among adults (ranging from 27% to 74% across studies).[56,82–84] One research cohort that used ATS/European Respiratory Society lower limit of normal criteria found that 19% of adults with SCD had obstruction.[8]

The longitudinal trajectory of lung function in SCD is not well understood. One study demonstrated a 2% to 3% decline per year in total lung capacity, FVC, and FEV_1 among children with SCD[85]; other studies found that lung function either does not change or declines at a much slower pace than 2% to 3% per year.[86,87] The group that demonstrated the steepest rate of decline subsequently found that the use of HU slows the rate of lung function decline.[88]

In contrast to the obstructive defects often noted in children with SCD, several studies have shown the development of a restrictive pattern on pulmonary function tests among adults with SCD (**Table 51-1**), characterized by reductions in total lung capacity, FVC, and FEV_1 with a normal FEV_1/FVC ratio.[82–84]

Many patients also have abnormalities in the diffusion capacity for carbon monoxide (D_{LCO}),[82,83,90] which worsen with age[83] and correlate with the level of dyspnea, independent of the degree of anemia.[90] Interpretation of D_{LCO} is complicated in SCD for a number of reasons. Oxygen (and carbon monoxide) carrying capacity of the blood is dependent on Hb concentration, but, in patients with active hemolysis and increased production of carboxyhemoglobin (COHb), the presence of COHb can decrease passive diffusion of carbon monoxide into erythrocytes, leading to underestimates of D_{LCO}. On the other hand, the rightward shift of the oxyhemoglobin dissociation curve in SCD (due to the decreased oxygen affinity of HbS compared to hemoglobin A; the increased production of 2,3-diphosphoglycerate seen in severe anemia, and carbon dioxide retention from hypoventilation) can lead to an adaptive release of oxygen into end-organ tissues, leaving more binding sites available on the Hb molecule and an overestimate of D_{LCO}. **Table 51-2** describes the different findings in several studies about D_{LCO} in SCD.

Table 51-1. Comparison of Pulmonary Function Testing Results Across Studies of Adults With Sickle Cell Disease

Study Details	Klings,[83] 2006	Sylvester,[82] 2006	Field,[84] 2008	Anthi,[89] 2007	
				Without PH	With PH
Number of subjects	310	33	92	15	24
Mean Age (years)	30.7	36	36	41	43
TLC (% predicted)	70	83	87	85	80
FVC (% predicted)	84	82	71	82	70
FEV_1 (% predicted)	83	83	79	85	71
FEV_1/FVC	0.99	0.85	0.85	0.80	0.78
Classification of Pulmonary Function Abnormalities					
Obstructive (%)	1	14	36		
Restrictive (%)	74	26	19		
Mixed (%)	2	11			

Abbreviations: FEV_1, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; PH, pulmonary hypertension; TLC, total lung capacity.

Table 51-2. Comparison of Diffusion Capacity Testing Results Across Studies of Adults With Sickle Cell Disease

Study	N	Findings	Comments
Wall MA,[91] 1979	12 children w/ HbSS vs 12 Black controls	DLCO greater in HbSS compared to controls	
Arteta M,[81] 2014	95 children	Median DLCO 95% of predicted 19% had DLCO < 80% of predicted	Decreased DLCO associated with decreased TLC and decreased Hb
Miller GJ,[92] 1971	25 adults	Mean DLCO 66% for men; 71% for women	Decreased DLCO attributed to reductions in permeability across alveolar capillary membrane
Young RC, 1988[93]	66 adults vs 16 Black controls	DLCO decreased in SCD (69% vs 100% in controls); "lung permeability constant" decreased compared to controls (0.76 vs 0.99)	Correlated with degree of anemia
Klings ES, 2006[83]	310 adults	Median DLCO adjusted for Hb: 62%	DLCO inversely associated with age
Sylvester KP, 2006[82] Lunt A, 2014[56]	35 adults	Median DLCO 75% Did not decline in follow-up study 9 years later	DLCO associated with degree abnormalities on HRCT HRCT abnormalities did not change over time

Abbreviations: DLCO, diffusion capacity for carbon monoxide; Hb, hemoglobin; HbSS, sickle cell anemia; TLC, total lung capacity; HRCT, high-resolution computed tomography.

Management

While there are insufficient data to support routine screening with pulmonary function testing for asymptomatic individuals with SCD, pulmonary function tests can be useful diagnostic tests for patients with respiratory symptoms, reduced exercise capacity, and other pulmonary issues.[94] Once identified, specific management strategies for lung function abnormalities include optimizing the care of the underlying SCD itself (ie, with HU) and having a low threshold to formally evaluate for the other commonly seen pulmonary conditions in this population, including asthma, SDB, and, in adults, pulmonary hypertension.

Pulmonary Hypertension

Overview

Pulmonary hypertension (PH) is defined as a resting mean pulmonary arterial pressure 20 mm Hg or greater.[95] Right-heart catheterization–confirmed PH occurs in 6% to 11% of adults with SCD and is a mortality risk factor.[96,97] In the past, an elevated tricuspid regurgitant jet velocity (TRV) by echocardiography of 2.5 m/s or greater was considered to be indicative of pulmonary hypertension. While we now know that an elevated TRV has a high false positive rate for PH,[98] an elevated TRV for adults, regardless of the presence of PH or not on a cardiac catheterization, is an independent mortality risk factor.[99]

In contrast to adults, an elevated TRV is not necessarily associated with increased mortality risk in children and adolescents with SCD.[100] Because there are no published studies of right-heart catheterization in children with SCD and there is known to be a high false positive rate of a high TRV for true PH in adults, the significance of an elevated TRV for a child with SCD remains unclear.

Pathophysiology

Gladwin and Vichinsky have described increased intravascular hemolysis resulting in progressive vasculopathy from endothelial dysfunction (resulting in priapism, stroke, and PH).[15] Chronic hemolysis leads to a deficiency in nitric oxide, causing increased vasoconstriction and increased intravascular adhesion due to impaired downregulation of endothelial adhesion molecules.[101] Intravascular hemolysis also leads to platelet activation and a hypercoagulable state.[102] Autopsy studies have shown the presence of in situ thrombosis in patients who had PH at the time of death.[10,103]

Clinical Features

The threshold values traditionally associated with a positive echocardiography screening for PH in individuals with SCD (mean pulmonary artery pressures of $\geq$25 mm Hg or a TRV of $\geq$2.5 to 3 m/sec)[9] are lower than values seen in symptomatic patients with other forms of PH. This is because patients with SCD are more likely to develop clinical manifestations at less elevated pulmonary pressures due to decreased oxygen-carrying capacity from chronic anemia as well as diffuse end-organ damage due to chronic microvessel dysfunction.[104] The most common symptom of PH is exertional dyspnea, which is also common in those with chronic anemia without PH. Individuals with SCD and PH had a significantly shorter mean 6-minute walk test distance compared with those without PH (320 m vs 435 m).[89]

As previously mentioned, the significance and progression of an elevated TRV in children is not clear. In a retrospective chart review of 61 children with screening echocardiograms, the 3 deaths that occurred were not in children with a high TRV.[100] In an observational study of 19 children with an elevated TRV, 12 children had a normal TRV on a follow-up echocardiogram 12 to 18 months later in the absence of any intervention. Five children started HU, and their follow-up echocardiogram was normal. In the largest study of echocardiography findings in pediatric patients with SCD,[105] 11% of 290 patients had an elevated TRV (defined in that study as >2.6 m/s). There was no difference in pulmonary vascular resistance derived by echocardiography between patients with SCD and age- and race-matched control subjects. Tricuspid regurgitant jet velocity was negatively associated with Hb concentration and oxygen saturation during a 6-minute walk test and was positively associated with a history of acute chest syndrome and multiple measures of increased pulmonary blood flow. A longitudinal study of 160 children and adolescents with HbSS over 22 months of follow-up noted that an increased TRV was associated with a longitudinal decline in the 6-minute walk distance and multiple markers of increased hemolysis.[106] Taken together, these findings suggest that an abnormal TRV is a marker of SCD severity. Long-term outcomes in children with an abnormal echocardiogram warrant further study.

Screening and Management

The optimal screening and management strategy for pulmonary hypertension in SCD is an important research priority.[107] The American Society of Hematology 2019 Guidelines for Sickle Cell Disease: Cardiopulmonary and Kidney Disease[94] recommend against routine screening echocardiography to identify pulmonary hypertension in asymptomatic patients with SCD. Signs or symptoms such as unexplained dyspnea, hypoxemia, chest pain, or exercise limitation; or a history of syncope, PE, or signs of heart failure or a new murmur should prompt a diagnostic echocardiogram or consultation with a pulmonary hypertension specialist. A symptomatic patient with a persistently elevated TRV should have consultation with a PH specialist for consideration of a right-heart catheterization. The management of SCD-related PH is complicated because of the lack of SCD-specific data on the safety and efficacy of pharmacologic agents used for PH in other populations. The guidelines support the use of pulmonary arterial hypertension-specific therapies under the care of a PH specialist, but only for those patients with right-heart catheterization–proven pulmonary arterial hypertension (not for other subtypes of SCD-PH).[94] In addition, American Thoracic Society guidelines on the management of PH in patients with SCD recommend HU for patients with an increased mortality risk, either because of right-heart catheterization–proven PH or in an adult with an elevated TRV.[108]

CASE REPORT 51-2

An 18-year-old with severe sickle cell anemia has been on hydroxyurea therapy for 6 months. He typically has 5 to 6 admissions for pain per year, recurrent priapism, nocturnal hypoxemia, and chronic dyspnea. His steady-state Hb averages 5 to 6 g/dL. He has had spirometry annually that has revealed long-standing, partially reversible airway obstruction, though for the past 2 years he has also developed a restrictive defect on plethysmography, with a recent total lung capacity of 72% of predicted. A recent 6-minute walk test demonstrated a resting oxygen saturation of 94% on room air, but he became hypoxic to 88% after 2 minutes of walking. His 6-minute walk distance was 390 m (median for healthy adult men = 580 m).[109] Transthoracic echocardiogram 1 month ago did not show an elevated TRV. After an initial period of noncompliance, he now uses a bilevel positive airway pressure ventilation device routinely during sleep. The frequency of painful episodes and priapism have decreased over the past 6 months; however, he continues to report significant dyspnea when walking across the campus of his community college. He has reluctantly agreed to a trial of portable, supplemental oxygen when he knows he has to walk long distances.

key points

- Pulmonary complications of SCD are a common feature of the disease and lead to significant morbidity and mortality.
- Management of ACS includes careful pain management, supplemental oxygen, antibiotics, bronchodilators, incentive spirometry, and red blood cell transfusion for patients with a significant drop in Hb.
- Children with SCD should be screened for asthma and, when indicated, managed according to guidelines established by the National Asthma Education and Prevention Program.
- Clinicians should take a detailed history and have a low threshold to evaluate children with SCD for SDB.
- While pulmonary function testing is not warranted as a screening test for asymptomatic patients with SCD, it can be a useful diagnostic test for individuals with respiratory symptoms.
- More research is needed regarding the optimal screening and management strategy for SCD-associated PH.
- Children with signs or symptoms of persistent asthma, SDB, recurrent ACS, or chronic dyspnea should be referred to a pediatric pulmonologist.

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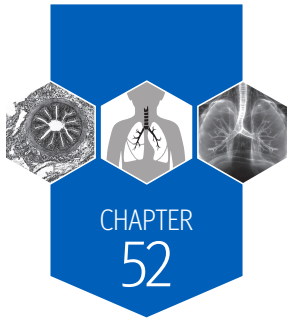
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Pulmonary Manifestations of Oncologic Disease and Treatment

Mary Bono Cataletto, MD, FAAP
Caitlin Hurley, MD

Introduction

An estimated 16,000 cases of pediatric cancers are diagnosed in the United States each year.[1] Despite numerous advances in the diagnosis and management of pediatric tumors, cancer remains the leading cause of death from disease in children from infancy up to 19 years of age.[1,2] Leukemia and lymphomas are 2 of the 3 most common tumors in this age group, and both can be associated with pulmonary manifestations at presentation.

Primary lung and airway tumors are relatively rare in children but are important to recognize because delays in diagnosis can have consequences for prognosis. In addition to complications of the primary neoplasms, cancer therapies, including chemotherapy and radiation, may have substantial effects on the lungs.

Lung Involvement in Hematologic Malignancy

Hematologic malignancies may cause pulmonary disease in children, including pulmonary leukostasis in the setting of hyperleukocytosis, leukemic cell lysis pneumonopathy, and leukemic infiltration. In addition, patients with leukemia or lymphoma presenting with a mediastinal mass may develop superior vena cava syndrome and airway compression.

Leukemia

Acute leukemias are the most common malignancy of childhood, accounting for approximately 30% of pediatric cancer cases, with the majority, nearly 75%, being acute lymphoblastic leukemia (ALL).[3] Mediastinal mass with leukemic infiltration is common at diagnosis, particularly with T-cell ALL.[3] Acute myeloid leukemia (AML) is less common; however, it may manifest with increased morbidity, especially with hyperleukocytosis, defined as peripheral white blood cell count exceeding 100,000 cells/μL at presentation.[4] Children with ALL, AML, or chronic myelogenous leukemia who present with hyperleukocytosis are at risk for leukostasis. Leukostasis is the result of increased blood viscosity

from the circulating large and stiff blast cells, as well as interactions between the blast cells and vascular endothelial cells. Leukostasis is more common in patients with AML at lower total white blood cell counts because of the larger size, shape, and decreased deformability of the AML blast cell.[5,6] The accumulation of circulating blasts results in elevated blood viscosity, microvascular obstructions, and, ultimately, tissue hypoxia. In the lung, this phenomenon causes pulmonary infiltrates, hypoxia, hemorrhage, and infarction. In pulmonary leukostasis, urgent cytoreduction therapy is required, and the type of cytoreduction depends on the leukemia subtype.[7,8] In addition to pulmonary leukostasis, the release of intracellular contents of blast cells after leukemic cell lysis causes pulmonary tissue damage and edema, which may lead to respiratory failure, a condition known as *leukemic cell pneumonopathy*.

Intensive multiagent chemotherapy is successful in inducing remission in about 70% of patients with AML.[4] Children and adolescents with ALL have an overall survival rate greater than 89% at 5 years from the time of diagnosis. Young adults with ALL have an overall survival rate of 61%. In infants younger than 12 months, ALL is extremely aggressive, with high relapse and low survival rates.[9,10]

Hematopoietic stem cell transplant (HSCT) is an important therapeutic option in ALL with very high-risk features and in ALL relapse. Immunotherapy has also changed the landscape of treatment for very high-risk or relapsed ALL.[11]

Lymphoma

Lymphomas are morphologically subdivided into 2 major categories—non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL).

In adolescents and young adults between 17 and 39 years of age, NHL accounts for approximately 8% of all cancers. Although NHL is a heterogeneous group of tumors, the most common subtypes include diffuse large B-cell lymphoma and anaplastic large cell lymphoma. Young adults are a unique subgroup of patients differing from both children and adults in terms of clinical presentation, histological findings, and outcomes.[12]

Hodgkin lymphoma is a B-cell lymphoma characterized by a trimodal age distribution curve with its highest peak in adolescence and young adulthood, followed by 2 smaller peaks in children younger than 15 years and in adults older than 50 years. The disease is histopathologically defined by the presence of Hodgkin and Reed-Sternberg cells. Presenting symptoms in children include painless lymphadenopathy; hepatosplenomegaly; and nonspecific symptoms such as fatigue, anorexia, and weight loss. Between 17% and 40% of children with HL have a mediastinal mass at the time of presentation. The bulky mediastinal mass may cause dysphagia, dyspnea, cough, stridor, or superior vena cava syndrome.

Mediastinal Tumors

The mediastinum is typically classified into 3 compartments on the basis of lateral chest radiographs—anterior, middle, and posterior. The anterior compartment is bordered by the sternum anteriorly and the pericardial sac posteriorly. The posterior mediastinum extends from the posterior aspect of the pericardium to the vertebral bodies, and the middle mediastinum includes the structures that lie between the anterior and posterior shadows of the pericardium. The middle mediastinum contains the trachea, main bronchi, and bronchial lymph nodes, as well as the heart and pericardium, the ascending aorta, the lower segment of the superior vena cava, and the bifurcation of the pulmonary artery.[13] The International Thymic Malignancy Interest Group has also proposed new definitions of the mediastinal compartments on the basis of computed tomography (CT) images—prevascular, visceral, and paravertebral.[14,15]

Most mediastinal masses in children are malignant, and more than one-half of these children have symptoms, typically dyspnea, cough, fever, and malaise. However, these symptoms are often nonspecific and can resemble common respiratory illnesses. There is a clinically significant risk of respiratory distress with acute airway compression, which can occur or worsen suddenly, especially in young children. Patients unable to lie supine or with greater than 50% compression of the airway during CT are at high risk of complete obstruction with anesthesia or other procedures and may be best treated in a pediatric center with extracorporeal membrane oxygenation support.[16,17]

Complications of Mediastinal Tumors

Superior vena cava syndrome occurs when the superior vena cava is compressed by mediastinal tumors. In a child, superior vena cava syndrome is most often caused by lymphomas (HL and NHL) and T-cell ALL. Clinical signs and symptoms include edema of the face, prominent superficial chest veins, cough, wheeze, shortness of breath, and stridor. Plethora or cyanosis of the face, neck, and upper extremities can also occur. The diagnosis is confirmed by means of Doppler ultrasonography or magnetic resonance imaging. Emergency treatment includes elevating the head of the bed, keeping the child calm, and administering supplemental oxygen. At times, diuresis or emergency treatment with steroids may be required.[8]

Anterior Mediastinum

Approximately one-half of all mediastinal masses are primary neoplasms in the anterior mediastinum. They can be congenital, inflammatory, or neoplastic. Thymomas are the most common primary tumor of the anterior mediastinum; however, most occur in middle-aged and older adults and infrequently in children and adolescents. Germ cell tumors (GCTs) of the mediastinum include teratomas, seminomas, and nonsematomatous malignant GCTs. They are

believed to arise from primitive germ cells misplaced in the anterior mediastinum during early embryonic development. The anterosuperior portion of the mediastinum is the most common extragonadal primary site. Teratomas are the most common GCTs in children.[18]

Primary mediastinal NHL constitutes about 5% of all NHL. Age-related differences in presentation, biological features, and outcome are seen with NHL. Children are more likely to have high-grade tumors, including Burkitt lymphoma, diffuse large B-cell lymphoma, lymphoblastic lymphoma, and anaplastic large cell lymphoma. Tumor lysis syndrome and symptoms related to compression of surrounding tissue can occur. Treatment outcomes for children younger than 16 years with newly diagnosed NHL are better than for those in older age groups.[12,19]

Posterior Mediastinum

The most common tumors in the posterior mediastinum are neurogenic in origin and arise from the sympathetic ganglia, intercostal nerves, and paraganglia cells.[13] The most common benign neurogenic tumor of the posterior mediastinum in children is the ganglioneuroma, which is composed of both ganglion cells and nerve fibers. This tumor typically manifests at an early age and may be identified as an incidental finding or less frequently because of symptoms secondary to nerve root or spinal cord compression. Magnetic resonance imaging is the imaging modality of choice to define the relationship of the tumor to adjacent structures, particularly the spinal cord. Surgical resection, either complete or partial, is the treatment of choice.

Neuroblastomas are highly malignant tumors that account for more than one-half of the neurogenic tumors of the posterior mediastinum. They arise primarily from the adrenal medulla and less often the sympathetic nervous system ganglia. They are most commonly seen in infants and children younger than 3 years and have frequently metastasized by the time of diagnosis. Regional lymph nodes, bone, bone marrow, brain, and liver are frequent sites of metastases, with lung rarely a site of metastasis. Clinical presentation and prognosis are variable and depend on patient age, tumor biological features, and tumor staging.

Ganglioneuroblastomas, composed of both mature and immature ganglion cells, are malignant and generally symptomatic at presentation. They are divided into 2 categories—composite ganglioneuroblastoma and diffuse ganglioneuroblastoma. In the first category, between 65% and 70% of patients will have metastatic disease at presentation, whereas in the latter, less than 5% of patients will develop metastases.[13]

Solid Tumors

Thoracic Tumors

Primary pulmonary neoplasms in the pediatric age group are relatively uncommon. The true incidence and etiologic predisposing factors are unclear. Abnormal fetal lung development has been implicated in some rare tumors. In a systematic review of 134 publications,[20] investigators analyzed congenital pulmonary malformations (CPMs) in 76 children and 92 adults. Congenital cystic adenomatoid malformation (CCAM) was the most frequent underlying CPM associated with pulmonary tumors in children. The tumor most frequently associated with CPM in children was pleuropulmonary blastoma (PPB). This finding differs from findings for adults with CPM, in whom bronchogenic cysts and CCAM are the most common underlying CPM and adenocarcinoma and bronchoalveolar carcinoma are the most commonly associated tumors. In both children and adults, the most common presenting symptom was cough.[20]

Table 52–1. Examples of Pediatric Thoracic Tumors

Anatomical Region	Malignant	Benign
Airway	Carcinoid Mucoepidermoid carcinoma	Infantile hemangioma Squamous papilloma
Anterior mediastinum	Lymphoma: Hodgkin and non-Hodgkin Germ cell tumors	Teratoma Lymphangioma
Middle mediastinum	Lymphoma: Hodgkin and non-Hodgkin Germ cell tumors Rhabdomyosarcoma	Teratoma Cardiac rhabdomyoma Bronchogenic cyst
Posterior mediastinum	Neuroblastoma Lymphoma	Ganglioneuroma Neurofibroma
Pulmonary parenchyma	Primary tumors Bronchoalveolar carcinoma Pleuropulmonary blastoma Metastatic solid tumors Lymphoma	Granulomatous disease Inflammatory pseudotumor Hamartoma
Chest wall	Ewing sarcoma family Rhabdomyosarcoma Osteosarcoma Lymphoma	Lipoma Hemangioma Osteochondroma Neurofibroma

Thoracic tumors can manifest at any age and often are identified as an incidental finding at chest imaging. Thoracic tumors can be malignant or benign. The diagnosis and surgical intervention may be delayed because of absent or nonspecific symptoms at presentation. An overview of benign and malignant pediatric thoracic tumors is provided in **Table 52–1**.[20–29] The tumors are grouped according to their anatomical locations.

Airway Tumors

Although airway tumors are rare in children, they are more likely to be malignant than benign.[21] Both tumor type and tumor location affect clinical symptoms, which can include recurrent cough, wheezing, chest pain, atelectasis, and hemoptysis. Similarities in presentation with asthma and respiratory tract infections are frequently associated with delays in diagnosis.[21–23] More than one-half of children with airway tumors present with persistent or recurrent pulmonary infections involving the same location, asymmetrical findings at auscultation, or persistent cough.[24]

Benign Airway Tumors

Infantile hemangioma and squamous papilloma are the most frequently occurring histological group of benign airway tumors in children.[23] Sporadic cases of inflammatory pseudotumor, leiomyoma, granular cell tumor, juvenile xanthogranuloma, tracheal lipoblastoma, and laryngotracheal chondroma have also been reported.[23]

Obstructive infantile hemangiomas typically occur at the level of the subglottis, and patients present with biphasic stridor and cough as the tumor enlarges. Cutaneous hemangiomas are seen in about one-half of infants with an airway hemangioma, with the greatest risk of airway hemangioma in children with cutaneous hemangioma of the head or neck.[30] In a small number of cases, there are other associated congenital anomalies. The most notable is PHACE syndrome, which includes **P**osterior fossa anomalies, **H**emangioma, **A**rterial lesions, **C**ardiac abnormalities/**C**oarctation of the aorta, and **E**ye anomalies. Patients with large segmental infantile hemangiomas of the head or neck have a 30% risk of PHACE syndrome.[31]

Recurrent respiratory papillomatosis is caused by infection with human papillomavirus. Most infections in infants occur during vaginal delivery from infected mothers, whereas in older patients human papillomavirus is transmitted sexually.[32] It is seen most frequently in the larynx but has been reported in the nasopharynx, tracheobronchial tree, and lung parenchyma. Malignant transformation to squamous cell carcinoma is rare but has been reported.[32]

Malignant Airway Tumors

The most common malignant airway tumors in the pediatric age group are carcinoids and mucoepidermoid carcinoma.[21] Bronchial carcinoids account for 63% to 80% of all malignant pediatric primary lung tumors. These tumors arise from the neuroendocrine cells within the bronchial epithelium and often appear as polypoid projections into the airway lumen. The more common are the typical carcinoids, which overall are less invasive, have a low malignancy potential, and have a more favorable prognosis, with greater than 90% survival.[25,28] The poorly differentiated carcinoid tumors are more aggressive, often with local invasion at the time of patient presentation. The excessive

secretion of vasoactive peptides from carcinoid tumors causing wheezing, flushing, palpitations, and diarrhea is referred to as *carcinoid syndrome* and is rare in the absence of metastases. Spread to the intrathoracic lymph nodes is the most common site of metastases.[28]

Lung Parenchymal Tumors

Pleuropulmonary blastomas are malignant, sarcomatous tumors arising from the lung parenchyma, pleural surfaces, or both and are the most common primary pulmonary malignancy in children.[33] Evolving from a pulmonary cyst, PPB can be divided into 4 types on the basis of progression—type I (purely cystic; median patient age of 8 months at presentation), type Ir (*r* stands for *regressing*; similar to type I and occurs in older children than type I; does not contain cancerous cells), type II (cystic and solid; median patient age of 35 months at presentation), and type III (purely solid; median patient age of 41 months at presentation). Pleuropulmonary blastoma is caused by a germline mutation in *DICER1*; DICER1 syndrome is a rare inherited disorder that increases the risk of tumors in multiple sites including the kidney, thyroid, and lung. Pleuropulmonary blastoma should be included in the differential diagnosis in children with spontaneous pneumothorax, multiple pulmonary cystic lesions, or a family history of pulmonary cysts and PPB. Because of the nonspecific nature of symptoms with childhood parenchymal tumors, there is a high rate of delayed diagnosis. Treatment decisions are made on the basis of tumor type.[34] Consultation with medical genetics specialists is an important component in the care of families of children with germline mutations.

Chest Wall Tumors

Primary chest wall tumors are also rare in the pediatric age group and are predominantly sarcomas from the Ewing sarcoma family.[35] These are aggressive tumors characterized by malignant, small round cell types. Other malignant tumors that can involve the chest wall include primitive neuroectodermal tumors, rhabdomyosarcoma, neuroblastoma, malignant fibrous histiocytoma, chondrosarcoma, osteogenic sarcoma, synovial sarcoma, chordoma, leiomyosarcoma, and fibrosarcoma.[36] Several benign tumors, including lipoblastoma, mesenchymoma, chondroma, and hamartoma, can also manifest as chest wall masses.[37] Tuberculosis and actinomycosis also can manifest as chest wall masses but only rarely.

Evaluation of chest wall masses begins with plain radiography followed by chest CT to facilitate delineation of tumor site, size, and infiltration into contiguous structures, as well as to screen for pulmonary metastases. Magnetic resonance imaging complements the previous studies to evaluate the soft tissue further, identify any fluid within the chest wall, and detect any extension into the spine or epidural space. Tissue biopsy is performed using either a core needle technique or a limited open approach.[36]

Pulmonary Metastatic Lesions

Table 52-2 lists some of the pediatric tumors known to metastasize to the lungs. Metastatic masses or nodules can be solitary or multiple and may be found at the time of diagnosis of the malignancy, or at a recurrence of the disease. The lung is the most common site for metastases from solid tumors.[38] Computed tomography is the preferred imaging modality to identify and follow up pulmonary nodules but lacks specificity to differentiate benign from malignant nodules, so biopsy may still be required, particularly in areas with high endemic fungal infection.[39]

Pulmonary metastases from pediatric solid tumors can be divided into 2 major categories according to the histological characteristics of the primary tumor—those that respond well to systemic adjuvant therapy and those that respond poorly. **Box 52-1** lists tumors according to this classification.[39] In children who respond well to systemic therapy, it is the primary and first-line treatment. Children whose malignancies respond poorly to systemic therapy are more likely to require surgical resection.[39]

Table 52-2. Pediatric Tumors That Metastasize to the Lungs

Primary Site	Common	Rare
Skeletal system	Osteosarcoma Ewing sarcoma	Chondrosarcoma
Musculoskeletal system	Rhabdomyosarcoma Soft-tissue sarcoma Synovial cell sarcoma Malignant fibrous histiocytoma	Chondrosarcoma Fibrosarcoma Liposarcoma Malignant neurilemmoma
Gastrointestinal tract	Hepatoblastoma Hepatocellular carcinoma Embryonal sarcoma of liver	Leiomyosarcoma Adenocarcinoma of colon
Genitourinary tract	Wilms tumor Malignant rhabdoid tumor of the kidney Malignant germ cell tumor	Trophoblastic choriocarcinoma
Endocrine system	Differentiated thyroid carcinoma	Adrenocortical carcinoma Neuroblastoma

Box 52-1

Classification of Pulmonary Metastases From Solid Tumors on the Basis of Treatment Response

Tumors responsive to adjuvant therapy

- Wilms tumor
- Hepatoblastoma
- Ewing sarcoma
- Neuroblastoma (uncommon)
- Rhabdomyosarcoma

Tumors less responsive to adjuvant therapy

- Nonrhabdomyosarcoma soft-tissue sarcoma
- Adrenocorticoid carcinoma
- Osteosarcoma

Derived from Croteau NJ, Heaton TE. Pulmonary metastasectomy in pediatric solid tumors. *Children (Basel).* 2019;6(1):6.

Pulmonary Complications of Cancer Therapies

Patients with malignancies treated with chemotherapeutic drugs, radiation,or newer biologic agents and immunotherapy are at risk for multiple infectious and noninfectious pulmonary complications. Patients undergoing HSCT are at particularly high risk for pulmonary complications.

Chemotherapy Pulmonary Injury

Traditional chemotherapy-related drug injury has long been recognized as having the potential for worsening by concomitant therapies such as radiation. Examples of classic chemotherapy drugs that induce injury include bleomycin, busulfan, and nitrosureas. Bleomycin is an alkylating agent associated with increased risk for acute respiratory distress syndrome, alveolar proteinosis, and pulmonary fibrosis. Approximately 8% of patients treated with bleomycin will develop symptomatic pulmonary injury. Cumulative doses greater than 500 mg or 400 U/m^2 and lung irradiation increase the risk for toxicity[40,41]; current therapy regimens limiting doses have helped reduce the frequency of substantial bleomycin injury. Nitrosoureas (carmustine and lomustine) have been linked to hypersensitivity pneumonitis, alveolitis, pulmonary veno-occlusive disease, and pulmonary fibrosis.[40,41]

Novel Cancer Therapy–Induced Pulmonary Injury

New innovative strategies to address recurrent and refractory pediatric cancers may have potential pulmonary toxicities. This field is rapidly evolving, and a review of all newer agents potentially associated with pulmonary complications is beyond the scope of this chapter. Pneumonitis is the most

common immune-related adverse effect associated with immune checkpoint inhibitors, which target immune cells rather than tumor cells; it can manifest as organizing pneumonia, nonspecific interstitial pneumonia, hypersensitivity pneumonia, or diffuse alveolar damage. Pneumonitis can develop quickly and can be fatal. Examples of immune checkpoint agents include ipilimumab, pembrolizumab, and nivolumab.[42–44]

Targeted molecular therapies, including monoclonal antibodies and tyrosine kinase inhibitors, are increasingly used in adult cancers and in some childhood cancers. Pneumonitis and interstitial lung disease can be associated with these agents and, rarely, can be fatal.[45–47] For biologic agents, which include rituximab, cetuximab, bevacizumab, alemtuzumab, and trastuzumab, the most common of pulmonary adverse effects is interstitial lung disease.[47]

Radiation-induced Pulmonary Injury

Radiation therapy plays a major role in the curative or palliative treatment of many intrathoracic and chest wall malignancies. With carefully targeted modern radiation therapy, most patients remain without symptoms and with minimal clinical manifestations of radiation-related changes. Children are particularly sensitive to the effects of radiotherapy because of rapid lung development, and pulmonary function abnormalities are common with radiation in children old enough to perform pulmonary function tests.[48]

Radiation pneumonitis has an insidious onset and may manifest as a nonproductive cough, dyspnea on exertion, low-grade fever, pleuritic or substernal chest pain, malaise, and weight loss. Physical examination may reveal crackles or a pleural rub, dullness to percussion if with effusion, and skin erythema outlining the radiation port. Tachypnea, cyanosis, and signs of pulmonary hypertension may be seen in advanced cases. Pulmonary function testing reveals a reduction in lung volumes, diffusing capacity, and lung compliance.

Radiographic changes are generally confined to the field of irradiation. Initially, there is a diffuse haze in the irradiated region with obscuring of vascular outlines. Patchy consolidations appear and then coalesce to form a relatively sharp edge that conforms to the treatment portals. These changes may clear gradually and disappear completely but may lead to fibrous changes in the case of severe injury.

Fibrous changes take 6 to 24 months to evolve but usually remain stable after 2 years. Chronic radiation fibrosis is indicated by findings of a well-defined area of atelectasis with parenchymal distortion, traction, bronchiectasis, mediastinal shift, or pleural thickening.

The diagnosis is based on history of exposure, including target, dose, and technique, with consideration of clinical symptoms, imaging findings, timing from completion of radiation therapy, laboratory studies, and exclusion of

alternate diagnoses such as infection. Treatment approaches generally include systemic corticosteroids for patients with symptoms.[49]

Pulmonary Complications of Hematopoietic Stem Cell Transplant

Hematopoietic stem cell transplant has made major progress as therapy after chemotherapy and radiation for several hematologic and nonhematologic malignancies. *Hematopoietic stem cell transplant* is a general term that covers transplant of progenitor cells from any source, such as bone marrow, peripheral blood, or umbilical cord, and can be either an autologous (self) or allogeneic (nonself) stem cell source.

Infectious and noninfectious pulmonary complications after HSCT have been well described and can lead to clinically significant morbidity and mortality in children and adolescents both in the short term and throughout long-term follow-up. Noninfectious complications include idiopathic pneumonia syndrome (IPS), diffuse alveolar damage, and chronic graft-vs-host disease (GVHD) and bronchiolitis obliterans syndrome (BOS).

Infectious complications are common after HSCT, and the type of infection risk varies with the underlying disease indication for HSCT, cell source, preparative regimen (nonablative vs myeloablative conditioning), and time from transplant. Infections are more common early after HSCT, especially before engraftment; however, infections can occur later in the course, especially in patients who have impaired immune reconstitution or develop GVHD. Infections include bacterial, viral, and invasive fungal disease. Noninfectious pulmonary complications can have early or late onset. Early onset is most commonly associated with IPS, which is an acute lung injury with a median onset at 21 days after transplant. Idiopathic pneumonia syndrome is defined by widespread alveolar injury without lower respiratory tract infection and the absence of pulmonary symptoms secondary to cardiogenic or renal causes. The syndrome may include chemotherapy-induced acute interstitial pneumonitis, acute respiratory distress syndrome, damaged vascular endothelium secondary to engraftment-related respiratory distress syndrome, and diffuse alveolar hemorrhage.[50,51] Risk factors include myeloablative conditioning, severe GVHD, acute GVHD, and an underlying diagnosis of acute leukemia or myelodysplastic syndrome. Critical care respiratory support, including mechanical ventilation, is often required in patients with IPS. Treatment includes high-dose systemic corticosteroids, as well as tumor necrosis factor α inhibition with etanercept, often with the addition of inhaled fluticasone, montelukast, and azithromycin and supportive care.[52,53]

Other examples of early-onset pulmonary complications include periengraftment respiratory distress syndrome, diffuse alveolar hemorrhage, cryptogenic organizing pneumonia, secondary pulmonary alveolar proteinosis, and drug-induced pneumonitis.

Late-onset, noninfectious pulmonary complications occur in up to 20% of recipients of HSCT. They can involve the airway, lung parenchyma, pleura, and vessels. Pulmonary function testing and chest CT are important in the diagnosis.[54] Bronchiolitis obliterans syndrome is the most frequent of the noninfectious late-onset complications. It typically occurs within the first 2 years after HSCT, although most often after the third month. Pulmonary function testing and high-resolution CT have replaced lung biopsy for the diagnosis of post-HSCT BOS and rely on the National Institutes of Health consensus criteria.[54] Overall, the morbidity and mortality associated with post-HSCT BOS remains high.

Other late-onset pulmonary complications after HSCT include interstitial lung diseases, organizing pneumonia, and pulmonary vascular disease.

Pulmonary function testing before HSCT is important because baseline impairments are associated with higher complications and mortality rates after transplant; the testing should be performed serially to allow early detection of lung dysfunction and facilitate early interventions.[55]

Long-term Pulmonary Outcomes After Childhood Cancer

Outcomes data available as of January 2018 show approximately 483,000 childhood cancer survivors alive in the United States.[2] A large-scale, long-term population-based study of survivors of childhood, adolescent, and young adult cancers showed a sevenfold increase in the risk of respiratory mortality in survivors of childhood cancers compared with that in the general population, and a twofold increase in the risk in respiratory mortality was seen in survivors of adolescent and young adult cancers. In addition, an increased number of excess respiratory deaths were found as survivors aged, although the excess number of respiratory deaths decreased in patients treated in later cohorts.[56] In the largest cohort study of long-term survivors, the St. Jude Lifetime Cohort Study, pulmonary function abnormalities were common (31% with restrictive defects) and were associated with decreased physical functioning.[57] Given a slightly increasing incidence of childhood cancers and overall improvement in survival, we can anticipate that the number of adult survivors with pulmonary complications will continue to increase.[2]

key points

- Malignant disease is an infrequent cause of pulmonary disease in children.
- Primary tumors of the airways, mediastinum, and lung parenchyma usually manifest with nonspecific symptoms such as cough, wheezing, dyspnea, and chest pain.
- A variety of pediatric tumors may metastasize to the lungs and are often seen radiographically as pulmonary nodules.
- Leukemias and lymphomas are the major systemic malignancies with pulmonary involvement in children.
- Pediatric cancer therapies, including some chemotherapeutic agents, radiation therapy, and bone marrow transplant, are all associated with substantial pulmonary morbidities.
- Monitoring the pulmonary function can be useful in identifying early changes resulting from pediatric cancer therapies.

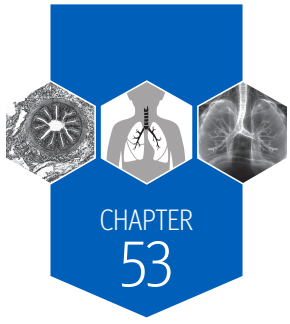
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Pulmonary Complications of Immunologic Disorders

Jay Jin, MD, PhD
Clement L. Ren, MD, MBA

Introduction

The respiratory tract is continuously exposed to pathogens through inhalation. To protect against infection, the lungs have a variety of defense mechanisms, including a mucociliary barrier, the innate immune system, and the adaptive immune system. This chapter focuses on pulmonary complications arising from congenital and acquired defects in innate and adaptive immunity. This chapter does not address the diagnostic workup of suspected immunologic conditions, which should be undertaken in collaboration with an experienced immunologist.

Each component of the immune system serves a specific role in host defense. A deficiency in any one element of the immune system renders individuals susceptible to specific groups of pathogens. **Table 53-1** summarizes the pattern of infections seen in children with different immunodeficiency syndromes.

Table 53-1. Typical Pathogens Associated With Specific Congenital Immunodeficiencies[a]

Element of the Immune System Affected	Example Diseases	Typical Pulmonary Pathogens
Neutrophils	Chronic granulomatous disease	*Aspergillus fumigatus* *Staphylococcus aureus* *Nocardia* sp *Burkholderia* sp
B lymphocytes	X-linked (Bruton) agammaglobulinemia Common variable immunodeficiency Specific antibody deficiency	*Streptococcus pneumoniae* *Hemophilus influenzae*
T lymphocytes	Severe: Severe combined immunodeficiency, AIDS Less severe: Ataxia-telangiectasia, Wiskott-Aldrich syndrome	*Pneumocystis jirovecii* pneumonia Viruses, fungi Bacterial pneumonia

[a]This table is not intended to provide a comprehensive list of immunologic disorders.

Infectious Complications of Immunodeficiency

Complications of Neutrophil Defects

Polymorphonuclear neutrophils (PMNs) are the primary phagocytic cells of the immune system. They play a key role in eliminating opsonized bacterial and fungal pathogens through release of proteolytic enzymes and reactive oxidant species. This function may be impaired through abnormalities in cell adhesion, cell signaling, cell number, granule function or formation, and intracellular killing.[1,2]

Chronic Granulomatous Disease

The most common PMN disorder is chronic granulomatous disease (CGD), with an estimated prevalence of 1 in 200,000 in the United States.[1,3] The primary defect in CGD is a loss of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase function. Chronic granulomatous disease exists in X-linked and autosomal recessive forms, depending on which gene coding for the NADPH oxidase complex is mutated; the X-linked form is more common. Loss of NADPH oxidase activity leads to a markedly reduced oxidative burst following phagocytosis. Polymorphonuclear neutrophils from patients with CGD can phagocytose bacteria but cannot kill them. The most common organisms that cause pulmonary infections in CGD are *Aspergillus* species, *Staphylococcus aureus, Burkholderia cepacia* complex, *Nocardia* species, and *Serratia marcescens*.[1]

Patients with CGD present with atypical or unusually severe lymphadenitis, skin abscesses, pneumonia, or osteomyelitis secondary to infections with the aforementioned agents. Hepatosplenomegaly due to non-cirrhotic portal hypertension is common as well. In addition, patients with CGD often develop granulomas involving a number of different organs, including the bladder, gastrointestinal tract, and lungs. Chronic granulomatous disease colitis can be mistaken for Crohn disease. Data from a national registry of 368 patients with CGD in the United States and 268 patients with CGD followed at the National Institutes of Health (NIH) provide considerable insight into the pulmonary complications of CGD.[4,5] Eighty percent of the patients in the US registry and 87% in the NIH cohort have had pneumonia at least once. *Aspergillus* was the most common causative organism, responsible for 41% to 55% of pneumonias. In the US registry, *Staphylococcus* species caused 12% of pneumonias. *Burkholderia cepacia* was the third most common cause of pneumonia (8%) but the second most common cause of death (18%). Other pathogens reported to cause pneumonia in these patients include *Nocardia,* mycobacteria, and gram-negative bacteria. Pulmonary abscesses also occur frequently in patients with CGD. Sixteen percent of patients in the registry had a lung abscess. Of those, the most common organism isolated was *Aspergillus* (23%), although *Nocardia* species, *B cepacia,* and *Staphylococcus* species can also cause abscesses.[4]

Aspergillus pneumonia with or without dissemination was the most common cause of death in patients with CGD, causing 35% of deaths in the US registry. Fungal infection was also the most common cause of mortality in the NIH cohort, with an *Aspergillus*-specific mortality rate of 9%. It should be noted, however, that the US registry was published prior to a large study showing that antifungal prophylaxis was effective and thus leading to widespread use of azoles for *Aspergillus* prophylaxis.[6] Accordingly, the updated NIH cohort showed that the overall rate of infections has decreased fourfold and the age at death has increased by almost 15 years since 1991. These improvements in morbidity and mortality have been attributed to effective infection prophylaxis, including the use of azole antifungals, trimethoprim-sulfamethoxazole, and interferon-gamma.[1,6,7]

In the active evaluation of respiratory infection in a patient with CGD, determination of the infecting microbe is still of great importance, as prophylaxis regimens may affect antimicrobial sensitivity patterns. Additionally, consultation with an immunologist and stem cell transplant physician may be beneficial, as stem cell transplant is an option for selected CGD patients.

Other Neutrophil Disorders

Other PMN disorders include hyper-immunoglobulin (Ig) E syndrome (also known as Job syndrome) and Chediak-Higashi syndrome.[1] Hyper-IgE syndrome is a rare disorder caused by heterozygous mutations in an intracellular signaling protein (STAT3). Patients typically present with characteristic facial features, recurrent skin infections, and extremely high serum IgE levels (typically >2,000 ku/L). A hallmark feature of pulmonary infection associated with the hyper-IgE syndrome is the formation of pneumatoceles and bronchiectasis. Although *S aureus* is the most common organism causing pneumonia in those with hyper-IgE syndrome initially, after pneumatoceles and bronchiectasis are present, these patients are predisposed to gram-negative pulmonary infections (frequently *Pseudomonas*), mold infection (typically *Aspergillus*), and nontuberculous mycobacteria. Alterations to STAT3 function affects maturation of Th17 cells and neutrophil chemotaxis. These defects are thought to confer the pattern of infection susceptibility seen in this condition. These infections are the main source of morbidity and mortality for these individuals. Chediak-Higashi syndrome is an autosomal recessive disorder resulting from mutations in a lysosomal protein transport gene. Patients with Chediak-Higashi syndrome have multiple abnormalities, including reduced PMN phagocytosis and chemotaxis. In general, pulmonary complications in these disorders are pneumonias but not pneumatoceles or bronchiectasis.

Complications of B Lymphocyte Disorders

B lymphocytes are the only source of Ig, or antibody.[8] There are 5 different Ig isotypes: IgM, IgG, IgA, IgD, and IgE. B cells initially express only surface IgM and IgD but, with appropriate T-lymphocyte help, they will switch to making other isotypes. Immunoglobulins play a key role in the opsonization and clearance of encapsulated bacterial organisms. Thus, patients with B-cell deficiencies are prone to infection with these organisms, primarily *Streptococcus pneumoniae* (pneumococcus) and *Hemophilus influenzae.* In contrast, because T-cell function is intact, patients tend to have normal defenses against viruses, fungi, and mycobacteria. Because maternal IgG crosses the placental barrier, babies with B-cell disorders receive passive protection from infection for the first 3 to 6 months after birth. After this age, patients will present with recurrent bacterial infections of the middle ear, sinuses, and lungs. Complications such as mastoiditis are common. Sepsis and osteomyelitis may also be seen.[8]

X-linked Agammaglobulinemia

The most severe forms of B-cell disorders arise from defects in B-cell development, leading to virtual absence of circulating B cells. Of this group, X-linked (Bruton) agammaglobulinemia (XLA) is the most common. The molecular defect in XLA is due to mutations in the Bruton tyrosine kinase (BTK) gene.[8] Absence of BTK results in a block in B-cell maturation at the pre–B-cell stage. Thus, patients with XLA have essentially no circulating B cells and make no antibody to antigenic stimulation/immunization. Pulmonary infections are very common in XLA, mainly due to *S pneumoniae* and *H influenzae*.[9] In contrast to other B-cell disorders, patients with XLA can develop *Pneumocystis jirovecii* pneumonia (PCP).[8] The reason for this is unclear, although it may be related to the role of B cells as antigen-presenting cells. Alternatively, it may be that loss of BTK function leads to subtle defects in cellular immunity.

Common Variable Immunodeficiency

Common variable immunodeficiency (CVID) is the name given to a heterogeneous group of disorders characterized by varying degrees of hypogammaglobulinemia with or without other abnormalities of T-cell function.[8] The prevalence of CVID is estimated to be 1 in 50,000 to 1 in 200,000 individuals.[10] Patients with CVID usually have normal numbers of B cells, but the function of these cells is impaired. Other immunologic abnormalities that can be seen in CVID include impaired lymphocyte proliferative response to antigens, deficiency of antigen-primed T cells, increased macrophage activation, and reduced production or expression of cytokines. Common variable immunodeficiency can frequently occur in older children or adults following

a viral infection; it is sometimes referred to as *acquired hypogammaglobulinemia*. Although patients with CVID may have subtle defects in T-cell function, they usually do not develop opportunistic infections. More commonly, patients with CVID are prone to recurrent bacterial infections, generally of the sinopulmonary tract. Because the condition may present in later childhood and the diagnosis may be delayed, many of these patients have bronchiectasis at the time of presentation.[10,11] Patients with CVID can also manifest a noninfectious, interstitial lung disease termed *granulomatous-lymphocytic interstitial lung disease,* which is characterized by non-necrotizing granulomas and lymphoid hyperplasia within the lung parenchyma. The development of granulomatous-lymphocytic interstitial lung disease portends a worse prognosis in the 10% to 15% of patients who manifest this condition.[12]

Immunoglobulin A Deficiency

Immunoglobulin A deficiency is the most common antibody deficiency, with an approximate incidence of 1 in 400 to 1 in 3,000 individuals, depending on the ethnicity of the population.[8] Most patients with IgA deficiency are asymptomatic, perhaps because of compensatory protection by IgG. Those who are symptomatic are at increased risk of gastrointestinal and sinopulmonary infections. Symptomatic IgA deficiency is often seen in association with IgG subclass deficiency.

Treatment Modalities

The introduction of intravenous Ig (IVIG) replacement therapy has had a significant effect on the morbidity and mortality of B-cell immunodeficiencies.[8,13,14] Both IVIG and the more recently introduced subcutaneous IgG (SCIG) are prepared from pooled plasma collected from a large number of donors. As a blood product, IVIG does carry a potential risk for pathogen transmission. However, improved purification protocols have rendered this risk extremely small.[14] Use of IVIG/SCIG therapy significantly reduces the incidence and severity of pneumonia and other respiratory tract infections in patients with XLA, CVID, and other antibody deficiency syndromes.[13] However, bronchiectasis can still develop in some patients in spite of IVIG/SCIG therapy[11,13] (**Figure 53-1**). Some patients may require concurrent treatment or prophylaxis with antimicrobial agents, but the risks of antimicrobial resistance and selection of resistant organisms should be taken into consideration.

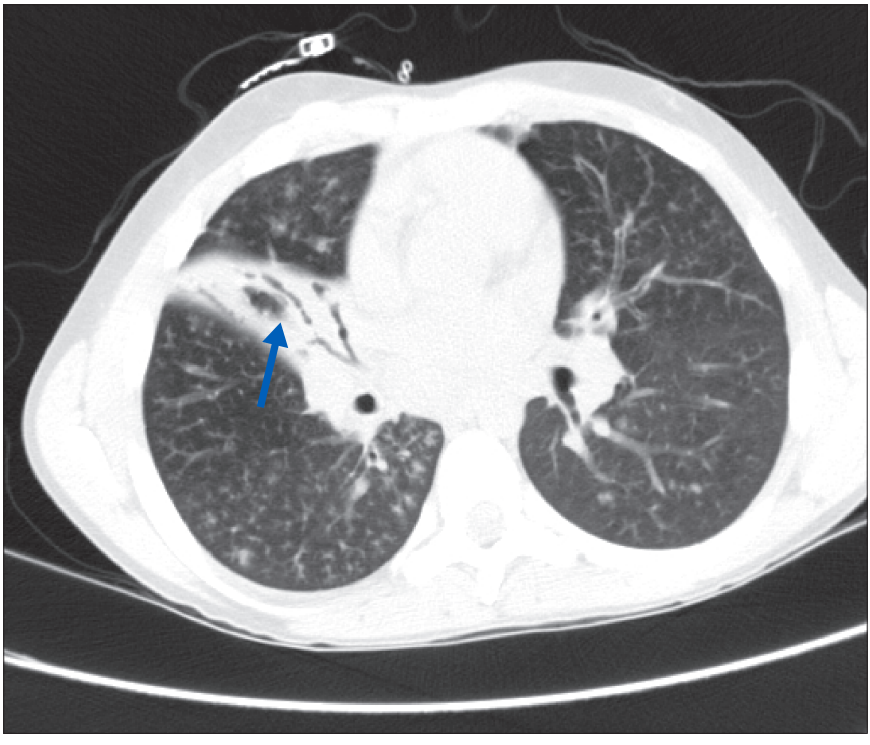


Figure 53-1. Chest computed tomography (CT) image from an 11-year-old girl with common variable immunodeficiency (CVID). This child was diagnosed with CVID at 3 years of age when she presented with chronic respiratory infections. Intravenous immunoglobulin therapy was started at that time. In the intervening years, she did not have acute episodes of pneumonia, but she was seen by a pulmonologist because of a 1-year history of increasing cough. A chest CT image was obtained. Consolidation and bronchiectasis of the right middle lobe can be seen (blue arrow).

Pulmonary Infections Associated With T Lymphocyte Disorders

T lymphocytes play important roles in coordinating the adaptive immune system and actively eliminating foreign pathogens.[15] Because of the multiple roles that T cells play in the immune system, impairment of their function may have profound consequences for immunity. T cells can be divided into multiple subclasses based on their cell-surface protein expression, gene expression, and function. Cytotoxic T lymphocytes (CTLs) usually express CD8 and are responsible for cell-mediated immune responses. Helper T (Th) cells usually express the cell surface receptor CD4 and are critical for B-cell activation and optimal antibody production. Helper T cells also coordinate the activity of CTLs. Regulatory T cells (Tregs) express CD4, CD25 (the alpha chain of the interleukin-2 receptor), and FOXP3, a forkhead transcription factor. Tregs are thought to play a vital role in autoimmune and allergic disease.[16] FOXP3 is critical for the development of Tregs, and loss of FOXP3

function results in immune dysregulation, polyendocrinopathy, enteropathy, and X-linked syndrome.[17] There are many other T-cell subsets that have recently been defined, but their role in primary immunodeficiency is not well defined at this time. Secondary T-cell defects associated with HIV infection are covered later in this chapter.

Severe Combined Immunodeficiency

Severe combined immunodeficiency (SCID) is the term used to identify the most severe forms of T-cell disorders. Severe combined immunodeficiency can result from a diverse array of genetic mutations that affect lymphocyte production, development, metabolism, or cell signaling.[15] Regardless of the underlying genetic defect, the immunologic consequence is near total loss of T-cell number or function. Because B lymphocytes and T lymphocytes develop from a single lymphoid lineage, many cases of SCID are also associated with absent B cells. In those cases with residual circulating B cells, the lack of T-cell help renders them nonfunctional.

The loss of T-cell function in patients with SCID leads to their being susceptible to opportunistic infections, such as PCP, fungi, and viruses. Patients with SCID tend to present early in infancy because of the severe loss of immune function. Pulmonary infections are a common initial presenting sign in SCID, and up to 67% of patients with SCID present with pulmonary disease at diagnosis.[18] In patients with pulmonary complaints at presentation, 60% present with a persistent pulmonary infiltrate and chronic cough, while the other 40% present with more acute symptoms of respiratory distress secondary to pneumonia. *Pneumocystis jirovecii* pneumonia is the most common cause of pneumonia and is associated with significant mortality (43%). Bacterial pneumonia can also occur, with *Klebsiella pneumoniae, S pneumoniae,* and *S aureus* being the most common pathogens isolated. Viral infections contribute to morbidity and mortality in these patients and can include parainfluenza, cytomegalovirus (CMV), adenovirus, and respiratory syncytial virus (RSV). In patients who are not treated with immune reconstitution (which includes bone marrow transplant, hematopoietic stem cell transplant, or gene therapy in selected conditions), pulmonary disease and failure to thrive are significant causes of morbidity and mortality. Subsequent pulmonary infection occurs in 80% to 100% of patients after initial diagnosis.[18]

The importance of early diagnosis of children with SCID cannot be overemphasized. Beginning in 2008 and concluding in 2018, all states in the United States have adopted a newborn screening (NBS) program for SCID. The screening assay quantifies T-cell receptor excision circles by polymerase chain reaction to estimate the number of naive T cells at birth. If below a specific threshold (determined by each state), these children are identified as potentially having SCID and referred to a tertiary care center for further

evaluation. This screening test does not identify children with a primary B-cell maturation defect, such as XLA.[19]

Besides SCID, immunodeficiency can also arise from other, less severe, defects in T-cell function. Because some degree of residual T-cell function persists in these other conditions, the severity of disease tends to be less than that of SCID. Often, these less severe conditions with T-cell defects are also identified by NBS for SCID because the initial T-cell receptor excision circle quantification will be low.[20] Early identification is preferable because pulmonary complications continue to be common in this group of patients. In rare cases, NBS for SCID may be falsely negative. In these instances, quantification of T cells may reveal the possibility of SCID at a later time. A high index of suspicion and early referral to a tertiary care center with immunologists and stem cell transplant physicians should be strongly considered in any infant with unusually severe, destructive, or difficult-to-treat infections.

Other T-Cell Disorders

DiGeorge Syndrome

DiGeorge syndrome results from errors in the formation of the third and fourth pharyngeal pouches during embryogenesis, resulting in hypoplasia or complete absence of the thymus and parathyroid glands.[15] Other midline structures may also be affected, such as the heart and great vessels, craniofacial bones and tissues, and upper limbs. The immunologic defect is due to thymic dysplasia and ranges from a severe depression of T-cell function in patients with no thymus (complete DiGeorge syndrome), to near-normal function in patients with mild thymic hypoplasia (partial DiGeorge syndrome). In contrast to patients with SCID or complete DiGeorge syndrome, patients with partial DiGeorge syndrome are not commonly infected with PCP. Bacterial pneumonia with gram-negative organisms is more commonly seen. Severe RSV infections have also been reported. Complete DiGeorge syndrome requires broad antimicrobial prophylaxis (similar to SCID) while awaiting thymus transplantation to correct the underlying immunologic defect.

Wiskott-Aldrich Syndrome

Wiskott-Aldrich syndrome (WAS) is an X-linked recessive T-cell disorder caused by mutations in the Wiskott-Aldrich syndrome protein (WASP) gene.[21] The classic clinical triad of WAS is thrombocytopenia, eczema, and recurrent bacterial infection. Although the exact function of WASP is still undetermined, loss of WASP function results in an inability to generate antibody to polysaccharide antigens. Patients with WAS are, therefore, susceptible to recurrent infections with bacteria that form polysaccharide capsules, such as *S pneumoniae* and *H influenzae.* Although the sites of infection tend to be the middle ear and sinuses, pneumonia can also be seen in this group of patients. Later in life, there is also an increased incidence of PCP.

Ataxia-Telangiectasia

Ataxia-telangiectasia (A-T) is a complex multisystem autosomal recessive syndrome with abnormalities of the nervous system, endocrine system, skin, liver, and immune system.[15] Immune dysfunction in A-T is variable and affects both T and B cells. Although A-T is classified as a T-cell immunodeficiency, B-cell dysfunction due to loss of T-cell help is the primary immune problem. Immunoglobulin A and IgG subclass deficiencies are commonly seen in patients with A-T. Pulmonary infections are a common complication in A-T and are a significant cause of mortality. Pneumonia in patients with A-T tends to be caused by bacteria, such as *S pneumoniae, S aureus*, *H influenzae, Mycoplasma pneumoniae,* and *Pseudomonas aeruginosa.* Respiratory syncytial virus and CMV can also cause lower respiratory tract infection in these patients, but fungi, mycobacteria, and PCP are rarely pathogens in this disease.[15] The underlying defect in A-T involves a defect in DNA repair, and patients with A-T are at high risk for the development of malignancy. In some patients with A-T, pulmonary lymphoma has led to cavitary lesions on chest radiographs that were mistaken for pneumonia.[22] It is, therefore, important to consider the possibility of malignancy when evaluating patients with A-T and pulmonary symptoms and to pursue an appropriate investigation.

Hyper-IgM Syndrome

Hyper-IgM (HIgM) syndrome is characterized by normal or elevated serum IgM levels with decreased or absent levels of IgG, IgA, and IgE.[15] Hyper-IgM syndrome exists in both an X-linked and autosomal recessive form. About 55% to 65% of the patients have the X-linked form that is caused by mutations in the gene for CD40 ligand (CD154), a T-cell surface molecule critical for induction of B-cell isotype switch. Because of the absence of CD154, B cells from patients with X-linked HIgM can only make IgM, with little or no production of other Ig isotypes. An autosomal recessive form also exists associated with a defect in CD40, the receptor for CD40 ligand. In addition, there are autosomal recessive forms that are caused by mutations in at least 3 different genes involved directly in B-cell isotype switch. Bacterial pneumonia is the most common pulmonary complication in HIgM syndrome, but PCP and other opportunistic infections are seen in the X-linked form and in CD40 deficiency, indicating that CD154/CD40 interaction also plays a role in T-cell innate immune cell interaction.

Noninfectious Pulmonary Complications of Immunodeficiency

In addition to impaired host defense, patients with immunodeficiency can also develop dysregulated immune responses.[23] Noninfectious pulmonary diseases that have been reported in association with immunodeficiency include interstitial lung disease, organizing pneumonia, and hypersensitivity pneumonitis.

The presumed mechanism for these disorders is that defects that result in an impaired ability to generate a protective adaptive immune response may also result in excessive inflammatory responses. Common variable immunodeficiency and A-T are the most common conditions associated with the aforementioned disorders,[8,15] although they have been reported in other immunodeficiencies.[24] Pulmonary and mediastinal adenopathy as well as lymphoma have also been reported in patients with antibody deficiency, cellular immune deficiencies, and DNA-repair defects. The hypothesized causes of the malignancy in these patients are susceptibility to Epstein-Barr virus infection, ineffective surveillance by dysfunctional natural killer cells and CTLs, and sensitivity to ionizing radiation. Any findings of mediastinal lymphadenopathy should be carefully evaluated for the possibility of a lymphoproliferative process. Graft-vs-host disease can also be seen in patients who have undergone a bone marrow transplant.[25]

Pulmonary Complications Associated With HIV Infection

Globally, HIV infection is the most common cause of acquired immunodeficiency.[26] HIV infects CD4-positive T helper (Th) cells, leading to their loss. As HIV infection progresses, patients have a near total depletion of CD4 T cells. The loss of Th cells impairs both CTL function and B-cell function.

Infectious Complications of HIV Infection

Pneumocystis jirovecii pneumonia is one of the most common complications of HIV[26,27] and may be the presenting feature in infancy. *Pneumocystis jirovecii* pneumonia infections in patients infected with HIV carry a high degree of morbidity and mortality.[26] Prophylaxis against PCP is an important part of HIV treatment and can be accomplished with either trimethoprim-sulfamethoxazole or inhaled pentamidine.

In endemic areas of developing nations, *Mycobacterium tuberculosis* has emerged as a major pulmonary complication and cause of death in patients infected with HIV.[26] Tuberculosis infections tend to be more severe and difficult to treat in patients infected with HIV. These infections can also be paucibacillary, making it harder to diagnose and detect antimicrobial resistance. Non-tuberculous mycobacteria, such as *Mycobacterium avium* complex (MAC), can also cause disseminated disease in adults with HIV. In contrast, the incidence of severe pulmonary MAC disease is less in children infected with HIV.[28]

Respiratory viral infections are another common complication in HIV infection. Respiratory syncytial virus, influenza A and B, and parainfluenza viruses can all cause severe lung disease in infants infected with HIV.[29] Cytomegalovirus can also cause pulmonary disease. However, because CMV is often shed asymptomatically, the diagnosis of true pneumonitis should rest on evidence

of systemic dissemination (eg, retinitis or hepatitis) or demonstration of viral inclusion bodies in lung biopsy specimens.

The other major group of respiratory pathogens in individuals infected with HIV is fungi. Histoplasmosis infection is rare, but, when present, it occurs as disseminated disease that often includes reticulonodular, miliary, or lobar infiltrates. It can often progress to septic shock and death if untreated. *Cryptococcus* and *Coccidioides* species can also cause pulmonary disease. Pulmonary aspergillosis is rare and presents as invasive pulmonary disease rather than as aspergilloma; this can be life-threatening, with poor prognosis despite antifungal therapy.[30]

Although patients with HIV primarily experience opportunistic infections as a consequence of their loss of cellular immunity, bacterial infections are also common, especially in children.[27,28,30] These occur despite normal or even elevated Ig levels in patients with HIV, because the loss of CD4-positive Th cells results in a failure to generate effective specific antibody titers. *S pneumoniae* is the most common cause of bacterial pneumonia in this patient population. Other common organisms include *S aureus*, group A *Streptococcus, Escherichia coli, P aeruginosa, H influenzae,* and *Salmonella.*

Noninfectious Complications of HIV Infection

Dysregulation of the immune system is another consequence of HIV infection, leading to an increased incidence of noninfectious disorders of the lung.[26,27] In children, the most common noninfectious pulmonary complication is lymphocytic interstitial pneumonitis (LIP). The precise pathogenesis of LIP is unknown. It is thought to represent a dysregulated immunologic response to Epstein-Barr virus infection. Between 30% and 40% of children who were perinatally infected will have LIP, with an average age of 2.3 years at presentation. Typically, patients with LIP present with gradual onset of cough and dyspnea. Generalized lymphadenopathy and clubbing are associated clinical findings. The chest radiograph demonstrates diffuse reticulonodular densities, frequently with hilar adenopathy. Lymphocytic interstitial pneumonitis is usually quite responsive to systemic corticosteroid therapy, which is the first line of treatment for this condition. The condition may recur, requiring repetitive courses of oral corticosteroids.

In addition to LIP, a nonspecific interstitial pneumonitis can also occur in patients infected with HIV, although this is less common in children. Nonspecific interstitial pneumonitis is thought to result from localized CTL activity against HIV-infected cells in the lung parenchyma. Therefore, it is more commonly seen early in HIV infection, when there is still some residual CD4-positive T-cell activity present. However, it can occur at any stage of the disease.

Pulmonary Complications Related to HIV Therapy

Combined antiretroviral therapy against HIV infection was introduced in the mid-1990s and has had a dramatic effect on the prognosis and clinical course of HIV infection.[26] One result of increased survival has been the increased incidence of chronic lung diseases, such as bronchiectasis.[31] The restoration of immune function in patients with previously long-standing immunodeficiency has also led to unexpected complications resulting from either exuberant inflammatory responses or unmasking of latent opportunistic infections.[32,33] As immune function is restored, there is an increased inflammatory response against underlying latent mycobacterial infections (*Mycobacterium tuberculosis* and MAC). Highly active antiretroviral therapy may also be associated with reactivation of latent PCP, leading to acute respiratory failure. Noninfectious complications that have been reported with combined antiretroviral therapy include a sarcoid-like syndrome, hypersensitivity pneumonitis, and pulmonary hypertension.[33,34] Notably, newer antiretrovirals (integrase strand inhibitors) have fewer reported hypersensitivity complications. Although most published reports have focused on adult patients, it is likely that this same phenomenon will be seen in children as combined antiretroviral therapy increasingly becomes the standard of care in HIV treatment.

Pulmonary Evaluation of the Patient With Immunodeficiency

The approach to evaluating a patient with immunodeficiency is summarized in **Box 53-1.** The evaluation begins with a thorough history and physical examination. The history should focus on symptoms of chronic infection or bronchiectasis. The patient or patient's parents should be questioned about the presence of cough and sputum production. However, patients with impaired host responses often do not feel as sick as they are, and they are often much less symptomatic than their degree of infection would cause in a normal host. Symptoms of wheezing may suggest an asthma or reactive airways disease component. Elements of the physical examination of particular importance include the patient's height and weight, chest examination, and extremity examination. The height and weight provide important information about the patient's nutritional status, which may be compromised in the setting of chronic pulmonary disease. Auscultation of the chest is important to identify areas of localized crackles or wheezes. The presence of digital clubbing on extremity examination is an indication of underlying bronchiectasis or hypoxemia. Other important aspects of the physical examination include evidence of skin infections, absence of lymphoid tissue (eg, tonsils and lymph nodes), and evidence of chronic or frequently recurring otitis media.

Radiography is an important tool in the evaluation of pulmonary disease in patients with immunodeficiencies. Plain chest radiographs can reveal areas of atelectasis or infiltrate. Although large areas of bronchiectasis can be seen by plain radiographs, high-resolution computed tomography is a more sensitive tool for the detection of early or mild bronchiectasis.[35,36] Computed tomography is also helpful for delineating lesions, such as pulmonary abscesses or lymph node pathology.

The results of pulmonary function tests in immunodeficient patients depends on the underlying pulmonary pathology. Patients with bronchiectasis demonstrate an obstructive pattern. (See Chapter 6, Pulmonary Function Testing.) Patients with interstitial lung processes will have a restrictive pattern, and the diffusion capacity may also be decreased. Pulmonary function tests can be helpful in establishing the severity of disease and in tracking disease progression. Pulmonary function tests can also provide objective assessment of response to medications, such as bronchodilators.

Bronchoscopy can be important for acute complications as well as for chronic conditions. For patients who present with acute pulmonary symptoms, bronchoscopy with bronchoalveolar lavage (BAL) can help in the diagnosis of infections such as PCP. For patients with bronchiectasis who cannot expectorate sputum, BAL can provide information about the organisms colonizing the lower respiratory tract. Transbronchial biopsy can also be performed to identify fungal or viral infections. Bronchoscopy can also be helpful in studying the airway anatomy, especially in patients in whom there is concern

Box 53-1

Evaluation of the Patient With Immunodeficiency

History

- Delayed umbilical cord separation
- History of infections
- Sites and etiologies of infections

Physical Examination

- Vital signs
  - Tachypnea
  - Head, eyes, ears, nose, throat
- Presence of tonsils
- Chest
  - Crackles
  - Wheezes
- Extremities
  - Lymphadenopathy
  - Clubbing

Radiographic Imaging

- Chest radiograph
- High-resolution computed tomography
  - Evidence of bronchiectasis
  - Presence of thymus

Pulmonary Function Testing

- Restrictive vs obstructive pattern
- Diffusion defects
  - Pulse oximetry or overnight pulse oximetry
  - Carbon dioxide levels via end-tidal carbon dioxide or blood gas

Bronchoscopy vs Transthoracic Needle Aspiration/Biopsy

for compression of the bronchi by enlarged reactive lymph nodes. In most cases, flexible fiberoptic bronchoscopy can be safely performed under moderate or deep sedation on this group of patients. It is important to be aware that BAL may not provide microbiological diagnosis, especially in fungal disease, but every attempt should be made to obtain BAL samples prior to the initiation of antimicrobial treatment. Percutaneous needle biopsy is another safe alternative and it has much higher diagnostic yield in patients with diseases like CGD.

Treating Pulmonary Complications in Children With Immunodeficiency

Treatment of the underlying immune defect is the best way to prevent pulmonary complications, but since this may require bone marrow or hematopoietic stem cell transplantation, temporizing measures are critical. For patients with SCID or other T-cell disorders, bone marrow transplantation, hematopoietic stem cell transplantation, or thymus transplantation can result in complete correction of the immune defect depending on the specific disorder.[15] Antibody deficiency syndromes can be treated with IVIG/SCIG replacement therapy with or without antimicrobial prophylaxis.[8,14] Combination antiretroviral therapy has had a dramatic effect on survival and the rates of infection in patients with HIV.[26] It is likely that as our understanding of the molecular and cellular basis of congenital and acquired immunodeficiency increases, more therapies aimed at correcting the underlying defect will become available.

Although specific therapy for immunodeficiencies is available, not all patients are candidates for bone marrow transplantation, and other therapies may not lead to complete absence of pulmonary complications. In this situation, antibiotic prophylaxis can be used to reduce the incidence of pulmonary infections. The choice of antibiotic depends on the pathogens most likely to be involved in the underlying disease process. For CGD, prophylaxis with trimethoprim-sulfamethoxazole covers all their bacterial pathogens, whereas for T-cell immunodeficiencies and HIV infection, PCP prophylaxis is the major concern. Itraconazole prophylaxis for *Aspergillus* in CGD has been used effectively in many centers.[37]

Many patients with immunodeficiency still develop bronchiectasis as a result of either delayed diagnosis or continued infection despite treatment. This is especially common in patients with B-cell disorders, such as XLA and CVID. (See Chapter 17, Bronchiectasis, for treatment information.) Unfortunately, many of the pulmonary changes that occur with immunodeficiency will continue to progress despite improved management of respiratory infections.[2,12]

For patients with irreversible or progressive respiratory failure, lung transplantation is an option. Lung transplantation has been performed on patients with immunodeficiency, but there are limited data on their clinical outcomes.[11,38]

Lung transplantation is an arduous process for patients and is associated with numerous short-term and long-term complications. Any decision to proceed with lung transplantation must be made after a careful and thorough consideration of the risks and potential benefits.

When to Refer

Consider referring patients with immunodeficiency to the pulmonologist if they have persistent respiratory symptoms, recurrent severe pneumonia, or signs of chronic lung disease (eg, baseline tachypnea, abnormal breath sounds, or clubbing). Conversely, patients presenting with possible signs of immunodeficiency, including pulmonary manifestations, should be referred to a tertiary care center with immunology and stem cell transplant services. Preliminary laboratory testing to consider would include complete blood cell count with differential, T- and B-cell enumeration by flow cytometry, IgG, IgA, IgM, and IgE levels, IgG titers to tetanus and pneumococcal vaccines, and assessment of HIV status (**Table 53-2**). It is important to keep in mind that these test results may appear to be "normal," even in the setting of a true underlying immunodeficiency condition. Any additional workup or more specific testing should be undertaken by an immunologist. In all cases, a multidisciplinary team approach is paramount for the appropriate management of these complex patients.

Table 53-2. Laboratory Testing and Associated Category of Immunodeficiency[a]

Laboratory Test	Category of Immunodeficiency	Example Conditions
Complete blood cell count with differential Peripheral smear	Innate immune deficiencies	Congenital neutropenia, leukocyte adhesion deficiency, Chediak-Higashi syndrome
T- and B-cell quantification HIV serologies and polymerase chain reaction	T-cell deficiencies	Severe combined immunodeficiency, combined immunodeficiency, Wiskott-Aldrich syndrome, ataxia telangiectasia, DiGeorge syndrome HIV/AIDS
	B-cell deficiencies	X-linked agammaglobulinemia
Quantitative immunoglobulins and vaccine titers	Humoral immune deficiencies	X-linked agammaglobulinemia, common variable immunodeficiency, specific antibody deficiency, immunoglobulin A deficiency Immunoglobulin E level > 2,000 kU/L could be a sign of hyper-IgE syndrome

[a] Not intended to be a comprehensive list. Additional workup should involve consultation with an immunologist.

key points

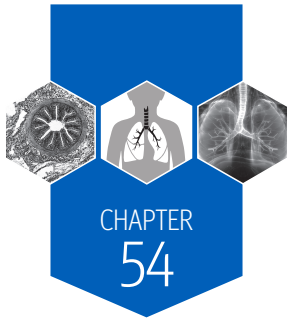
- Pulmonary complications are common in patients with immunodeficiency, and pulmonary infections are frequently the initial presenting sign.
- It is important to identify the microbe so that therapy can be directed aggressively to the appropriate organism.
- Defects in different parts of the immune system result in distinctive patterns of infection.
- Although IVIG and antibiotics can help prevent severe infections, bronchiectasis can often still develop in patients with immunodeficiency.
- Noninfectious pulmonary diseases, such as interstitial lung disease, can also develop.
- The primary care provider should be aware of the presenting signs of primary immunodeficiency and evaluate patients appropriately.
- The primary care provider should maintain close follow-up of patients with immunodeficiency and evaluate their respiratory status on a regular basis or if signs and symptoms of lung disease develop.

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Pulmonary Complications of Neuromuscular Disorders

Girish D. Sharma, MD, FAAP, FCCP

Introduction

Neuromuscular disorders (NMDs) may be associated with a gradual loss of muscle function over time, and children with these disorders are at risk of developing clinically significant respiratory morbidity from recurrent respiratory infections and chronic respiratory insufficiency.[1–4] However, other groups of nonprogressive NMDs, such as cerebral palsy or static encephalopathy, may lead to the development of pulmonary complications requiring aggressive airway clearance, assisted ventilation, or secretion management. The approach for the evaluation and management described in this chapter is also applicable to such disorders. Knowledge of the expected course of the NMD is helpful in planning the management of pulmonary complications (**Table 54-1**).

Loss of respiratory muscle strength that leads to ineffective cough and decreased ventilation may result in atelectasis, decreased lung volumes, chronic respiratory insufficiency, and respiratory failure.[1] In some children, muscle weakness may lead to oropharyngeal incompetence,[5,6] gastroesophageal reflux, feeding problems, and malnutrition (**Figure 54-1**).[7,8] These complications may be prevented or their onset delayed by careful serial assessment of respiratory function, blood gas monitoring, and investigations to diagnose and treat associated problems, such as obstructive sleep apnea (OSA),[9,10] oropharyngeal aspiration, gastroesophageal reflux, pneumonia, and asthma.[11–13]

Table 54-1. Natural History of Neuromuscular Disorders (Without Disease-modifying Treatments)

Course	Example of a Disorder	Remark
Progressive	Duchenne muscular dystrophy	Rate of progression may vary from patient to patient
	Spinal muscular atrophy	Severity varies according to type
Variable	Congenital fiber type disproportion myopathy	Some patients may show improvement with age
Slowly progressive	Post-polio syndrome	—
Possibility of reversibility	Guillain-Barré syndrome	—
Rapidly progressive	Amyotrophic lateral sclerosis	Adult population
	Acute flaccid myelitis	Pediatric population

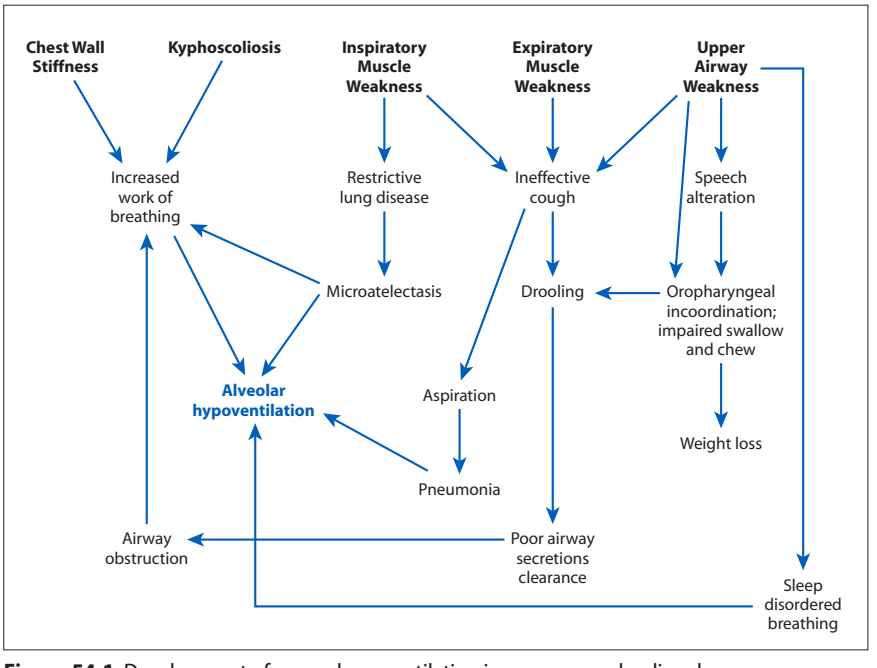


Figure 54-1. Development of severe hypoventilation in neuromuscular disorders.

CASE REPORT 54-1

A 12-year-old boy with Duchenne muscular dystrophy was referred to the pulmonary clinic for evaluation and clearance for Achilles tendon release surgery. The muscular dystrophy was diagnosed when the patient was 3 years old and underwent examination for delayed motor milestones, frequent falls, and inability to stand. The muscle weakness has been progressive, and he has used a wheelchair for the last few weeks. The physical examination results were remarkable for a weak cough and reduced air exchange during auscultation of the chest, and the pulmonary function test results showed evidence of a mild restrictive defect.

Pathophysiological Characteristics of Respiratory Impairment in Patients With NMDs

Knowledge of normal respiratory function and control is essential to understand the pathophysiological characteristics of respiratory impairment in NMDs. Three basic components of respiratory control[14] are as follows:

- Sensors, which gather afferent information: central chemoreceptors located in the medulla, carotid, and aortic bodies and the stretch receptors in the lungs
- Respiratory center in the brainstem, which acts as the central controller by processing afferent impulses and sending out efferent impulses to the periphery
- Effectors, which are the respiratory muscles responsible for ventilation or coughing

Respiratory control occurs subconsciously. The cortex can temporarily override the automatic nature of this mechanism if voluntary control is desired. A motor unit comprises an anterior horn cell, its peripheral nerve axon, the neuromuscular junction, and the muscle fibers it innervates.

One way of explaining the pulmonary involvement in a patient with an NMD is to use the paradigm of a respiratory pump (respiratory muscles and central drive) working against pulmonary mechanics (lung and chest wall compliance, airway characteristics, and frictional forces). Adequate ventilation requires a balance between these 2 components; however, muscle weakness due to an NMD tips the balance, resulting in pulmonary complications caused by inadequate ventilation, impaired cough, and airway clearance.

Neuromuscular disorders can involve anterior horn cells, peripheral motor nerves, and muscle fibers. Patients with NMDs often do not report dyspnea until the diaphragm is involved.[15] Diseases affecting the muscles of respiration or their nerve supply include poliomyelitis, Guillain-Barré syndrome, myasthenia gravis, muscular dystrophies, and spinal muscular atrophy (SMA).

Young children with NMDs have high chest wall compliance normalized to body weight.[16] Therefore, the chest wall deforms during tidal breathing, resulting in inefficient breathing[17] that predisposes the child to developing atelectasis and chest deformities. A combination of lung compliance reduced due to generalized and widespread atelectasis (increased elastic load on the pump) and chest wall deformity due to reduced chest wall compliance results in increased work of breathing and chronic respiratory insufficiency. Reduced lung stretch because of suboptimal expansion, in conjunction with chest wall deformities, may also result in reduced lung growth.[18]

Tests of respiratory muscle strength, such as maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP), can be used to assess respiratory pump function. Forced vital capacity (FVC) and fractional lung volumes are the result of interplay between respiratory pump and the load and can be used to monitor the progress of patients with NMDs.

Patients with extreme muscle weakness due to an NMD may not be able to show the normal response to hypoventilation in the form of increased tidal volume but may have tachypnea. Inspiratory muscle weakness leads to chest wall stiffness and restrictive lung disease and contributes to ineffective cough and microatelectasis. Expiratory muscle weakness results in ineffective cough, inadequate airway clearance, aspiration, pneumonia, and alveolar hypoventilation. Upper airway muscle involvement results in oropharyngeal incompetence, difficulties with swallowing and chewing, speech alteration, and sleep-disordered breathing (SDB). In addition to muscle weakness due to NMDs, musculoskeletal deformities, such as kyphoscoliosis, contribute to restrictive lung disease. These consequences are summarized in **Box 54-1**.

Box 54-1

Consequences of Compromised Respiratory Muscle Function

- **Poor clearance of lower airway secretions because of impaired cough**
- **Hypoventilation during sleep**
- **Recurrent infections that exacerbate muscle weakness and impair the integrity of the lung parenchyma**
- **Chest wall underdevelopment in a growing child**

Clinical Manifestations

The consequences of NMDs depend on the stage of the disorder. Most of the disorders are progressive, with resultant pulmonary and nutritional issues. The major findings discovered by means of history and physical examination are detailed in **Box 54-2**.

Box 54-2

Pulmonary and Associated Consequences of Neuromuscular Disorders

Pulmonary
- Weak and ineffective cough
- Tachypnea, respiratory distress, retractions, cyanosis
- Recurrent respiratory infections and pneumonia (secondary to aspiration)
- Restrictive lung disease
- Chronic respiratory insufficiency and failure

Sleep
- Snoring, irregular breathing, apneic episodes, nocturnal awakening
- Sleep-disordered breathing
- Daytime somnolence, fatigue

Nutritional
- Difficulty in chewing, swallowing
- Oropharyngeal incompetence (nasal regurgitation), aspiration
- Malnutrition
- Weight loss
- Drooling

Others
- Speech alteration, weak voice
- Musculoskeletal deformities, scoliosis

Evaluation and Anticipatory Guidance

In a patient with an NMD, in addition to the usual history and physical examination, attention should be given to the strength and efficacy of cough, speech alteration (weak, nasal), drooling, feeding difficulties (feeding with interruptions, choking, coughing, gagging, and nasal regurgitation), weight loss, and a history of recurrent respiratory infections. Arm muscle weakness may interfere with the patients' ability to feed themselves. A history suggestive of SDB (snoring, apnea, awakening, daytime somnolence) will help the physician decide which investigations, such as a sleep study, are necessary. The physical examination should include asking the patient to cough to assess the cough strength clinically and looking for breathing patterns, signs of respiratory distress, tachypnea, paradoxical thoracoabdominal movements, and cyanosis.

Pulmonary Function Tests

Indications for pulmonary function tests (PFTs) include the following:

- Evaluating the patient's respiratory status at the time of diagnosis
- Monitoring the progression and course of pulmonary limitation
- Evaluating during pulmonary infections
- Evaluating before surgical procedures
- Providing an assessment of prognosis

Because PFTs require the patient's voluntary participation, they are of limited use in children younger than 6 years. In such patients, clinical observation for work of breathing, respiratory rate, paradoxical thoraco-abdominal movements, and cyanosis may provide useful information. Infant lung function tests, including tidal flow-volume loop, partial flow-volume curves, raised-volume rapid thoracic compression, and infant whole-body plethysmography, are available in specialized centers.[19–21]

Forced Vital Capacity

During the FVC maneuver, the patient takes a maximum breath and, depending on the effort, fills the lungs up to the total lung capacity and then forcefully exhales to the maximum. The total volume of air expelled during forced exhalation after maximal inspiration is FVC. Some physicians measure vital capacity with the patient sitting, supine, lying on one side, or wearing a thoracolumbar stabilizing device, which may produce more realistic information. A greater than 25% decrease in FVC from sitting to supine may indicate that diaphragmatic weakness is out of proportion to chest wall muscle weakness.[22] A supine change in lung function has been correlated with chronic respiratory failure in patients with myotonic dystrophy.[23] Seated FVC has been proposed as the primary pulmonary outcome measure for tracking the natural history of pulmonary progression in Duchenne muscular dystrophy (DMD) and for assessing the effect of new therapies. Forced expiratory volume in 1 second, MIP, MEP, cough peak flow (CPF), peak expiratory flow rate, and sniff nasal inspiratory pressure are considered secondary end points, pending further validation.[24]

Peak Expiratory Flow Rate and Cough Peak Flow

Muscle weakness due to NMDs results in reduced values for peak expiratory flow.[25] The use of CPF can minimize effort-related variation. Thus, in patients with neuromuscular weakness, CPF is a better and more reliable measurement of expiratory muscle strength. Cough peak flow is measured by using a peak flow meter with a mask attached. Cough peak flow may be measured in the primary care physician's office, patient's home, or pulmonologist's office by asking the patient to cough in it while using maximal expiratory force. This inexpensive, simple device monitors expiratory muscle strength. The patient

can maintain a journal with weekly or monthly readings. Cough peak flows correlate directly to the ability to clear secretions from the respiratory tract,[26] and values lower than 160 L/min have been associated with ineffective airway clearance.[27] An expiratory CPF rate of 270 L/min has been used to identify patients who would benefit from assisted cough techniques. A 2020 study of CPF highlighted lower values in children,[28] revealing a need to revise the guidelines.

Assisted CPF

In assisted CPF, the patient deeply inhales successive tidal breaths without exhaling (air stacking), then coughs while an abdominal thrust is applied. The CPF is measured with a peak flow meter. Because the air stacking requires patent glottis function and adequate glottis closure, the difference between assisted and unassisted CPF can be used to measure glottic integrity, which may be affected if there is bulbar muscle involvement or weakness.

Forced Expiratory Volume in One Second

In patients with an NMD and respiratory muscle weakness, FEV_1 is reduced in proportion to FVC. Thus, the FEV_1/FVC ratio remains normal. A ratio of FEV_1/FVC less than 70% predicted suggests an obstructive process that may coexist with the restrictive disorder.

Respiratory Muscle Strength

Maximal and minimal inspiratory pressure are measured while the patient inhales or exhales maximally against a closed shutter; the pressure measured is the composite of pressure generated by the inspiratory muscles and the elastic recoil of the lung and the chest wall.[29,30] The MIP and MEP are the most sensitive indicators of decreased respiratory muscle strength. However, investigators have found wide interindividual variability in the inspiratory/respiratory muscle function in children, and they have attempted standardization.[31–33]

Sniff Nasal Inspiratory Pressure

In the sniff nasal inspiratory pressure test, a pressure transducer is placed in the nostril, which is sealed using a plug while the patient sniffs maximally through the contralateral nostril from functional residual capacity.[30] The maneuver can be performed easily in children with NMDs and used for monitoring their progress.[34]

Measurement of Gas Exchange

Hypoventilation leading to hypercapnia occurs much earlier than hypoxemia. Therefore, a low pulse oximeter reading is a late finding and suggests respiratory insufficiency. Pulse oximetry results and carbon dioxide levels should be evaluated with the patient awake at least annually in conjunction with other tests. Capnography is ideal for this purpose. If capnography is not available, a venous blood gas or capillary gas test should be performed to assess for

alveolar hypoventilation. Nocturnal transcutaneous carbon dioxide measurement can be used to identify patients with hypoventilation at risk for subsequent need of home mechanical ventilation.[35]

Choice of Pulmonary Function Test

Choice of PFT depends on the patient's age and disease severity. Most children with severe manifestations of SMA may be too weak or too young to perform PFTs. Therefore, the most useful evaluation of respiratory muscle function may be observation of cough ability.[2] The MIP, MEP, and CPF tests can be used in older patients and those who have relatively mild disease but are wheelchair users to monitor their respiratory muscle function. Older patients and those with still milder disease (those able to walk) may be able to perform PFTs and respiratory muscle function tests.

Palliative and End-of-Life Care

Emerging therapies showing promising results in the treatment of NMDs include dystrophin replacement therapies, anti-inflammatory agents, ataluren for stop codon read-through, eteplirsen for exon skipping for eligible patients with DMD,[36,37] gene therapy, antisense oligonucleotides, and splicing modifiers for SMA and other conditions.[38] However, most patients with NMDs continue to have a progressively worsening course; therefore, supportive and palliative care to improve quality of life is critical.

Ventilatory and palliative care options should be discussed early and before complications requiring such interventions occur. Quality-of-life judgments should be made with the informed participation of the patient and family.[1] All long-term treatment options, including invasive and noninvasive mechanical ventilation, should be discussed even when the treating physician predicts a poor quality of life with long-term ventilation.[39] Such options must be presented in an open, fair, and balanced manner. End-of-life directives established by the patient, family, and health care team must be clearly documented and must be available in case of an emergency. Patients choosing to forgo long-term ventilation should be provided with palliative care, which may include management of pain and dyspnea and attending to the psychosocial and spiritual needs of patients and their families.

Nutrition

Patients with NMDs may have feeding and swallowing problems because of bulbar dysfunction and can develop complications such as aspiration pneumonia. Gastrointestinal dysfunction can lead to constipation, delayed gastric emptying, and gastroesophageal reflux.

Ideal body weight percentage and body mass index should be evaluated, and the family should be counseled accordingly. Regular follow-up and evaluation

by a nutritionist are indicated. Clinical evaluation for oropharyngeal incompetence and confirmation with studies such as a videofluoroscopic swallowing study should be considered. Patients should be evaluated for need of supplemental nutrition.

Cardiac Evaluation

Cardiac involvement may be due to cardiomyopathy, such as that in patients with DMD. Chronic respiratory insufficiency may result in pulmonary hypertension or arrhythmia. Therefore, when it is clinically indicated, the patient should be evaluated by a cardiologist who may order an electrocardiogram, an echocardiogram, and medications, as well as regular follow-up appointments.

Sleep Evaluation

Patients with NMDs have a prevalence greater than 40% of SDB,[40] a tenfold greater occurrence than that in the general population.[41] They have a much higher incidence of OSA, gas exchange abnormalities, disrupted sleep architecture, and central apnea.[4,41] Dysfunction of upper airway muscles results in OSA, and dysfunction of diaphragm and intercostal muscles results in hypoventilation. In patients with NMDs, airway resistance during sleep may be increased because of weakness of the pharyngeal dilator muscles, which is worse during the rapid eye movement (REM) stage when these muscles are atonic. In patients with NMDs,[42] OSA often precedes hypoventilation. Hypoventilation during sleep as a result of blunting of the response to hypoxia and hypercarbia worsens as muscle weakness progresses. Furthermore, the presence of kyphoscoliosis can contribute to restriction of lung capacity and impaired ventilation.[43]

The nature of SDB in patients with NMDs reflects the distribution of respiratory muscle involvement.[44] When patients have severe diaphragm dysfunction, suppression of intercostal and accessory muscles during REM sleep leads to hypoventilation. However, if diaphragm strength is intact but the upper airway or intercostal muscles are weak, then obstructive apneas or hypopneas are more likely to occur. In some NMDs, such as myotonic dystrophy, primary abnormalities in ventilatory control may also contribute to SDB, often complicated by nocturnal or even diurnal hypoventilation.[45] The arousal response seen with hypoventilation is compensatory because it prevents prolonged hypoxia or hypercarbia, but it does so at the expense of adequate sleep and results in daytime fatigue and hypersomnolence. With time and disease progression, ventilatory chemosensitivity is reset and the arousal response is blunted, leading to prolongation of the REM stage during which alveolar hypoventilation occurs. Eventually respiratory drive is depressed, resulting in severe hypoventilation and ultimate respiratory failure (**Figure 54-2**).[45]

Nocturnal hypoventilation is not well defined in children. In adults, sleep-related hypoventilation, according to the *International Classification of Sleep Disorders, 3rd Edition*,[46] is defined as a level of arterial carbon dioxide greater than 55 mm Hg for at least 10 minutes or an increase of at least 10 mm Hg above the awake value to a level of at least 50 mm Hg for 10 minutes or longer. In children, the level must be greater than 50 mm Hg for more than 25% of total sleep time.[46] Sleep-related hypoxemia is defined as oxygen desaturations to 88% or lower in adults, or 90% or lower in children, for at least 5 minutes.[46] Quality of sleep and symptoms of SDB should be reviewed at each visit (see Chapter 33, Obstructive Sleep Apnea Syndrome). Polysomnography should be performed annually in patients with NMDs from the time they are wheelchair users or when the clinical situation warrants. If polysomnography cannot be performed, nocturnal pulse oximetry with or without capnography is an alternative.

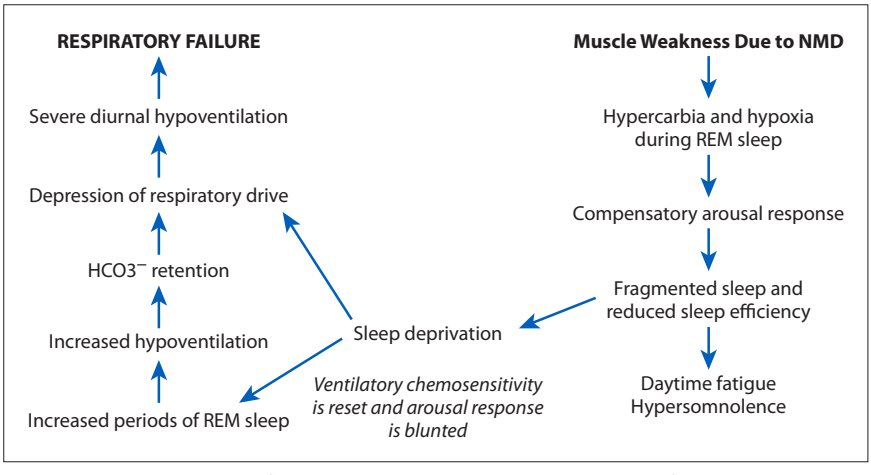


Figure 54-2. Development of sleep-disordered breathing and respiratory failure in patients with neuromuscular disorders. Abbreviations: $HCO3^-$, bicarbonate; NMD, neuromuscular disorder; REM, rapid eye movement.

Management

Multiple approaches are available for reducing the effect of the progression of neuromuscular weakness. The approach to investigating and treating symptoms depends on the clinical course and is summarized in **Table 54-2**.

Table 54-2. Suggested Approach to Examine and Treat Patients With Progressive Respiratory Muscle Involvement

Clinical Features	Relevant Investigations	Suggested Interventions
No clinical evidence of respiratory muscle involvement	Normal FVC, normal cough peak flow (>270 L/min)	Follow up regularly in the clinic (every 6 months), monitor spirometry results and cough peak flow rate, encourage use of incentive spirometer
Evidence of respiratory muscle involvement, weak cough, and pooling of secretions	Reduced FVC (<60% predicted), cough peak flow (<270 L/min), maximal expiratory pressure < 60 cm H_2O	Initiate lung volume recruitment and/or airway clearance (cough assist device)
Snoring, sleep-disordered breathing, nocturnal awakenings due to breathing difficulty, daytime somnolence	Evidence of sleep-disordered breathing during a sleep study, evidence of chronic hypoventilation on blood gas (elevated CO_2 and bicarbonate levels) test results, hypoxia (reduced oxyhemoglobin saturation, Po_2 levels on blood gas test results), and elevated end-tidal CO_2 levels	Consider noninvasive ventilation during sleep
Hypoventilation, hypercarbia during awake periods	Awake Pco_2 >50 mm Hg Oxyhemoglobin saturation <92%	Extend noninvasive ventilation during daytime; may be intermittent to begin with
Persistent or worsening hypoventilation, hypercarbia, and hypoxia	Awake Pco_2 >50 mm Hg Oxyhemoglobin saturation <92%	Use long-term ventilation: may be noninvasive to begin with, and if there is contraindication or failure of noninvasive ventilation or patient or family preference, consider long-term tracheostomy and ventilation

Abbreviations: CO_2, carbon dioxide; FVC, forced vital capacity; H_2O, water; P_{CO_2}, partial pressure of carbon dioxide; P_{O_2}, partial pressure of oxygen.

Airway Clearance

There are 2 components of effective airway clearance: mucus mobilization from peripheral to central airways by means of the mucociliary escalator and mucus extraction. Cough, a primary mechanism to clear secretions from the central airways, may be affected by respiratory muscle weakness and result in impaired airway clearance leading to pooling of secretions, which may result in airway obstruction and increased work of breathing and contribute to

chronic respiratory insufficiency. Ineffective cough may be suspected clinically when there is a history of lack of secretions while coughing, recurrent pneumonia, and reduced values for CPF. Cough peak flow may be measured in the primary care physician's office, patient's home, or pulmonologist's office by attaching a mask to a peak flow meter and asking the patient to cough in it (**Figure 54-3**).



Figure 54-3. A face mask attached to a peak flow meter for use as a cough peak flow meter.

Courtesy of Girish D. Sharma, MD, Rush University Medical Center, Chicago.

This inexpensive, simple device monitors expiratory muscle strength, and the patient can maintain a journal with weekly or monthly readings. Similarly, an MEP less than 45 cm H_2O has been considered an indication for assisted cough techniques. Therefore, airway clearance (using either manual chest physiotherapy or a mechanical device) is very important to prevent respiratory complications, including pneumonia, atelectasis, and respiratory failure. In the initial stages, airway clearance by means of manual chest physiotherapy along with postural drainage may help. However, as the disease progresses, resulting in pooling of secretions, more aggressive methods, such as the use of a mechanical insufflation-exsufflation (MIE) device, are needed.

Use of a high-frequency chest wall oscillation (HFCWO) device alone may not help much if the patient has weak or ineffective cough. In that case, assisted cough for airway clearance is needed. Use of HFCWO in a patient with clinically significant musculoskeletal deformities (kyphoscoliosis) may be

uncomfortable. However, investigators in some studies have suggested the usefulness of HFCWO in patients with NMDs.[47,48]

Various techniques have been developed to overcome ineffective cough in patients with neuromuscular weakness. Patients or caregivers should be taught strategies to improve airway clearance and how to use those techniques early and aggressively. Patients with clinically weak or ineffective cough and clinical evidence of poor airway clearance should be started on a regular airway clearance regimen. Use assisted cough techniques in patients whose clinical history suggests difficulty in airway clearance, whose CPF is less than 270 L/min, and/or whose MEPs are less than 60 cm H_2O. An MIE device (cough assist device) is helpful.

Manually Assisted Cough Technique

Manually assisted coughing involves inspiratory assistance followed by augmentation of the forced expiratory effort. An increase in inspiratory capacity can be achieved by the use of glossopharyngeal breathing (in essence, forcing air into the lungs using one's mouth), air stacking (taking a series of tidal breaths without exhaling between them), positive pressure with a self-inflating bag and mask, an intermittent positive pressure breathing device, or a mechanical ventilator. Interfaces for inspiratory assistance include a face mask, mouthpiece, or direct attachment of the assisting device to a tracheostomy tube. Forced exhalation is augmented by pushing on the upper abdomen or chest wall in synchrony with the subject's own cough effort.

Mechanical Techniques

Mechanical insufflator-exsufflators (also known as *cough assist devices*) simulate a cough by providing a positive pressure breath followed by a negative pressure exsufflation. This technique is superior to both breath stacking and manual cough assistance.[25] In patients with tracheostomies, MIE offers a number of advantages over traditional suctioning, including clearance of secretions from peripheral airways, avoidance of mucosal trauma from direct tracheal suction, improved patient comfort,[49] and prevention of atelectasis. Bronchoscopy has been used in selected patients with DMD, generally in cases of persistent atelectasis, but has not been of proved benefit, so it should be considered only after all noninvasive airway clearance techniques have been unsuccessful and a mucus plug is suspected.

Lung Volume Recruitment

Lung volume recruitment using a self-inflating manual ventilation bag applied once or twice daily may have an immediate positive effect on CPF and a long-term effect on rate of FVC decrease in patients with an NMD and respiratory muscle weakness.[24,50,51] Regular use of MIE, in addition to airway clearance, also contributes to lung recruitment.

Respiratory Muscle Training

The rationale for respiratory muscle training in patients with DMD is based on the assumption that improved muscle strength and endurance may lead to improved preservation of lung function over time. Low-intensity inspiratory muscle training at home may improve respiratory muscle endurance in children with DMD, and the effectiveness of training appears to depend on the quantity of training.[52] Training with an inspiratory threshold load (70%–80% of the maximal inspiratory mouth pressure) provides a stimulus that increases both the pressure- and flow-generating capacities of the respiratory muscles and therefore may provide a practical approach to inspiratory muscle training in both children and adults with NMDs.[45]

Noninvasive Nocturnal Ventilation

The onset of moderately severe muscle weakness as evidenced by physical examination results, weak or ineffective cough, pooling of secretions, and hypoventilation or hypoxia during sleep or wakefulness differs from patient to patient and disease to disease. For example, a patient with SMA can develop such a weakness much earlier than a patient with DMD. Use of noninvasive ventilation (NIV) may improve quality of life, slow the decreases in vital capacity and maximal static inspiratory and expiratory pressures,[53] and reduce the high morbidity (SDB, including hypopnea, central and obstructive apnea, and hypoxemia) and early mortality associated with NMDs such as DMD.[1] A combination of NIV and airway clearance using MIE may decrease the need for intubation.[54] In children, long-term home mechanical ventilation is being increasingly used; most of these patients have NMDs and receive NIV.[55,56]

Nocturnal nasal intermittent positive pressure ventilation with a bilevel positive airway pressure generator or mechanical ventilator has been used successfully in the treatment of SDB and nocturnal hypoventilation in patients with DMD and other NMDs.[1] Family and demographic factors, especially maternal education, may influence adherence to the positive airway pressure therapy.[57] The type of NIV interface (nasal, oronasal, nasal pillows) is chosen based on individual needs and fitting. Improper fitting may cause air leak resulting in inadequate ventilation; sleep disruption; skin irritation or excoriation; and, more importantly, poor adherence with NIV. Discomfort, aerophagia, abdominal distention, dry mouth, nasal congestion, and interference with secretion management may occur. In children, long-term use of an orofacial mask may lead to midfacial hypoplasia.[58,59] In older patients with an NMD requiring intermittent NIV during the day, mouthpiece ventilation is gaining wider acceptance.[60]

Polysomnography should be performed to confirm the presence and extent of SDB, hypoxia, and hypercarbia; to titrate for treatment initiation with optimum ventilator settings; and to ensure response to treatment. In the

absence of polysomnography, overnight pulse oximetry with continuous carbon dioxide monitoring can be used to monitor nighttime gas exchange.[1] Daytime ventilation should be considered when measured waking P_{CO_2} exceeds 50 mm Hg or when oxygen saturation remains less than 92% while the patient is awake. Additional periods of assisted ventilation may be added during acute episodes such as respiratory infection. Follow-up visits should include monitoring for daytime hypoventilation, polysomnographic assessment of nocturnal NIV adequacy, and the patient's and/or caregiver's feedback. In certain situations, data downloaded from the device (eg, time the device was used, air leak, tidal volume, pressures) is helpful to ensure adequacy of ventilation. During the outpatient clinic visit, assessment of ventilator parameters to ensure adequacy of ventilation (eg, expiratory tidal volume, end-tidal carbon dioxide measurement, mask assessment to check for leak) is helpful. Depending on the ventilation adequacy assessment results, additional hours of ventilation during the day or round-the-clock ventilation may be needed. With an increase in the understanding of the mechanism of respiratory insufficiency in patients with NMDs, new modes and devices for NIV and monitoring have evolved,[61–63] resulting in improved adherence and outcomes.[64] However, oxygen supplementation alone should not be used to treat sleep-related hypoventilation without ventilatory assistance because of the potential for exacerbating carbon dioxide retention and resultant acute respiratory failure.

Tracheostomy and Invasive Ventilation

Tracheostomy should be considered when the patient cannot achieve adequate ventilation with NIV or contraindications to NIV are present. For example, the patient may have an aversion to NIV, lack sufficient oromotor or neck control to use a mouthpiece interface during the daytime, or tolerate other interfaces poorly.[1]

Factors such as available resources and financial burden on families and the health care system[65,66] should be considered; however, they may not be used to deny a patient an indicated intervention such as tracheostomy or invasive ventilation. Other important considerations include the discharge criteria from the hospital to home and the equipment and resources needed.[67] However, tracheostomies have many potential complications, including generating more secretions; impairing swallowing and increasing the risk of aspiration; bypassing of airway defenses, likely increasing the risk of infection; and a higher risk of airway occlusion by a mucus plug.[68] Because tracheostomies also impair speech, communication may be restored using a relatively small tracheostomy tube, allowing a "leak" around the airway, and a speaking valve (Passy-Muir valve).

Respiratory Care for Patients With NMD Undergoing Sedation or Anesthesia

Preoperative pulmonary evaluation[69] and consultation should be performed. Pulmonary function tests, including FVC, MIP, MEP, CPF, and oxyhemoglobin saturation measurement in room air, should be performed. An FVC value less than 50% is associated with increased risk, and when the values are less than 30%, preoperative training for NIV should be provided. If these procedures are indicated, the child should undergo extubation to NIV, such as nasal bilevel positive airway pressure, and appropriate pain management should be provided. Aggressive airway clearance should begin as soon as the patient can tolerate it.[69–71]

Pulmonary Infections in Patients With NMDs

Ineffective cough and airway clearance due to respiratory muscle weakness and associated dysphagia and resultant aspiration may lead to recurrent respiratory infections in patients with NMDs (**Figure 54-1**). In a patient with a clinical course suggestive of acute bacterial infection, as evidenced by fever, purulent secretions, leukocytosis, or radiological evidence of pneumonia, empiric use of antibiotics is warranted after relevant workup for such respiratory cultures. Patients or caregivers should receive a sick plan (including increasing the frequency of airway clearance, using home oximetry, and communicating with the pulmonary team) to decide the need for antibiotics. Some clinics have used remote assessment via telehealth visits to assess respiratory status and ventilator parameters and to change equipment settings. A timely approach like this may obviate the need for a hospital visit and admission and may also reduce the duration and severity of sickness and associated morbidity.

Use of a 23-valent pneumococcal polysaccharide vaccine in children older than 2 years and annual influenza vaccine is important. When a respiratory infection is suspected, appropriate investigations, appropriate antibiotics, and increased airway clearance are indicated.[72] The COVID-19 pandemic also highlighted the importance of looking for risk factors for severe COVID-19 infections, adjustment of disease-modifying therapies, and treatment of pneumonia in this patient population.[73,74] The COVID-19 vaccine, approved for children aged 6 months or older as of 2022, should be used.

When to Refer

Pulmonologist

- Shortly after diagnosis for respiratory care evaluation and discussion of treatment options, including identification of goals for chronic and acute respiratory care; regular follow-up of pulmonary status should be performed once or twice a year after the patient starts to use a wheelchair
- Before a proposed surgery for evaluation of pulmonary status and to assess fitness for the proposed anesthesia, sedation, or surgery
- In case of acute respiratory illness

Cardiologist

The cardiologist should be consulted to diagnose and treat cardiomyopathy and pulmonary hypertension. Cardiac evaluation should be performed for evidence of cardiomyopathy and cardiac dysrhythmias and pulmonary hypertension. Patients with NMDs are at high risk of developing adverse effects during the perioperative period because of hypoxemia, anemia, and other causes of impaired tissue oxygen delivery. Intravascular shifts can result in congestive heart failure and impaired ventricular load.[75]

When to Admit

- **At the time of diagnosis:** Patients with late diagnosis who may have clinically significant pulmonary compromise as evidenced by lung function, or laboratory evidence of respiratory failure or cardiac involvement, may benefit from hospitalization.
- **Inadequate or lapsed home nursing**: The family or caregiver at home cannot provide 24/7 care.
- **In case of acute respiratory illness:** Patients may need aggressive airway clearance; increased respiratory support, such as NIV; management of nutrition; hydration; and initiation of antibiotic therapy. In case of acute respiratory decompensation due to causes such as aspiration pneumonia in a patient already using long-term NIV, a change of ventilator and, uncommonly, short-term endotracheal intubation may be warranted.
- **For elective procedures:** These include gastric feeding tube placement, scoliosis surgery, elective tracheostomy and initiation of invasive ventilation, and sleep studies.

key points

- The history in a patient with an NMD should include questions about the strength and efficiency of coughing, activity or exercise intolerance, and respiratory distress.
- Regular monitoring of PFT results, especially FVC, should be initiated as soon as the child is mature enough to perform the maneuver.
- Early and proactive use of devices to facilitate lung recruitment, cough assistance, and airway clearance is important for preservation of respiratory function.
- Sleep-disordered breathing associated with NMDs should be suspected and tested for if there is a history of snoring, irregular breathing, apneic episodes during sleep, or nocturnal awakenings due to breathing difficulty (not for change of position because of discomfort).
- A history of recurrent respiratory infections and pneumonia may suggest chronic aspiration due to oropharyngeal incompetence. A videofluoroscopic swallowing study may help to confirm any oropharyngeal incompetence and associated aspiration.
- Involve the palliative care team to discuss ventilatory and palliative treatment options before they become necessary.

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CHAPTER
55

Airway Clearance Techniques

Karen Ann Hardy, MD, FATS

Introduction

Normal Airway Clearance

Typically, the clearance of airway secretions relies on 2 defense mechanisms: the mucociliary escalator and cough clearance. The mucociliary escalator requires normally functioning cilia and a normal airway surface liquid and mucus layer. These components of airway clearance function in the small airways as well as the larger cartilaginous airways (**Figure 55-1**). Cough clearance function is limited to the larger central airways and requires normal inspiration, vocal cord closure, and expiration, as well as adequate rigidity of the airway.

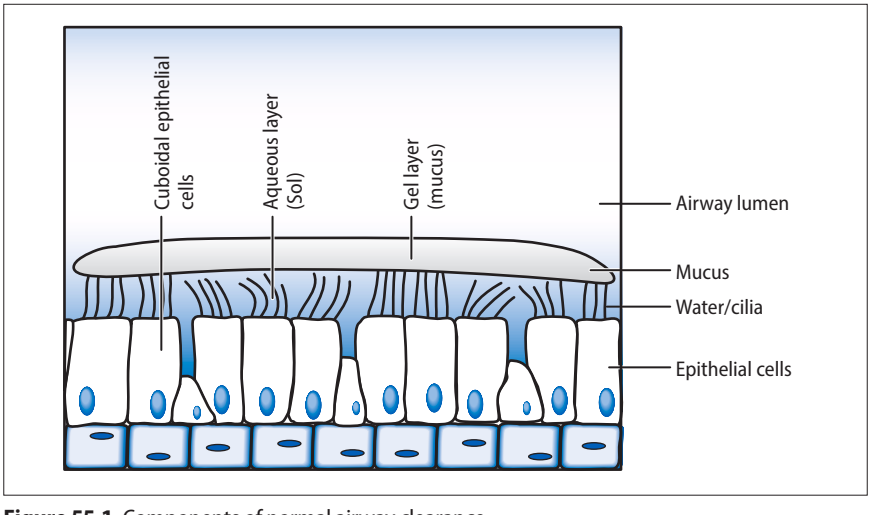


Figure 55-1. Components of normal airway clearance.

Abnormal Airway Clearance

Children who lack any factor involved in the 2 main mechanisms, mucociliary escalator or cough clearance, will have difficulty with normal airway clearance. See **Table 55-1** for the types of abnormalities that relate to lack of the required components for appropriate airway clearance.

Table 55-1. Abnormalities Related to the Lack of Physical Components of Airway Clearance

Diagnostic Category	Anatomical or Functional Abnormality	Pathophysiology
MUCOCILIARY ESCALATOR		
Cilial dysfunction	Primary ciliary dyskinesia	Cilia immotile or dyskinetic
Abnormal airway surface liquid/ mucus layer	Cystic fibrosis	Reduced airway surface liquid; thick and viscous mucus layer; increased inflammatory mediators; increased destructive compounds (elastases, proteases)
	Pseudohypoaldosteronism	Increased volume of airway surface liquid; intermittent airway obstruction and infection as young children, typically younger than 6 years
	Asthma	Abnormal and increased mucus Airway edema
COUGH CLEARANCE		
Neuromuscular disease	Duchenne muscular dystrophy, spinal muscular atrophy, congenital myopathies	Combined respiratory motor defects with abnormal inspiratory pressure generation (limiting full inspiration) and/or expiratory pressure generation (limiting peak cough flow rates and shear force); bulbar dysfunction with aspiration and/or gastroesophageal reflux (causing chronic injury to epithelium, further altering function)

Table 55-1. Abnormalities Related to the Lack of Physical Components of Airway Clearance *(continued)*

Diagnostic Category	Anatomical or Functional Abnormality	Pathophysiology
Neuromotor disease	Cerebral palsy	Inability to control and/or sense secretions in the airways or pharynx, bulbar palsy, direct aspiration, severe muscle imbalance causing scoliosis; can be associated with impaired cough, poor nasopharyngeal motor tone with subsequent upper airway obstruction and possible obstructive sleep apnea
	Phrenic nerve injuries	Profound diaphragmatic dysfunction sometimes associated with paradoxical motion
	Traumatic or postoperative head and spinal cord injury	Can damage phrenic nerve and innervation of intercostal muscles and accessory muscles, affecting bellows function
	Meningomyelocele (spina bifida)	Bellows dysfunction and progressive scoliosis variable depending on spinal level affected
Neurologic	Bulbar palsy and encephalopathy	Inability to control oral secretions and/or swallow, may include direct aspiration
Unstable airways	Airway malacia	Airways narrow/collapse with dynamic pressure changes during inspiration and/or expiration; phase of ventilation affected varies: inspiratory for obstruction above thoracic inlet or expiratory for obstruction below thoracic inlet
	Tracheoesophageal fistula, VACTERL syndrome	See airway malacia; direct airway damage from aspiration
	Bronchiectasis (bronchiolitis obliterans, cystic fibrosis, immunodeficiency, primary ciliary dyskinesia, postinfection/tuberculosis)	Progressive infection/injury causing cartilage destruction with collapsible and dilated airways similar to airway malacia.
Obstructed airway	Tracheal stenosis	Inadequate lumen for airflow and secretion clearance
	Scoliosis	Airway rotational deformities ("kinking") and muscle imbalance that can be progressive

Abbreviation: VACTERL, vertebral anomaly, anal atresia, cardiac defect, tracheoesophageal fistula, renal, limb abnormalities.

Considerations Unique to Infants and Children

For several reasons, children are more susceptible than adults to complications related to compromised airway clearance. The mucus of children is more acidic and may have greater viscosity. Infants and children have an overly compliant chest wall and relatively stiff lungs, leading to a lower functional residual capacity. Furthermore, the airways are smaller, have less cartilage support, and tend to collapse more easily than in adults. Finally, the bronchioles and alveoli of children have fewer channels for collateral ventilation than those of adults.[1]

Airway clearance therapy (ACT) is more difficult in infants and children because of difficulties in obtaining cooperation. In addition, gastroesophageal reflux is common but can be difficult to diagnose and can be aggravated particularly by a head-down drainage position.[2,3] Unfortunately, data regarding the use of ACT in children are limited. Children who require ACT often have rare diseases; adequately powered trials are the exception rather than the rule. Placebo-controlled studies are not possible, and the length of time needed to judge treatment efficacy for chronic conditions can be long, making studies costly and increasing the likelihood of nonadherence and attrition. Much of what is known is based on case reports, small single-center studies, and clinician experience, although increasingly meta-analyses and Cochrane reviews are available. A meta-analysis and multiple Cochrane reviews found low-quality evidence that chest and airway oscillatory devices and a mix of ACTs reduce symptoms of breathlessness and cough and improve ease of sputum expectoration compared to no treatment. The 2015 Cochrane review includes an overview of multiple prior reviews on non–cystic fibrosis (CF) bronchiectasis, finding airway clearance techniques may reduce sputum production and improve quality of life. The most recent review of 2019 gives overview of all reviews pertaining to CF and concludes that no treatment is superior and other factors often drive selection of ACT. [4–9] Patients with CF are the most frequently studied and account for the majority of reports in children.

Airway Clearance Techniques

Airway clearance therapy may be independently performed, relying on the patient's breathing skills, or may depend on other persons or machines. For any patient, the appropriate method is one that is effective, affordable, feasible, and repeatable. Importantly, a patient's ability to choose their method of airway clearance can also improve adherence. **Box 55-1** lists the various airway clearance techniques divided into the independent and dependent skills categories with reference to the known physiological effects, costs, and preferences. Parents and caregivers can teach children a vocabulary regarding breathing that helps them learn to cooperate and participate in

clearing secretions. This can include simple words and phrases like *breathe in, breathe out, cough, take a big breath, blow,* and *hold your breath.*

Box 55-1

Airway Clearance Techniques

Independent Methods (free once trained; no equipment or assistance needed)

- Directed cough huff maneuver
- Active cycle of breathing techniques
- Autogenic drainage

Dependent Methods (variable cost, free if family member helping or costly if persons outside the home required)

- Chest physical therapy, also known as postural drainage and percussion and vibration
- Manual cough assist

Handheld Device Required (minimal expense, $15–$200)

- Manual percussor for chest physical therapy
- Positive expiratory pressure valve (example: threshold or flow positive-pressure valves)
- Oscillating positive expiratory pressure devices (examples: TheraPEP, Flutter, Aerobika)

Large Machine Required (most expensive: $400–$17,000, depending on rent vs purchase and manufacturer vs reseller)

- High-frequency chest wall compression (examples: The Vest, AffloVest, SmartVest)
- Mechanical in-exsufflator (examples: cough assist device)
- Intrapulmonary percussive ventilator

Independent Techniques

Huff Cough Maneuver

Coughing clears normal airways quite effectively in healthy people. The components of cough include inspiration, glottic closure, and expulsion via forced exhalation. Coughing causes compression of the airways that moves secretions from the smaller to the larger airways and toward the mouth.[10] A cough is less effective if the airways are unstable and collapsible, and a modification of cough (huff cough or forced expiratory maneuver) can help decrease the compression of these airways. The huff maneuver is performed by inhaling at various lung volumes and then exhaling with a slightly open glottis.[3] This is easily mimicked by the skill of "fogging a mirror." The force of exhalation is adjusted to avoid wheezing and airway collapse. Maintenance of the open glottis avoids the excessive transmural pressures that cause airway closure and limit secretion clearance. This skill is easy to teach and effective for patients with collapsible airways.

Active Cycle of Breathing Technique

Active cycle of breathing techniques (ACBTs) combine the huff maneuver with 2 other skills: diaphragmatic (or relaxed) breathing and thoracic expansions (or deep rib breathing). Relaxed, diaphragmatic breathing occurs during gentle inhalation using the diaphragm and allowing the abdomen to expand.[3] Children often call this "belly breathing." A child may learn this skill by placing a favorite stuffed animal on the abdomen and watching it rise up and down. During exhalation, the abdominal muscles are used and, with successive breaths, large volumes are moved with improved ventilation of the dependent lung tissue. Thoracic expansions rely more on intercostal muscles with prominent chest expansion that improves upper lung expansion and ventilation. The use of alternating cycles of diaphragmatic breaths with thoracic breaths and huff maneuvers in ACBT can effectively and efficiently mobilize and clear airways.[11] This independent skill can be mastered and then used anytime in any position, although it requires attention to be most effective.

Autogenic Drainage

The most advanced and challenging independent skill is autogenic drainage.[12] This technique is applied widely in adults and some children with CF but also is used for adolescents and adults with bronchiectasis from any cause. The skill is difficult to learn and typically requires a series of visits to a skilled teacher. The patient is trained in 3 phases or levels that are serially completed: breathing first at low-lung volumes to dislodge the mucus, then at mid-lung volumes to collect the mucus, and then at high-lung volumes to expel the mucus (**Figure 55-2**). Skilled performance of this technique is associated

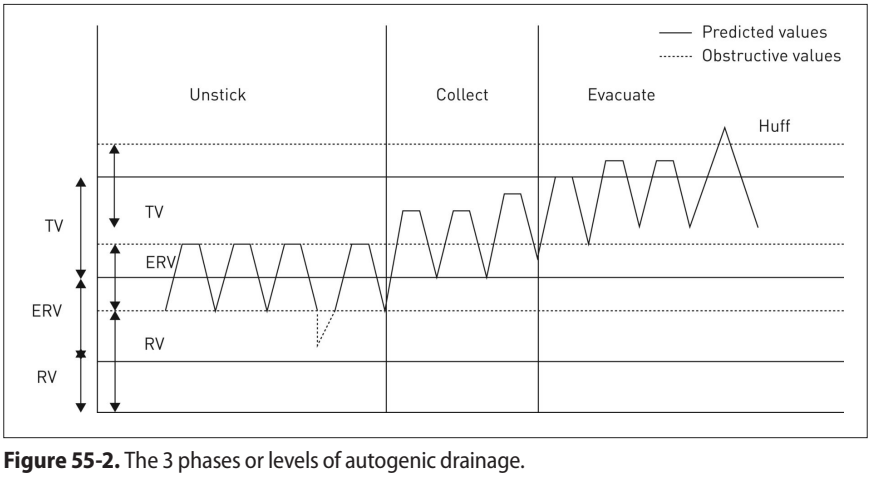


Figure 55-2. The 3 phases or levels of autogenic drainage.

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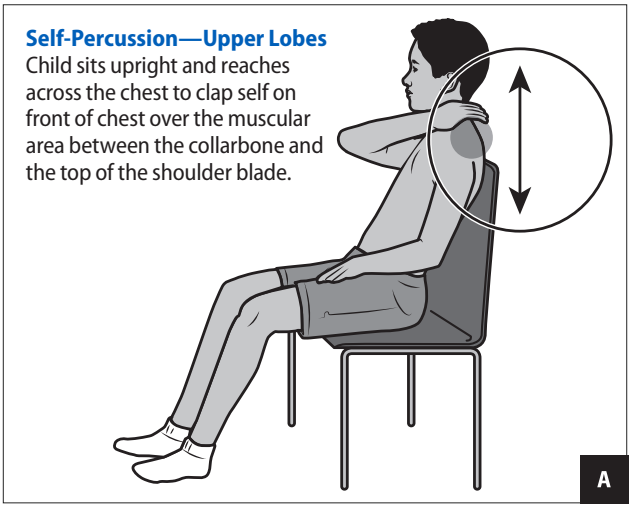
with improved oxygenation and minimization of work to expectorate.[13] It also is associated with improved oxygenation and minimization of work to expectorate.[13] Additionally, it reduces the likelihood of coughing fits that are typically caused by forced coughing in those with unstable airways and excessive secretions. A recent Cochrane review of autogenic drainage compared to multiple other clearances found it not superior; studies were inadequately powered to determine if the technique was non-inferior. Larger studies, including quality of life outcomes, are needed.[14]

Dependent Techniques

Chest Physical Therapy

Chest physical therapy (CPT) may include postural drainage, percussion, and vibration. Though multiple alternative strategies for ACT exist, this is the first developed and still used for infants with a number of illnesses that impair airway clearance. Parents are taught the technique and use it until an infant's chest circumference is large enough to fit a vest or until the child develops language skills to permit teaching other ACTs. Classically, patients are placed into a position to permit gravity to assist in mucus flow. The chest wall is percussed to loosen the mucus during both inspiration and expiration; intermittently, a prolonged exhalation with chest wall vibration is applied as a final attempt to move mucus. Applying the vibrations is the most difficult component for the respiratory therapist, physical therapist, and families and, as a result, can be omitted. This technique is widely practiced but has a number of drawbacks. Complications have been shown to include desaturations, gastroesophageal reflux, aspiration, pain, fractured ribs, and headaches.[3] In addition, this technique requires assistance, leading to poor adherence as long-term therapy when patients begin to seek independence.[11,13,15,16] Care providers performing CPT can also experience pain or musculoskeletal abnormalities.[3] This can be partially circumvented by the use of mechanical devices. Typical postural drainage positions for children are shown in **Figure 55-3**.

Augmented cough, also known as manual cough assist, is used for patients with neuromuscular disease who cannot generate an effective cough. This maneuver involves a Heimlich-like procedure where the caregiver uses the heel of the hand to thrust from the abdomen toward the diaphragm in concert with patient efforts to cough. Manual cough assist is most effective if the child is supine.[17]



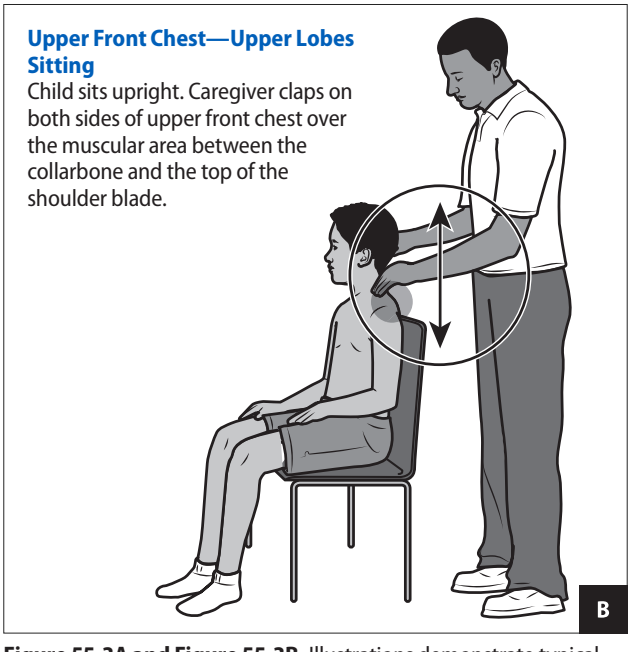


Figure 55-3A and Figure 55-3B. Illustrations demonstrate typical chest physical therapy drainage positions for children.

Upper Back Chest—Upper Lobes
Child sits up and leans forward on a pillow over the back of a soft chair at a 30-degree angle. Caregiver stands or sits behind child and claps both sides of the upper back, taking care not to clap on child's backbone.



Upper Front Chest—Upper Lobes Lying
Child lies on their back with arms to sides. Caregiver stands behind child's head and claps both sides of child's chest between the collarbone and nipple.

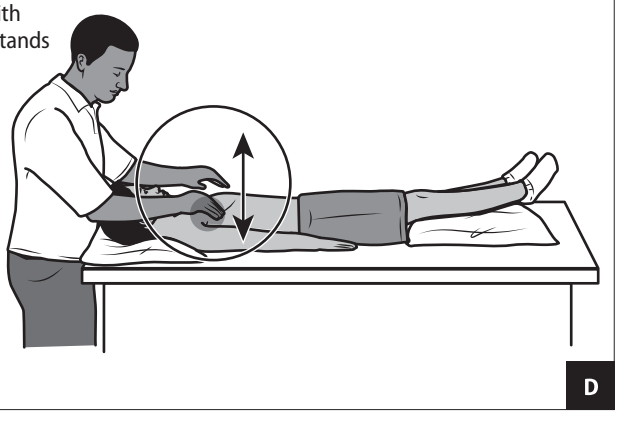
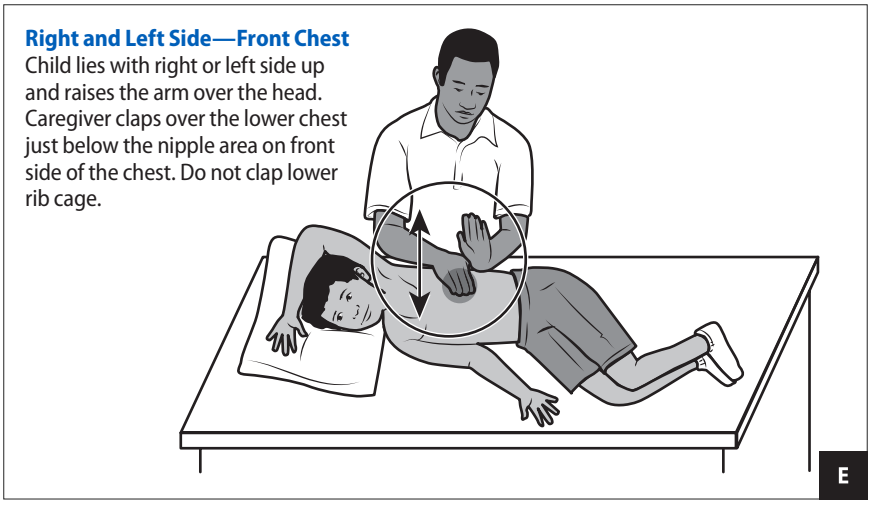


Figure 55-3C and Figure 55-3D. Illustrations demonstrate typical chest physical therapy drainage positions for children.



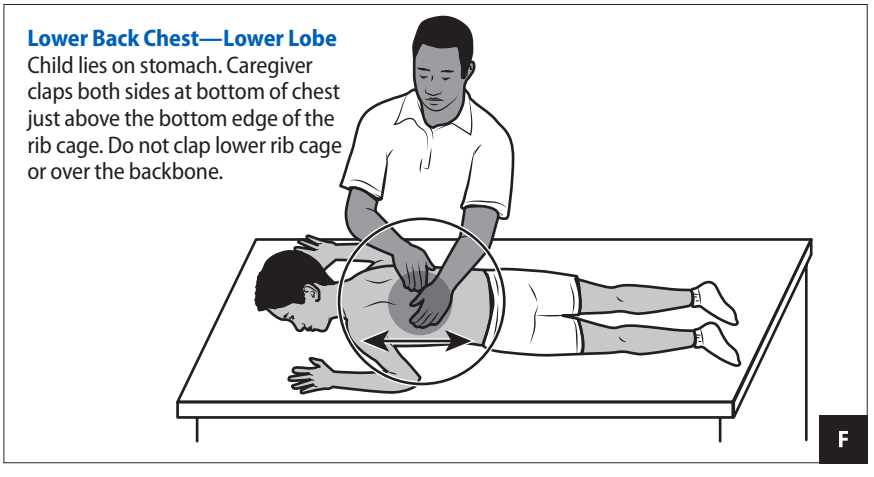


Figure 55-3E and Figure 55-3F. Illustrations demonstrate typical chest physical therapy drainage positions for children.

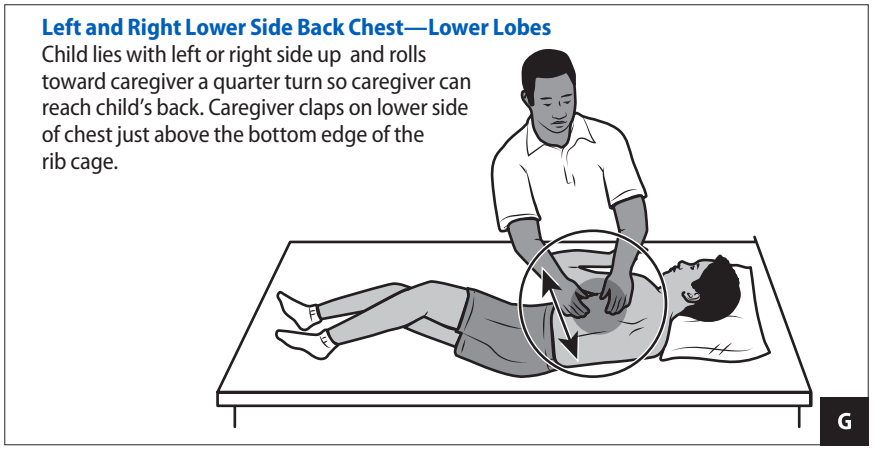


Figure 55-3G. Illustrations demonstrate typical chest physical therapy drainage positions for children.

Positive Expiratory Pressure

Small handheld devices are often used for generating positive expiratory pressure (PEP),[15,18] which may be constant or oscillatory. In this technique, the patient breathes in and out 5 to 20 times through a flow resistor, which creates a positive pressure in the airways during exhalation. After a series of breaths, the patient performs the huff cough maneuver. Positive-pressure devices cause motion of air via collateral channels of ventilation (alveolar pores of Kohn and bronchiolar-alveolar channel of Lambert) to equalize alveolar filling and facilitate mucus clearance with the huff cough. PEP devices can be inexpensive, ranging from $10 for the valve alone up to $150 for a valve with visual feedback attachments. One example is shown in **Figure 55-4**.



Figure 55-4. Example of a positive expiratory pressure valve.

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Oscillating PEP Devices

High-frequency oscillations were added to PEP therapy initially with the advent of the flutter valve device (**Figure 55-5**), which was then followed by a number of alternative devices, including the Acapella valve and the Aerobika, that have different mechanisms by which they produce the desired oscillations. As the patient exhales actively into the devices, PEP is initially generated that rapidly subsides and then recurs. The oscillations produced by the devices augment shear forces during exhalations along the airway walls to loosen mucus. The flutter valve produces these oscillations with the flutter of a steel ball inside the device that moves during use. The Acapella valve uses magnets adjusted at a specific distance to produce vibrations. Two Acapella colors designate devices designed for younger (blue—low flow) and older (green—high flow) children (**Figure 55-6**). The Aerobika Oscillating Positive Expiratory Pressure device uses a proprietary pressure oscillation dynamic that provides intermittent resistance and creates positive pressure and oscillations simultaneously (**Figure 55-7**). The PEP valve and the Aerobika can pair with

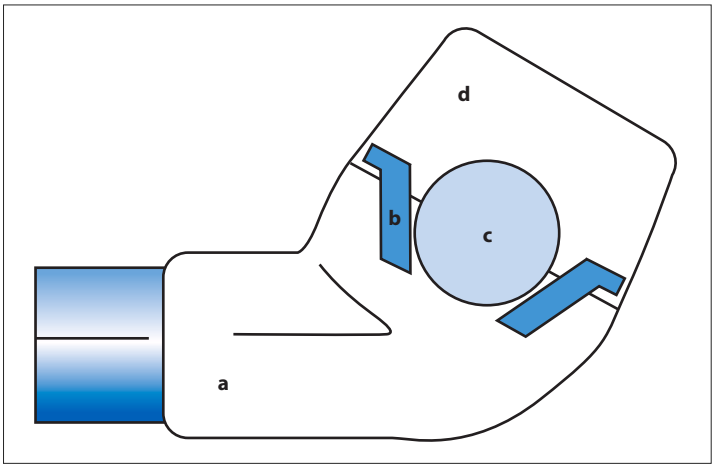


Figure 55-5. Example of the flutter valve, an oscillating positive expiratory pressure (PEP) valve. The device comprises a mouthpiece (**a**), a plastic cone (**b**), a steel ball (**c**), and a perforated cover (**d**). During exhalation through the device, the tracheobronchial tree undergoes internal vibrations together with repeated variations of the exhaled airflow against the resistance (PEP) and oscillations of the endobronchial pressure (oscillating pressure). Oscillating PEP is most commonly performed with the flutter device or the Acapella device.

aerosol delivery devices to reduce treatment times and improve drug deposition. The Aerobika is dishwasher safe. Resistance is position dependent for the flutter, but independent for the Acapella and Aerobika devices. These oscillating PEP devices are similar in cost. All require exhalation via a mouthpiece or mask, thus requiring adequate muscle strength to form a tight seal around the device, since oscillations and pressure can be lost in the oral cavity. Pressure loss can be prevented by tightening the cheek muscles or holding them with thumb and fingers, compressing the cheeks. Cochrane reviews comparing multiple PEP techniques, both constant and oscillatory, find the overall study quality is low and no particular device is superior.[18]



Figure 55-6. Example of the Acapella device, a handheld positive expiratory pressure (PEP) oscillation device designed using magnets; color-coded units (green for high flow, blue for low) help customize treatment for younger and older children.

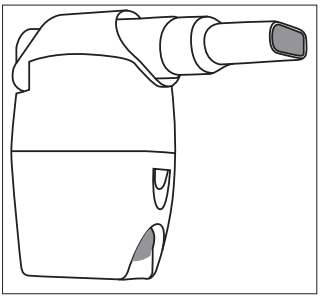


Figure 55-7. Example of the Aerobika, a handheld oscillating positive expiratory pressure device.

High-Frequency Chest Wall Compression: Vests

A number of manufacturers have devised portable machines that apply variable high-frequency oscillations directly to the chest wall via an inflated jacket. Collectively, these machines are called *vests.* The devices require power sources and tubing to connect the generator to the jacket. The personally fitted jacket is applied to the chest and inflated to avoid frictional loss of energy at the chest wall and to effectively transmit oscillations simultaneously over the entire chest wall. The inflation pressure can be adjusted, as can the oscillatory frequency. Vest devices move mucus from the periphery to central airways, but actual clearance is required through huff or cough to expectorate

mucus (**Figure 55-8**). Small studies and case series of patients with cerebral palsy and neuromuscular disease suggest that recurrent pneumonia in these patients can be lessened or avoided with routine use.[19] Some devices are considered portable; most are stationary. Multiple companies market this technology; the primary care clinician may consult with local CF center providers and adult pulmonology teams for help selecting the best product. Some devices are self-contained battery-powered jackets with oscillating pods that are incorporated into the jacket, making it portable for moving during therapy without a tethering cord to a power source (**Figure 55-9**). These devices are suited for older teens and young adults with US Food & Drug Administration approval gained in 2017. Infants can be fitted for a vest once chest circumference at the nipple is at least 16 inches or 18 inches, depending on the specific device.

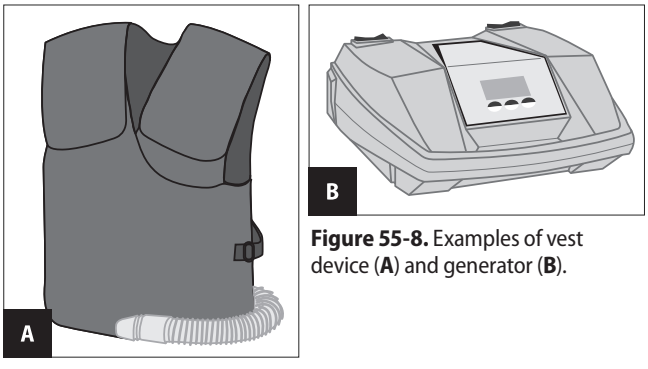


Figure 55-8. Examples of vest device (**A**) and generator (**B**).

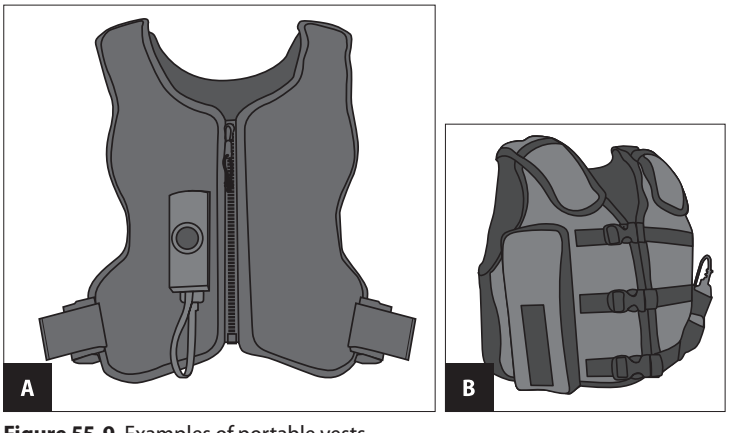


Figure 55-9. Examples of portable vests.

Cough Assist Device

The cough assist device (CAD) is used to augment weak and ineffective cough in patients with conditions such as neuromuscular diseases and spinal trauma. Initially called the insufflator-exsufflator, the machine was renamed the cough assist device and has been modified and updated to become truly portable (**Figure 55-10**). This device generates both positive and negative pressure breaths and can be used in a manual or automatic mode. The interface between the patient and the device can be a mouthpiece, mask, or airway tube (either endotracheal or tracheal). Weaker patients benefit by coughing along with the machine as able or can remain fully passive with glottis open. Even young children and infants can be assisted by using this device. More extensive explanations of teaching and performing these cough assist skills are referenced.[17,20]



Figure 55-10. Example of a cough assist device.

Intrapulmonary Percussive Ventilator

The intrapulmonary percussive ventilator (IPV) is another large machine that provides a mouthpiece, mask, or tube interface. In this ventilator, positive pressure is generated with jet pulses of air with carefully controlled flow via pistons. The inspiration to expiration ratio is fully controlled so that expiration time always exceeds inspiration time, ensuring that mucus clearance proceeds in the direction of the mouth. Continuous aerosol is required in conjunction with this device because the combination of large airflows and minute volumes is excessively drying to the airways. Epinephrine or selective bronchodilators are made for continuous airflow use. A recent pediatric review compared 9 trials, 3 in patients with CF and 6 in patients with non-CF bronchiectasis. Intrapulmonary percussive ventilator was not superior to other methods of airway clearance, but in patients without CF, it showed promising results to treat and prevent atelectasis and reduce hospital length of stay without adverse effects.[21]

Upkeep and Cost Considerations

Devices used for airway clearance require regular cleaning. The prescribing physician should provide detailed information to the family and the primary care physician regarding specific upkeep and maintenance considerations for the specific devices. All the large devices for airway clearance are significantly more costly than handheld devices (**Table 55-2**). Adherence is monitored via Bluetooth technology to generate reports transmitted to the practitioner for review. Disposable vests have also been developed to decrease costliness and are able to function for approximately 1 year before requiring replacement. The standard vest, CAD, and IPV are durable machines that serve patients for many years. Cost may be borne by insurance companies, but used devices, without maintenance contracts, are also available via online retailers for deep discounts. Replacement is most often stimulated by the desire for a newer, more portable device modification rather than a machine failure. These large airway clearance devices can be used passively or combined in the cooperative patient with active respiration strategies as described previously.

Table 55-2. Cost Comparisons of Airway Clearance Therapy Equipment

Airway Clearance Therapy Type	Device Cost	Respiratory Therapy Training (approximately 1 hour per session)
Chest physical therapy	NA	1–2 sessions
Huff	NA	1 session
Active cycle of breathing technique	NA	2 sessions
Autogenic drainage	NA	4–6 sessions
Positive expiratory pressure valve	~ $30	1 session
Flutter valve	~ $60–$150	1 session
Acapella	~ $30	1 session
Aerobika	~ $85	1 session
Vest	~ $7,900	1 session
Monarch Vest	~ $16,425	1 session
Cough assist device	~ $3,700	2–3 sessions
Intrapulmonary percussive ventilator	~ $9,500	1 session

Abbreviation: NA, not applicable.

Selection of Airway Clearance Technique

Infants or very young children typically require assistance and dependent methods of ACT, traditionally using CPT or large machines. Vest jackets have been developed even for infants with a chest size of 19 inches or more. Multiple options are available, and therapies may be modified to suit maturity and lifestyle. Additionally, offering patients input and choice of techniques can

increase adherence. Action plans are generally supplied to the patient with a well plan using the ACT of choice for that patient at the frequency that maintains health, and a sick plan for more frequent therapy to support the child through illnesses at home. Most sick plans include treatments at a maximum of 4 times daily. Other enhancers of airway clearance can include exercise, playing wind instruments, and vocal training.[22] Many of the techniques in this chapter are demonstrated in online videos; a listing of some helpful video links can be found in **Table 55-3**. Many respiratory therapists and some physical therapists who teach these skills become very proficient and can assist providers in selecting and refining skills for airway clearance.

Table 55-3. Instructional Videos of Airway Clearance Techniques

Airway Clearance Therapy Type	Video Training/Demonstration: YouTube Videos
Chest physical therapy	Chest physical therapy for infants https://www.youtube.com/watch?v=4W1PSPJReRI
Huff	Huff technique: Primary Children's Hospital https://www.youtube.com/watch?v=8UKd-GRNUFk
Active Cycle of Breathing Technique (ACBT)	ACBT: Primary Children's Hospital https://www.youtube.com/watch?v=dJ2--HnSEEM ACBT: Derriford Hospital National Health Service (NHS) https://www.youtube.com/watch?v=XvorhwGZGm8&t=8s
Autogenic drainage	Autogenic drainage technique: Derriford Hospital NHS physiotherapy https://www.youtube.com/watch?v=_n0nuy8VWmI
Positive expiratory pressure valve	Positive expiratory pressure technique: NHS physiotherapy https://www.youtube.com/watch?v=lqKD_XxwnAM
Acapella	Acapella therapy for cystic fibrosis: NHS https://www.youtube.com/watch?v=MNtdVQe9BDQ
Aerobika	Aerobika OPEP: Primary Children's Hospital https://www.youtube.com/watch?v=F7YFJRXecjk
Vest	Vest therapy for cystic fibrosis Multiple options for hill rom, smartvest, afflo vest
Monarch Vest	Monarch therapy for cystic fibrosis https://www.youtube.com/watch?v=v8wlaVa5Wik
Cough assist device	Cough assist device: Cincinnati Children's https://www.youtube.com/watch?v=0hAslVzfFLs
Intrapulmonary percussive ventilator	Percussionaire https://www.youtube.com/watch?v=COlzQWaRjpM

Abbreviation: OPEP, oscillating positive expiratory pressure.

Inhaled Medications and Airway Clearance Techniques

Pharmacologic therapies to aid in airway clearance have primarily been devised for and evaluated in patients with CF. Dornase alfa (recombinant human deoxyribonuclease [DNase]) enzymatically cleaves DNA that is found in high concentration in the sputum of patients with CF. The DNA is present because of the necrosis of neutrophils that have been drawn into the airway in response to infection. DNase has a significant impact on mucus viscosity, improves pulmonary function in patients with CF, and decreases pulmonary exacerbations in trials lasting 6 months to 2 years. Adverse effects are minimal, including voice alteration and rash.[23] It is sometimes used in children with other conditions, but there is no evidence of effectiveness outside of CF.[8] Hypertonic saline (7%) has also been shown to be of benefit in patients with CF, presumably by osmotically augmenting airway surface liquid.[24] N-acetyl cysteine (10% solution) is thought to lyse disulfide bonds in mucin and improve the liquidity and ease of removal, but there is little supporting evidence for efficacy when inhaled, per a 2013 review.[25] Subsequent to this review, oral administration, which may affect glutathione production, was proven to stabilize lung function compared to placebo in a randomized controlled trial in patients with CF.[26] Bronchodilators are helpful to relieve or prevent bronchoconstriction in patients with airway hyperreactivity but are not universally beneficial and might be detrimental in patients with tracheomalacia or bronchomalacia, who depend on smooth muscle tone to maintain airway patency.[27–29]

Some children have copious oral secretions and continuous drooling and chronically aspirate. Anticholinergics are often given and may be effective and helpful. Alternatively, the child may be treated with botox injection to salivary or submental glands to determine if temporary cessation of output is helpful to airway clearance. This may help about 75% of patients but is most often effective for 6 months. If so, more permanent gland ablation can be performed sugically.

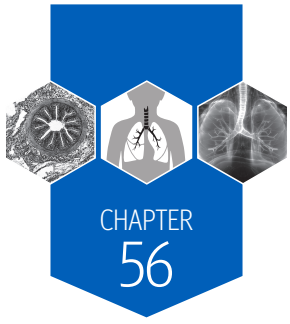
key points

- A wide selection of independent and dependent techniques is available to improve airway clearance in patients.
- Use CPT for infants and very small children.
- Teach concepts related to breathing at a young age. Children need to learn a vocabulary for these skills. Parents can teach them *cough, breathe in, breathe out, blow,* etc. Preschool-aged children can learn diaphragmatic breathing and the huff cough.
- Most pulmonary and respiratory specialists become skilled in the application of these techniques and can assist generalists in decision-making regarding the selection and refinement of ACT skills.
- Weaker patients with poor cough are best managed with manual cough assistance or the CAD.
- The Cystic Fibrosis Foundation has developed comprehensive new guidelines on airway clearance technique (https://www.cff.org/cf-airway-clearance-therapies-clinical-care-guidelines), which are a good reference for patients with CF or other diseases causing bronchiectasis and productive cough.

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CHAPTER 56

Aerosol Delivery of Medication

Ariel Berlinski, MD, FAAP, FAARC

Introduction

Inhaled therapy is a mainstay of treatment for a wide variety of respiratory diseases in children. Disease management guidelines recommend inhaled corticosteroids and bronchodilators for controlling asthma, and mucoactive agents and antibiotics for treatment of lung disease in cystic fibrosis (CF).[1,2] There is also interest in using aerosols for systemic delivery of molecules that would otherwise be degraded in the gut or require injection.

The challenges of successful delivery of drugs to the lungs are much greater than those of either oral or systemic drug delivery. The respiratory tract is efficient at filtering out foreign materials. Aerosol devices and breathing techniques must be able to bypass these defenses to deposit drugs in the lungs. The success of aerosol delivery depends on several complex, interrelated factors. Improper use of aerosol devices is associated with poorer clinical outcomes,[3] so it is crucial that children and their caregivers be familiar with aerosol principles and the correct operation of different aerosol delivery devices.

Aerosol Principles

Advantages of Aerosols

Inhaled topical therapy potentially provides a high *in situ* concentration and usually requires lower doses than systemic treatment, thus maximizing the desired effects while reducing systemic effects.[4] In the case of inhaled bronchodilators, the onset of action is far quicker than oral therapy, providing rapid relief of bronchospasm. The improved therapeutic index of corticosteroids delivered by inhaled route helps to minimize side effects of adrenal and growth suppression. Antibiotics like tobramycin inhalation solution can achieve 100-fold the concentration in airway secretions vs the intravenous route for children with CF, while reducing the risk of ototoxicity and nephrotoxicity. The gut renders protein-based drugs inactive (eg, dornase alfa for CF), making inhalation the best modality.

Aerosol Drug Delivery

An aerosol is a suspension of solid or liquid particles in a carrier gas. There are numerous factors that influence particle deposition, including characteristics of the aerosol itself as well as variables pertaining to the person inhaling the aerosol[4] (**Box 56-1**).

Aerosol Variables Affecting Drug Delivery

Particle size distribution of an aerosol is one of the important factors that determine the likelihood of lower airway deposition. Aerosols are characterized by the mass median aerodynamic diameter (MMAD) (ie, the size for which half of the mass of the drug is contained in particles that are larger, and half in particles that are smaller), and by the geometric standard deviation (GSD). The MMAD and GSD are measures of central tendency and distribution around it respectively. Drug deposition occurs due to different mechanisms: inertial impaction, gravitational sedimentation, and Brownian diffusion (random motion at the alveolar level). Fast-traveling aerosols, those with MMAD greater than 3 mcm, and those that have to negotiate sudden changes in direction are deposited by inertial impaction. This is the main deposition mechanism in upper and large airways. This explains in part why newer inhaled corticosteroids formulated as solutions (MMAD closer to 1 mcm) have lower upper airway deposition. Aerosols between 0.5 and 3 mcm are mainly deposited by gravitational sedimentation. This is the basis for recommending the use of a breath-holding maneuver when possible.[4] Finally, particles smaller than 0.5 mcm are either exhaled or deposited by Brownian diffusion. Most pharmaceutical aerosols are polydisperse (GSD greater than 1.2). In theory, the larger particles deposit more centrally and the smaller ones deposit more distally in the airways.

Box 56-1

Factors Determining Aerosol Deposition

Aerosol Factors

- Particle size
- Velocity
- Hygroscopic properties
- Drug viscosity and surface tension
- Suspension vs solution
- Use of add-on devices

Patient Factors

- Breathing pattern (eg, tidal volume, rate)
- Age
- Inspiratory flow rate
- Nasal vs mouth breathing
- Anatomical differences
- Cognitive abilities
- Behavior
- Acceptance of interface
- Contrivance
- Adherence

Patient Variables Affecting Drug Delivery

Patient variables, including tidal volume and respiratory rate, are important for aerosol deposition. In general, the larger the inhaled tidal volume and the slower the respiratory rate, the higher the lung deposition. In addition, as previously noted, a breath hold at the end of inspiration improves deposition for pressurized metered dose inhalers (pMDIs) but not for a continuously operating nebulizer.

Upper airway anatomy influences the degree of lung deposition. Nasal breathing can filter half of an aerosol drug before it can reach the lower airways.[5] The upper airways of infants and young children are much smaller than those of an adult and also filter a considerable amount of drug before it reaches the lungs. Probably for this reason, as well as for their shorter inspiratory times and lower tidal volumes, infants and young children do not require a dose adjustment based on size, since the amount reaching the lung is proportionately smaller.

Lower airway obstruction, as found in asthma, bronchiolitis, and CF, results in more central and patchy intrapulmonary deposition. Infants and young children also tend to deposit aerosol more centrally since their lower airways also have a smaller caliber. Therefore, successful aerosol delivery to the peripheral lung in sicker and younger patients is much more challenging.

A quick review of factors determining aerosol deposition (see **Box 56-1**) highlights the challenge of delivering aerosols to infants and young children. They are preferential nose breathers and have smaller upper and lower airway sizes, smaller tidal volumes, and more rapid respiratory rates. They do not have the cognitive ability to follow commands or understand specialized inhalation maneuvers, so they are restricted to devices that only require tidal breathing, and those with a mask as the interface between device and patient. Nebulizers and pMDIs attached to a valved holding chamber (VHC) can have mask attachments, but the masks must be applied close to the child's face with a nebulizer to prevent escape of aerosol, and they must be tight fitting with a VHC to draw the medication out of the chamber. Unfortunately, a high proportion of young children do not tolerate masks, even with repeated use, and become fussy or cry during the treatment.[6] The crying child exemplifies the challenges faced by physicians because crying involves a prolonged exha- lation, followed by a rapid inhalation. Thus, drug is wasted from the device during the long exhalation, and the rapid inhalation increases impaction in the upper airways, resulting in low lung deposition.[7]

To optimize aerosol delivery in small children, first choose the delivery device and interface that are best tolerated. This will require some trial and error, and the prescribed drug must be available in the desired delivery devices. Second, distract the child during aerosol administration with toys or videos, and try to

make a game out of it with incentives for good performance. They should not regard their treatments as a form of punishment, and they may not comprehend that the medication is to make them feel better. Using the blow-by technique with a nebulizer (holding the mask away from the face) is discouraged, based on in vitro and deposition studies.[7] Finally, there is evidence that providing aerosols with less than 2.5 mcm to children younger than 3 years may enhance aerosol delivery to the lungs.[8]

Aerosol Delivery Devices

Systems for delivery of inhaled medications include wet nebulizers, pMDIs, soft mist inhalers, and dry powder inhalers (DPIs). Each of these systems has unique advantages and disadvantages, but most of these technologies are decades old and are relatively inefficient in terms of the proportion of the nominal dose reaching the lower airways (especially in children). These inefficiencies have been tolerated for bronchodilators and inhaled corticosteroids because their dose-response curves are steep at low doses and their therapeutic indexes are high. Novel delivery technologies have been designed to improve delivery efficiency for newer therapies that are expensive, have a lower therapeutic index, or require precision targeting to a particular part of the airway (eg, gene therapy in CF).[9]

Nebulizers

Nebulizers are aerosol devices that convert a liquid solution or suspension into an aerosol for inhalation. The 3 main types of nebulizers are the jet nebulizer (sometimes called small-volume nebulizer); ultrasonic nebulizer; and mesh nebulizer. The jet nebulizer is the type most commonly prescribed by pediatricians, probably because of the relatively low cost and availability. Some advantages and disadvantages of jet nebulizers are listed in **Box 56-2.**

Jet Nebulizers

Jet nebulizers deliver compressed gas (supplied by an electric compressor, hospital air, or oxygen) through a small jet orifice, generating a negative pressure that draws fluid from the nebulizer cup. The fluid is entrained in the stream of gas and sheared into particles. Larger, non-respirable particles impact against a baffle and are recirculated, whereas smaller aerosol particles are directed to the patient. Some evaporation and cooling occur when particles are recycled, causing an increase in drug concentration in the residual volume that remains in the nebulizer cup after the nebulization is complete. In general, the residual volume ranges between 0.5 and 3 mL, thus wasting a large proportion of the loaded dose. Practitioners should avoid the practice of decreasing loading volume as a way of decreasing patient dose because of the fixed residual volume.[10] The aerosol characteristics and delivery efficiency may differ by severalfold among different compressor-nebulizer combinations.[11]

Box 56-2

Advantages and Disadvantages of Jet Nebulizers

Advantages

- Easy technique (tidal breathing)
- Can use at any age
- Can use with any disease severity
- Can be used with artificial airways
- Can be used with mechanical ventilation
- High doses possible (eg, can be used to deliver antibiotics)
- Inexpensive

Disadvantages

- Bulky, less portable than pressurized metered-dose inhalers or dry-powder inhalers
- Longer treatment times
- Require cleaning and disinfection
- Noisy (may disturb infants)
- Require power source
- High variability between nebulizer and compressor brands

Electronic compressors decay over time, resulting in longer-than-usual delivery times.

There are 3 different types of jet nebulizers. Continuous output jet nebulizers are the most common and least expensive type. These devices waste aerosol during exhalation. Breath-enhanced jet nebulizers incorporate a one-way valve that entrains air into the drug reservoir during inspiration. This results in increased aerosol output during inspiration and decreased waste during exhalation. Breath-actuated nebulizers only release aerosol during inspiration, resulting in no waste during exhalation. If a unit dose of drug is used, the length of treatment may be longer but delivered dose will be higher. Depending on the drug characteristics (dose-response curve, side-effect profile), dose adjustments may be necessary with a breath-actuated nebulizer. Since a certain inspiratory flow is necessary to trigger the release of aerosol from these devices, practitioners need to make sure that young patients can indeed achieve this inspiratory flow.

Ultrasonic Nebulizers

Ultrasonic nebulizers operate with piezoelectric crystal that vibrates at a set frequency and transfers energy to the fluid placed in a reservoir to produce a mist.[4] Ultrasonic nebulizers are quieter and faster than jet nebulizers, though they produce a larger particle size than jet nebulizers, which may reduce the dose that reaches the lungs. Ultrasonic nebulizers cannot effectively deliver suspensions like budesonide[12] and could potentially denature protein drugs like dornase alfa due to heating produced during aerosolization.

Mesh Nebulizers

Mesh nebulizers are the most recent addition to the nebulizer menu. These devices use a piezo element to either move a perforated membrane against the solution to "micro-pump" the fluid through the holes (Aeroneb, Aerogen, and eFlow, PARI Pharma), or to move a vibrating horn that shoots the fluid through a mesh to create the aerosol (MicroAir, Omron).[9] Mesh nebulizers are small and silent, have small residual volumes, and are faster than most jet nebulizers.

Many mesh nebulizers are designed to only deliver a specific drug by matching it to the size of the apertures of the plate. The available "open" devices are designed to give approximately the same performance efficiency as a breath-enhanced jet nebulizer. To do this, the particle size is larger to compensate for the lower residual volume, thus offering no advantage other than speed. Also, the micron-sized holes in the mesh are easily clogged, so these devices are not suitable for suspensions like budesonide. These devices are expensive and not always covered by insurance.

Nebulizer-Patient Interface

The interface between the nebulizer and patient is very important. Although masks and mouthpieces seem to provide similar clinical benefits,[13] the use of the latter avoids drug filtering in the nose and decreases facial deposition and potential side effects.[14] Transition to mouthpiece can usually be done at age 4 years. Mask design is an important factor in minimizing side effects. Several studies have shown that front-loaded masks lead to less ocular deposition than bottom-loaded masks.[14]

Nebulizing Multiple Drugs

The nebulization of several drugs together is discouraged because of potential changes in their characteristics. Albuterol and ipratropium bromide are an exception, though this combination is available commercially. Also, combining unit-dose drugs will significantly increase the delivery time (more fluid to nebulize), so combining drugs in the nebulizer would only be advantageous if one of them is in a concentrated form.

Nebulizer Maintenance

Routine maintenance of nebulizers is often ignored. All nebulizers need to be cleaned after each use and disinfected according to manufacturer's instructions. Cleaning can be done by washing with soapy water followed by rinsing and air-drying. Disinfection can be done by several methods, including boiling in water for 5 minutes, immersion in 70% isopropyl alcohol (5 minutes) or 3% hydrogen peroxide (30 minutes). Rinsing with sterile or filtered water will be necessary if either alcohol or peroxide is used. Other options include microwaving in water (5 minutes) or using a dishwasher (30 minutes), provided water remains hotter than 158°F.[15] Disinfection with a steam sterilizer (like those used for baby bottles) is advisable for mesh nebulizers and can be used for jet nebulizers as well. It is also important to change compressor filters per manufacturer's recommendations.

Pressurized Metered-Dose Inhalers

Pressurized metered-dose inhalers are popular as delivery systems because they are small and convenient to use. However, many errors in the inhaler technique have been reported in both patients and caregivers.[16,17] Each pMDI canister contains micronized drug suspended (fluticasone) or dissolved (beclomethasone and ciclesonide) in a propellant (hydrofluoroalkane). A metering valve holds a few microliters of the suspension/solution, and when the device is actuated, the metering chamber is exposed to the atmosphere and the reduction in chamber pressure causes the rapid boiling of the propellant, releasing the contents at a high velocity. A delay between shaking and firing results in a significant variance of delivered dose of suspensions.[18]

The newer steroid formulations have a smaller MMAD (1.1–1.2 mcm) that minimizes upper airway deposition[19] and could be potentially advantageous for younger children compared to solutions that have a larger MMAD.[8,20]

Spacers and Valved Holding Chambers

Metered-dose inhalers are often used with add-on devices like spacers and VHCs. Spacers are valveless tubes that work by allowing deceleration of the aerosol and shrinkage of the particles. Conversely, VHCs incorporate a one-way valve to contain the aerosol in the chamber for a few seconds until the valve is opened by the patient's inspiratory effort and to divert the expiratory flow away from the chamber. Both spacers and VHCs reduce the high oropharyngeal deposition (and local side effects) of pMDIs, but only VHCs help overcome the difficulty in coordinating actuation with inhalation; they are, therefore, favored over simple spacers.

Some of the advantages and disadvantages of pMDIs and VHCs are reviewed in **Box 56-3.**

Box 56-3

Advantages and Disadvantages of Metered-Dose Inhalers

Advantages

- Compact, portable
- Rapid delivery
- Multidose convenience
- Any age (when used with a valved holding chamber)
- Most products have dose counters

Disadvantages

- Cleaning and priming instructions are specific for each product
- Requires coordination for actuation and inhalation
- High oropharyngeal dose if not used with valved holding chamber/spacer
- Intolerance of tight face mask (young children)
- Limited number of drugs available

These delivery systems are portable and noiseless, can be used for children of any age, and can be used with artificial airways (tracheostomies, intubated patients). The biggest attraction is that they are less time-consuming than nebulizers. There are only a few types of drugs available in pMDIs, including bronchodilators and inhaled corticosteroids (asthma medications).

Most VHCs allow insertion of the pMDI mouthpiece into a connector, thus using its own boot (plastic holder). Some VHCs require the pMDI canister to be removed from its own plastic boot and inserted into a universal boot for actuation. This could potentially change the aerosol characteristics; thus, this type is not ideal.

There are several brands and designs of VHCs, leading to a high degree of variability in dose delivery between devices.[21] Many early devices are made from polycarbonate, which has a high electrostatic charge and can reduce the drug output. Most newer VHCs are manufactured with a charge-dissipating material to overcome this problem. The electrostatic charge of older devices can be neutralized by washing the VHC in soapy water and letting it air-dry without rinsing the inside. Although VHCs overcome the need for precise coordination, the aerosol does not stay suspended for more than a few seconds, so a delay in inhalation will significantly decrease drug output. Also, the delay between shaking and actuation should be minimal. Patients requiring more than one actuation of medication should allow a 30-second interval between them and shake the canister right before actuating it. Patients should inhale the drug after each actuation.

Some VHCs have whistle systems that provide feedback when high inspiratory flows are achieved. However, these signals are largely inaccurate and vary with the design of pMDI.

Care and Use of Inhalers

The care of hydrofluoroalkane inhalers requires frequent cleaning of the actuator's orifice to avoid clogging. Inhalers need to be primed with their first use and each time they are not used for prolonged periods (varies between products but may be as short as 2–3 days). Unfortunately, each device has different instructions for cleaning and priming. The prescriber should be familiar with the specifics of each drug.

The VHCs with mask attachments allow infants and young children to use medication via pMDI. It is important to choose a mask with a small dead space made of flexible material that forms a good seal with the face.[22,23] A good seal is necessary for the child to open the valve of the VHC, allowing access to the medication in the chamber. For young children who tolerate a close-fitting face mask, the pMDI with VHC is the preferred method for delivery of inhaled asthma medications. However, more than one-third of infants and toddlers do not tolerate the tight-fitting mask and should use the alternate delivery system.[6]

A transition to a VHC with mouthpiece is encouraged at about 3 to 4 years of age to avoid drug filtering by the nose and eliminating facial exposure. Young children can use tidal breathing (3–4 breaths) with the VHC until they are old enough to comprehend single-breath technique.[24] When children reach 4 to 6 years of age, they can be taught to exhale first, seal their lips around the mouthpiece, actuate the pMDI, and slowly inhale to full lung capacity, with a 10-second breath hold to allow particles to settle in the airways. The same technique applies for a pMDI without a VHC, though with corticosteroids the use of a VHC reduces topical oropharyngeal effects.

Most pMDIs have dose counters that document the number of remaining doses. Patients should be reminded not to use the pMDI once the counter reaches zero. The use of pMDIs without a counter is discouraged due to patients' inability to easily know when the device is empty.

Recently, beclomethasone pMDI was changed from regular pMDI to a breath-actuated one. The latter requires an inspiratory flow of at least 20 L/min to actuate the device, making it not a viable option for either young children or those who use VHCs. Breath-actuated devices are ideal for teens, who do not typically like to use VHCs.

Soft Mist Inhalers

Soft mist inhalers are propellant-free inhaler devices that produce aerosol by using the mechanical energy generated by a spring.[25] The aerosol is 10-fold slower than in a pMDI and lasts for 1.5 seconds. It is marketed to be used without a VHC. Currently, the only drug with US Food & Drug Administration (FDA) approval for pediatric age is tiotropium bromide. These devices also need to be primed and should be disposed of 90 days after they are opened.

Dry Powder Inhalers

Dry powder inhalers are drug-device combinations that require breath actuation to either release or generate and release the medication for inhalation. The advantages and disadvantages of DPIs are listed in **Box 56-4**. There are a variety of DPI devices, including capsule-based, single-dose devices and multidose devices with either a bulk drug reservoir or individual doses protected by foil. Generally, the drug is milled into very small particles in the respirable size range. However, small, micronized drug particles have strong forces of attraction and tend to stick together. Passive systems require the inspiratory energy generated by the patient to deagglomerate the powder into particles that can be inhaled. As the inspiratory flow increases, the amount of drug available in small particles also increases and offsets the losses from impaction of the high-velocity particles in the oropharynx.[4] Often, lactose is added as a carrier to improve the separation and flow of small drug particles. Active systems such as the newer breath-actuated devices look similar to a pMDI and require a minimum flow to release the metered drug dose. Novel

Box 56-4

Advantages and Disadvantages of Dry Powder Inhalers

Advantages

- Compact, portable
- Rapid delivery time
- Breath-actuated
- Multidose with counters
- No need for valved holding chamber, spacer

Disadvantages

- Need strong and consistent inspiratory effort
- High oropharyngeal deposition
- Vulnerable to humidity
- Not suitable for young children
- Technique confusion is possible if used with other devices that require slow inhalation

DPI formulations (antibiotics, insulin) use light, hollow, porous particles to improve particle separation and deliver higher payloads.[26] These devices have drug delivery that is independent of respiratory effort once the inspiratory flow threshold is reached.

Inspiratory Effort and Dry Delivery

The ideal inspiratory effort is different for various passive DPI devices depending on their internal resistance. It is a myth that low-resistance devices are better suited for children. Simple physics dictates that with the same inspiratory effort, the flow rate will be higher through a low-resistance device, and vice versa. However, higher-resistance devices have internal channels that help the deagglomeration process, and higher resistance may open the glottis to allow more drug to pass the larynx. Another misconception is the belief that patients who have asthma are unable to attain sufficient inspiratory flow to derive clinical benefit from a higher-resistance DPI.[27]

Use of Dry Powder Inhalers

The main limiting factors for DPI use in young children are that they lack the inspiratory flow necessary to power the device and that young children may not comprehend the maneuver to operate a DPI. Young children sometimes would rather blow into a device than inhale from it, which would moisten the powder and make it impossible to aerosolize. For these reasons, it is reasonable to exclude the use of DPIs until about 6 years of age, whether or not they are approved for younger ages.

There are many types of DPIs that look and operate differently. Each pharmaceutical company has its own proprietary device with a unique set of instructions. This can be confusing for patients who require more than one device for control of their asthma or other lung disease. Therefore, patients would have to learn to inhale forcefully from their DPI controller medication and inhale their rescue drug slowly from their pMDI. More recently, a multidose platform of a breath-actuated DPI was approved in the United States. The platform includes a short-acting bronchodilator, a corticosteroid, and a corticosteroid/long-acting bronchodilator combination. Patients with CF are often treated with inhaled antibiotics, both FDA approved and non–FDA

approved. The most common of those inhaled antibiotics, tobramycin, which was traditionally prescribed in nebulizer form, is also now available as a DPI. Practitioners need to learn about the specifics for each device they prescribe.

Choosing the Appropriate Delivery Device

The increasing number of device choices can be confusing and intimidating to patients and clinicians alike. There are hundreds of papers that argue the merits of one device versus another, but a comprehensive meta-analysis of this literature provided evidence-based guidelines in a variety of inpatient and outpatient settings,[28] concluding that each of the aerosol devices works equally well in a variety of clinical settings *in patients who can use the device appropriately.* Clinicians have to educate themselves to properly educate their patients in the correct techniques for use and maintenance of their devices. The use of peak inspiratory flow meters with variable resistance can facilitate the correct choice of the inhaler device for a given patient.[29] Given the high rate of device misuse, review of inhaler technique at each clinic visit is advised.

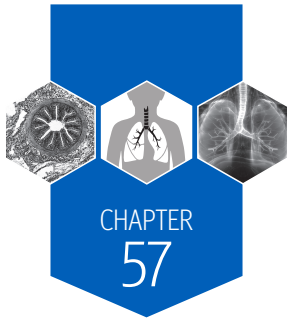
key points

- Some medications may require choosing a specific delivery device (eg, nebulized budesonide and inhaled antibiotics that have been evaluated in clinical trials).
- The choice of delivery system depends on the age, comprehension, and capability of the child. This will often require a trial in the office to evaluate.
- The third-party payer may dictate which device is covered. Unfortunately, this is often state-specific and changes frequently.
- Cost, time savings, and portability should be considered when choosing the device. Decreasing the burden of care enhances adherence to the medical regimen.
- The technique of medication delivery should be reviewed often with the caregiver to ensure that the device is being used correctly. Clinicians need to be familiar with the various devices to be able to teach how to use them.
- Acceptability by the child and family is of paramount importance for adherence and clinical outcomes. Sometimes a trial with different delivery systems may be necessary, or using 2 types of delivery systems may be appropriate (eg, using a nebulizer at home and a pMDI with VHC at child care for best clinical outcomes).
- An updated comprehensive guide on aerosol delivery is available from the American Association for Respiratory Care.[30] This invaluable guide has pictures and detailed instructions for how to use and care for each device.

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Bronchodilators

John Welter, MD
H. William Kelly, PharmD
Leslie Hendeles, PharmD

Introduction

Bronchodilators are used in a number of obstructive respiratory diseases of childhood for the relief of airway smooth muscle contraction (ie, bronchospasm). Although bronchodilators are approved by the US Food & Drug Administration (FDA) only for the treatment of asthma and chronic obstructive pulmonary disease (COPD), they are commonly prescribed for children with cystic fibrosis (CF), bronchiolitis, and bronchopulmonary dysplasia (BPD), despite lack of consistent evidence of efficacy for these conditions.

Neonates are born with fully functional airway smooth muscle whose mass relative to airway size is fully developed by 25 weeks' gestation.[1] Neonatal bronchial tissue responds to both β_2-agonists and cholinergic stimulation similarly to adult bronchial tissue because neonatal β-adrenergic receptors are similar in density to the airway smooth muscle in adults.[2,3] Thus, differences in response to the various bronchodilators between infants, children, and adults will more likely be due to issues involving mechanisms of airway obstruction, dosing, responsive capacity of the lung, and drug delivery than to pharmacologic responsiveness of the smooth muscle.

Bronchodilator Mechanisms

Three categories of bronchodilators are used clinically. These include β_2-agonists, methylxanthines, and anticholinergic drugs.

β_2-Agonists

The β_2-agonists are the most effective bronchodilators used in clinical practice. The β_2-adrenergic receptor is a G protein–coupled transmembrane receptor that exists in a conformational equilibrium between the activated and inactivated states. Agonist binding shifts the equilibrium to the activated state, leading to increased intracellular production of cyclic adenosine

monophosphate and a corresponding, proportional decrease in smooth muscle tone. Continued stimulation by an agonist will result in desensitization that occurs within 1 to 2 weeks of regular administration, levels off, and does not then worsen over time.[4] It is a receptor phenomenon; therefore, cross-tolerance to all of the β_2-agonists occurs. Concomitant use of corticosteroids can attenuate the β_2 tolerance.

Synthetic β_2-agonists differ in their potency and selectivity for β_2-adrenergic receptors. Naturally occurring epinephrine equally stimulates α-adrenergic receptors (smooth muscle constriction), β_1-adrenergic receptors (cardiac tissue contraction and conductance), and β_2-adrenergic receptors, whereas early synthetic agents such as isoproterenol are selective β-agonists, equally potent for the β_1-adrenergic and β_2-adrenergic receptors.[4] The currently available short-acting β_2-agonists (SABAs)—albuterol and terbutaline—are equally β_2 selective, whereas the inhaled long-acting β_2-agonists (LABAs) are slightly more β_2 selective.[4] The LABAs have a duration of action of 12 to 24 hours compared with the 2- to 4-hour duration of SABAs, due to LABAs' increased lipophilicity, allowing them to be retained in the lung tissue for prolonged periods.[4,5] Retention in the lung also improves their therapeutic index (bronchodilation to systemic effect ratio) over the SABAs.[6] Although all LABAs have a similar duration, the onset of effect for formoterol is similar to that of a SABA.

The synthetic β_2-agonists exist as racemic mixtures of equal amounts of 2 enantiomers (mirror image chemicals) with the exception of levalbuterol and arformoterol, which contain only the most active enantiomers, (R)-albuterol and (R,R)-formoterol, respectively. The inactive isomers do not significantly compete for the receptor.[6]

Anticholinergics

The anticholinergics competitively block acetylcholine at the muscarinic receptors in the airways.[7] Unlike the β_2-adrenergic receptors, the distribution of muscarinic receptors in the lung diminishes as the airways become more peripheral, as does the cholinergic innervation.[7] Atropine is a tertiary ammonium compound that is readily absorbed across membranes, including the central nervous system, so it is of limited clinical utility as an anticholinergic due to adverse effects.[7] The quaternary ammonium compounds, such as ipratropium bromide and tiotropium, are very poorly absorbed across membranes, causing minimal to no systemic effects when applied topically. Umeclindium, aclidinium, and tiotropium have a longer duration of action (24 hours) due to greater lipophilic nature than ipratropium bromide (duration 6 hours).[5] Unlike with β_2-agonists, bronchodilation tolerance does not appear to occur in response to anticholinergics.[5]

Methylxanthines

Theophylline is the only methylxanthine that has been used clinically as a bronchodilator. It has modest bronchodilator effects at optimal serum concentrations. In addition, it has modest anti-inflammatory, immunomodulatory, and bronchoprotective effects, which contribute to its efficacy as a controller medication for persistent asthma. It increases intracellular concentrations of cyclic adenosine monophosphate in airway smooth muscle and inflammatory cells by nonspecific phosphodiesterase inhibition.

Theophylline is used infrequently for asthma because of its risk of adverse effects. It may be considered, however, when patients are unable to tolerate first-line therapies. The benefits and risks from theophylline are closely correlated with serum concentrations. The maximum potential benefit with the least risk of adverse effects is achieved at peak concentrations of 55.50 to 83.25 mcmol (10 to 15 mcg/mL). Because of variable rates of metabolism, concentrations can vary greatly among children receiving the same dose; therefore serum concentrations must be measured to adjust dosage.[8]

Pathophysiology and Clinical Features of Airway Obstruction

Airway obstruction in children with asthma is produced by bronchospasm, airway edema, desquamation of airway epithelium, and mucus plugging. The rapid response to bronchodilators seen in most patients with acute severe asthma exacerbations suggests that much of the obstruction is caused by bronchospasm. The excessive bronchospasm triggered by external stimuli, such as irritants, exercise, chemicals, and allergens, is termed *bronchial hyperresponsiveness* (BHR) and is a cardinal feature of asthma.[9] While asthma is primarily an inflammatory disease, it is clear that bronchodilators play an important role in treating and preventing ongoing symptoms and reducing the severity of exacerbations.

Bronchospasm plays a less prominent role in the airway obstruction of airway diseases other than asthma; thus, bronchodilators are less likely to be effective. The airway obstruction of children with CF is caused by chronic bacterial infection leading to airway inflammation and mucus with increased viscosity that is difficult to clear from the airways.[10] Bronchopulmonary dysplasia has a component of neutrophilic inflammation as well but is primarily caused by a maturational failure of airway development combined with damage from either the high oxygen or barotrauma secondary to mechanical ventilation.[11] Airway edema, increased airway resistance, and BHR are features of BPD.[11] The bronchospasm seems to be primarily induced via cholinergic mechanisms similar to that seen in COPD of adults, where the

inflammatory process is also primarily due to neutrophils and not eosinophils.[12] Acute severe bronchiolitis, generally secondary to respiratory syncytial virus and other viruses, induces airway obstruction via inflammation, edema, and mucus plugging.[13] Wheezing, hyperinflation, dyspnea, retractions, and cough are all signs of airway obstruction, regardless of mechanism; therefore, the differential diagnosis is broad and includes a number of conditions that are not responsive to bronchodilators.[9] Nonetheless, given the difficulty of establishing a clear diagnosis, many clinicians will give a trial of bronchodilators to assess response.

Clinical Pharmacology and Disease Management

Asthma is the only disease for which β_2-agonists, anticholinergics, and theophylline are approved for children by the FDA.[9] Furthermore, the use of any bronchodilators in children younger than 2 years and the use of metered-dose inhalers (MDIs) in children younger than 4 years is off-label. These therapies have not been evaluated adequately for FDA approval despite extensive clinical experience and use.[14,15] The dosages in **Table 57-1** are based on clinical trials or clinical use that was not controlled. Tiotropium is approved for use in children 6 years and older with asthma; the remainder of the anticholinergic bronchodilators are approved only for COPD in adults.[16]

Acute Bronchospasm

The β_2-agonists are the most effective bronchodilators for reversing bronchospasm in asthma.[9] As functional antagonists, they can reverse bronchospasm secondary to any mediator or neurogenic mechanism.[12] Aerosolized SABAs are the drugs of choice for both the relief of symptoms associated with mild bronchospasm and the initial treatment of severe asthma exacerbations together with systemic corticosteroids to treat the inflammatory component. (See **Table 57-1** for dosing.)[9] In settings of increased inflammation in the outpatient management of bronchospasm, such as viral-induced exacerbations and nocturnal asthma, the usual dose of SABAs can be insufficient to reverse the bronchospasm and the doses may be repeated 3 times at 20-minute intervals depending on the severity of symptoms.[17] The short-acting anticholinergic ipratropium bromide provides additive efficacy with SABAs in severe acute exacerbations, but only improves lung function another 10% to 20% (reversing the cholinergic component) over frequent administration of high-dose SABAs.[9] However, the addition of frequent dosing of inhaled ipratropium bromide to SABAs has resulted in a significant reduction in hospitalizations of children presenting to the emergency department (ED) with severe obstruction.[18] It has not been shown to be beneficial in any other clinical scenario in childhood, either at home or in the hospital. Theophylline and intravenous aminophylline have not demonstrated additive benefit to optimal aerosolized β_2-agonists in the ED.[19]

Table 57-1. Bronchodilator Medication Dosing Chart[a]

Medication	Years of Age		
	<5	5–11	≥12
Inhaled SABAs			
Albuterol MDI 90 mcg/puff, 200 puffs/canister (Use VHC; add mask for children < 4 years of age) **OR** Albuterol dry powder inhaler FDA approved for children 4 years and older	**Home:** 2–6 puffs with VHC + face mask every 4–6 hours as needed for symptoms. May give 2 doses 20 minutes apart as needed for initiation of treatment of acute exacerbation. **ED:** 4–8 puffs with VHC + face mask every 20 minutes for 3 doses, then every 1–4 hours as needed. **Hosp:** 4–8 puffs with VHC + face mask every 1–4 hours as needed.	**Exercise:** 2–6 puffs with VHC 5 minutes prior to exercise. **Home:** 2–6 puffs with VHC every 4 hours as needed for symptoms. May give 2 doses 20 minutes apart as needed for initiation of treatment of acute exacerbation. **ED:** 4–8 puffs with VHC every 20 minutes for 3 doses, then every 1–4 hours as needed. **Hosp:** 4–8 puffs with VHC every 1–4 hours as needed.	**Exercise:** 2–6 puffs 5 minutes prior to exercise. **Home:** 2–6 puffs every 4 hours as needed for symptoms. May give 2 doses 20 minutes apart as needed for initiation of treatment of acute exacerbation. **ED:** 4–8 puffs with VHC every 20 minutes for 3 doses, then every 1–4 hours as needed. **Hosp:** 4–8 puffs with VHC every 1–4 hours as needed.
Albuterol nebulizer solutions 0.63 mg/3 mL 1.25 mg/3 mL 2.5 mg/3 mL 5.0 mg/mL (0.5% diluted with 2–3 mL of normal saline)	**Home:** 1.25–2.5 mg up to every 20 minutes by face mask for up to 2 doses, then every 4 hours as needed. **ED:** 0.15 mg/kg (minimum 2.5 mg) every 20 minutes for 3 doses then 0.15–0.3 mg/kg up to 10 mg every 1–4 hours as needed or 0.5 mg/kg/h by continuous nebulization. **Hosp:** 0.15–0.3 mg/kg up to 10 mg every 1–4 hours as needed or 0.5 mg/kg/h by continuous nebulization.	**Home:** 1.25–2.5 mg every 4 hours as needed for symptoms. May give up to every 20 minutes for up to 2 doses for initiation of treatment of acute exacerbation. **ED:** 0.15 mg/kg (minimum 2.5 mg) every 20 minutes for 3 doses, then 0.15–0.3 mg/kg up to 10 mg every 1–4 hours as needed or 0.5 mg/kg/h by continuous nebulization. **Hosp:** 0.15–0.3 mg/kg up to 10 mg every 1–4 hours as needed or 0.5 mg/kg/h by continuous nebulization.	**Home:** 2.5–5 mg every 4 hours as needed for symptoms. May give up to every 20 minutes for up to 2 doses for initiation of treatment of acute exacerbation. **ED:** 2.5–5.0 mg every 20 minutes for 3 doses, then 2.5–10 mg every 1–4 hours as needed or 10–15 mg/h by continuous nebulization. **Hosp:** 2.5–10 mg every 1–4 hours as needed or 10–15 mg/h by continuous nebulization.

(*continued*)

Table 57-1. Bronchodilator Medication Dosing Chart[a] *(continued)*

Medication	Years of Age		
	<5	5–11	≥ 12
Inhaled SABAs *(continued)*			
Levalbuterol MDI[b] 45 mcg/puff, 200 puffs/canister	See albuterol MDI doses above.	See albuterol MDI doses above.	See albuterol MDI doses above.
Levalbuterol nebulizer solutions 0.31 mg/3 mL 0.63 mg/3 mL 1.25 mg/3 mL	**Home:** 0.63–1.25 mg up to every 20 minutes by face mask for up to 3 doses, then every 2–4 hours as needed. **ED:** 0.075 mg/kg (minimum 1.25 mg) every 20 minutes for 3 doses, then 0.075–0.15 mg/kg up to 5 mg every 1–4 hours as needed or 0.25 mg/kg/h by continuous nebulization. **Hosp:** 0.075–0.15 mg/kg up to 5 mg every 1–4 hours as needed or 0.25 mg/kg/h by continuous nebulization.	**Home:** 0.63–1.25 mg every 4 hours as needed for symptoms. May give up to every 20 minutes for up to 3 doses for initiation of treatment of acute exacerbation. **ED:** 0.075 mg/kg (minimum 1.25 mg) every 20 minutes for 3 doses, then 0.075–0.15 mg/kg up to 5 mg every 1–4 hours as needed or 0.25 mg/kg/h by continuous nebulization. **Hosp:** 0.075–0.15 mg/kg up to 5 mg every 1–4 hours as needed or 0.25 mg/kg/h by continuous nebulization.	**Home:** 1.25–2.5 mg every 4 hours as needed for symptoms. May give up to every 20 minutes for up to 3 doses for initiation of treatment of acute exacerbation. **ED:** 1.25–2.5 mg every 20 minutes for 3 doses, then 1.25–5 mg every 1–4 hours as needed or 5–7.5 mg/h by continuous nebulization. **Hosp:** 1.25–5 mg every 1–4 hours as needed or 5–7.5 mg/h by continuous nebulization.
Injectable epinephrine 1:1,000 (1 mg/mL)	**ED:** 0.01 mg/kg up to 0.3–0.5 mg sq every 20 minutes for 3 doses sq.	**ED:** 0.01 mg/kg up to 0.3–0.5 mg sq every 20 minutes for 3 doses sq.	**ED:** 0.3–0.5 mg sq every 20 minutes for 3 doses.
Injectable terbutaline (1 mg/mL)	**ED:** 0.01 mg/kg up to 0.25 mg sq every 20 minutes for 3 doses sq, then every 2–6 hours as needed.	**ED:** 0.01 mg/kg up to 0.25 mg sq every 20 minutes for 3 doses sq, then every 2–6 hours as needed.	**ED:** 0.25 mg sq every 20 minutes for 3 doses.

Medication	Years of Age		
	<5	5–11	≥12
Anticholinergics			
Ipratropium bromide MDI 17 mcg/puff, 200 puffs/canister	**ED:** 4 puffs with VHC + face mask every 20 minutes times 3 doses, then every 1 hour up to 3 hours	**ED:** 4 puffs with VHC every 20 minutes times 3 doses, then every 1 hour up to 3 hours.	**ED:** 8 puffs every 20 minutes as needed up to 3 hours.
Ipratropium nebulizer solution 0.25 mg/mL (0.025%)	**ED:** 0.25–0.5 mg every 20 minutes, then as needed. (May mix with albuterol nebulizer solution.)	**ED:** 0.25–0.5 mg every 20 minutes, then as needed. (May mix with albuterol nebulizer solution.)	**ED:** 0.5 mg every 20 minutes, then as needed. (May mix with albuterol nebulizer solution.)
Ipratropium/albuterol nebulizer solution 0.5 mg/2.5 mg per 3 mL	**ED:** 1.5 mL every 20 minutes for 3 doses, then as needed.	**ED:** 1.5–3 mL every 20 minutes for 3 doses, then as needed.	**ED:** 3 mL every 20 minutes for 3 doses, then as needed.

Abbreviations: ED, emergency department; Hosp, hospitalized patient; IV, intravenously; MDI, metered-dose inhaler; SABA, short-acting β_2-agonist; sq, subcutaneously; VHC, valved holding chamber.

[a] All doses for asthma unless otherwise indicated.

[b] At equimolar doses, levalbuterol is neither more effective nor does it have fewer systemic effects than racemic albuterol.

Derived from National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program. *Full Report of the Expert Panel: Guidelines for the Diagnosis and Management of Asthma (EPR-3).* US Department of Health and Human Services, National Institutes of Health; 2007. https://www.nhlbi.nih.gov/guidelines/asthma

Intravenous magnesium sulfate has been used for adults and children with severe asthma that is unresponsive to the usual doses of SABAs in the ED.[20] Magnesium sulfate is a moderately potent smooth muscle relaxant, and some studies, but not all, have demonstrated improved bronchodilation and reduced hospitalizations in children when it is added to usual SABA therapy in the ED.[9,20] There are no studies comparing magnesium sulfate with other treatment strategies in patients with severe, unresponsive asthma, including the addition of frequent doses of ipratropium bromide or providing continuous nebulization of SABA, both of which improve lung function and reduce the risk of hospitalization.[9] Thus, the National Heart, Lung, and Blood Institute's National Asthma Education and Prevention Program's Expert Panel Report 3 (EPR-3) Guidelines for the Diagnosis and Management of Asthma states that magnesium sulfate can be considered but falls short of recommending its use.[9]

During hospitalization, the dosage of SABAs is based on the severity of the asthma and the patient's response to therapy.[9] As the patient improves, lowering the dose and spreading out the dosing interval may proceed quickly. Once the child is hospitalized, the addition of ipratropium bromide to SABAs has not been shown to improve outcomes and is not recommended in the EPR-3.[9]

Administration of aerosolized SABAs is more effective and produces fewer adverse effects than oral or parenteral administration, making inhalation the preferred route of SABA administration.[9] Aerosolized SABAs can be administered by either jet nebulization or MDI with equivalent results. A nebulizer or valved holding chamber fitted with appropriately sized face masks may be used for delivery to infants and children younger than 5 years.[9] (See Chapter 56, Aerosol Delivery of Medication.) In addition to requiring higher doses in severe asthma exacerbations, the duration of significant bronchodilation is decreased so more frequent administration (every 20 minutes initially) and even continuous nebulization can improve outcomes over administration on an hourly basis in patients with more severe asthma.[21]

Administering high doses of SABAs can lead to β_2-agonist–mediated systemic side effects, including tachycardia, hypokalemia, hyperglycemia, and prolonged QTc interval, so these should be monitored.[9] Although QTc interval is prolonged by all β_2-agonists, reports of significant cardiac arrhythmias, such as torsades de pointes, are exceedingly rare.[5,6] Metabolic acidosis is a common finding in those who are quite ill with asthma and who are on β_2-agonist therapy. Due to vascular dilatation, SABAs can also slightly worsen the ventilation/perfusion mismatching seen in severe exacerbations, so low-flow oxygen should always be administered during severe exacerbations and transcutaneous partial pressure of oxygen should be monitored.[9] Tachycardia from hypoxemia and stimulation of irritant receptors is common in severe

asthma exacerbations and is not a contraindication for high doses of SABAs. Indeed, the heart rate often decreases in patients receiving high-dose aerosolized SABAs as the airway obstruction improves.[9]

There is no advantage among any of the β_2-selective SABAs (albuterol, levalbuterol, or terbutaline) when given in equipotent doses.[6,9] They all produce a similar degree of bronchodilation and amount of β_2-adrenergic–mediated side effects. Isoproterenol and epinephrine have the potential to produce significantly greater cardiac toxicity. The use of intravenous isoproterenol in children with severe asthma has resulted in myocardial ischemia and is an outdated practice.[9]

Asthma

The SABAs are indicated for as-needed treatment of symptoms associated with bronchospasm (cough, wheezing, and dyspnea) in the outpatient management of asthma.[9] They constitute the primary treatment of intermittent asthma and the primary prevention of exercise-induced bronchospasm (EIB).[9] They are not indicated for regular maintenance administration. Patients who require as-needed SABA therapy for more than 2 days per week, not counting prevention of EIB, generally should not be considered well-controlled and should either be placed on regular anti-inflammatory controller therapy or have their regular controller therapy increased if their compliance is adequate.[17] The use of 2 or more SABA canisters per month has been associated with a significant increase in the risk of severe asthma exacerbations, including death, and the use of 1 or more canisters every 1 to 2 months indicates poor asthma control and an increased risk of needing ED care.[9]

The inhaled β_2-agonists are the most effective preventive therapy for EIB.[9] The SABAs have a duration of protection of 2 to 4 hours, whereas the LABAs protect for up to 12 hours after a single dose. However, the duration of protection against EIB from LABAs when taken regularly decreases to 4 to 6 hours due to tolerance.[6,12] Despite the tolerance from regular administration of a β_2-agonist, most patients are fully protected against EIB in the 1 to 2 hours following SABA administration.[6] Leukotriene receptor antagonists are only partially effective for prevention of EIB, and they are ineffective in up to 40% to 50% of children.[22]

Because of their lack of clinically significant anti-inflammatory effects, LABAs are currently only indicated as adjunct therapy in patients incompletely controlled on low to medium doses of inhaled corticosteroids.[9] They improve base-line lung function and decrease symptoms and as-needed SABA use when added to inhaled corticosteroid therapy. Early studies in which monotherapy with a LABA was added to the usual therapy in children showed an increased risk of serious asthma exacerbations (hospitalization for

asthma).[9,23] This same finding did not occur in studies of combination LABA and inhaled corticosteroids.[24,25] Currently, LABAs are not FDA approved for use in children younger than 4 years. However, enough evidence has accumulated that the 2020 National Heart, Lung, and Blood Institute asthma guidelines recommend combination therapy in infants and toddlers not responding to medium-dose inhaled corticosteroids.[17]

The LABA formoterol is less lipophilic than salmeterol, which allows for a more rapid onset of bronchodilation similar to the SABAs albuterol and terbutaline.[4,12] Some studies have reported improved outcomes compared with SABAs as measured by fewer exacerbations requiring oral corticosteroids or ED visits.[6] In addition, combination inhalers containing both a corticosteroid and formoterol now are recommended by the EPR-3 as a maintenance plus relief medication because clinical trials in children and adults have demonstrated fewer exacerbations with lower overall corticosteroid dosing compared with standard dosing of combination or higher-dose inhaled corticosteroids plus SABAs as reliever.[17,25] The FDA-approved labeling for combination budesonide/formoterol states the drug is only for maintenance therapy and states it should not be used for treatment of acute bronchospasm.

Sustained-release theophylline is still considered an alternative, not preferred, maintenance and adjunctive therapy to the inhaled corticosteroids in children 5 to 11 years of age but not in children 0 to 4 years of age.[9] It is not recommended by the EPR-3 in 0- to 4-year-olds because of a lack of clinical trial data on efficacy and the potential for serious adverse effects in young children and infants.[26] When using theophylline in 5- to 11-year-old children, serum drug concentration monitoring is required to prevent serious toxicity.

The short-acting anticholinergics do not have an FDA-approved indication in children with asthma and have not been shown to improve outcomes in clinical trials.[27] Some have advocated that ipratropium bromide could be used as a reliever in patients unable to tolerate SABAs. It has been used successfully as a reliever in clinical trials involving patients with mild asthma but has a slower onset of action and is not as effective as SABAs.[9] The long-acting anticholinergic tiotropium has been shown to improve lung function in children and adolescents and is FDA approved for maintenance therapy of asthma in children 6 years and older.[16]

Bronchiolitis

The use of bronchodilators in the treatment of acute viral bronchiolitis has been controversial for years. Systematic reviews of SABA use indicate a modest short-term improvement in clinical scores but no improvement in hospitalization rates or duration of hospitalization.[28] However, some of the studies may have included infants with recurrent wheezing and family histories of asthma. Some experts have advocated aerosolized epinephrine for its α-agonist effect producing pulmonary vascular constriction, thus decreasing airway edema.[29] Studies show no benefit of epinephrine in hospitalized infants but show a slightly greater benefit compared with albuterol in outpatient treatment.[28] However, the studies comparing epinephrine as either a single isomer or racemic mixture often used doses of epinephrine that were higher than that of albuterol in terms of β_2-adrenergic potency, so it is unclear whether the slight difference was due to an α-agonist effect or just greater β_2-agonist dose. A large study giving equivalent β_2-agonist doses found no difference between epinephrine and albuterol.[30] Due to potential adverse effects and lack of significant clinical benefit, the current recommendation from the American Academy of Pediatrics is that SABAs not be used in acute bronchiolitis.[31]

Bronchopulmonary Dysplasia

Aerosolized bronchodilators, both SABAs and ipratropium bromide, reduce airway resistance and improve dynamic compliance in infants with BPD.[11] Use of bronchodilators does not prevent the development or change the natural history of BPD and is, therefore, indicated for symptomatic control of increased airway resistance. Continuous treatment without evidence of symptomatic improvement is not indicated. Albuterol and ipratropium last 4 to 6 hours and, in some patients, produce an additive effect when used together.[11]

Cystic Fibrosis

Some patients with CF have a component of BHR, and recurrent wheezing or dyspnea that responds to a SABA is an indication for the short-term use of bronchodilators.[32] Albuterol is often given before hypertonic sodium chloride, chest physiotherapy, and inhaled tobramycin[32] to prevent reflex bronchospasm, but it has not been assessed in controlled trials. The LABAs also improve lung function in the short term but have produced inconsistent long-term effects. Thus, current guidelines recommend neither for nor against chronic use of β_2-agonist in people with CF.[32] Currently, Anticholinergics have not demonstrated beneficial responses in people with CF and are not routinely indicated.[33]

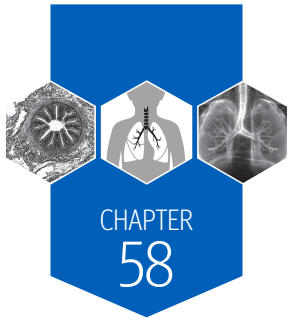
key points

- The SABAs are the most effective bronchodilators for all clinical situations involving bronchoconstriction.
- Although desensitization occurs with regular β_2-agonist use, it is not progressive and is easily overcome with 1 or 2 extra doses of a SABA.
- The LABAs and long-acting muscarinic antagonists should only be used as adjunctive therapy to inhaled corticosteroids.
- Short-acting anticholinergics are second-line agents that should only be used in specific indications (acute severe asthma in the ED, and BPD).
- Numerous pulmonary diseases other than asthma (ie, CF, BPD, bronchiolitis) are associated with wheezing that may or may not be secondary to broncho-spasm. Bronchodilators should only be used if there is a documented positive response.

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Antibiotics for Pulmonary Conditions

Michael J. Light, MD
Nanda Ramchandar, MD, MPH, FAAP
John S. Bradley, MD, FAAP

Introduction

There are many considerations for the choice of antibiotic, as there are with any prescription. The product label (package insert) provides the indications that have been approved by the US Food & Drug Administration (FDA). The FDA-approved indication means that adequate and controlled clinical trials have been conducted and reviewed by the FDA. Accepted medical practice often includes drug use that is not reflected in approved drug labeling. Lack of approval for an indication does not necessarily mean lack of effectiveness but indicates that appropriate regulatory studies have not been performed and submitted to the FDA for approval for that indication. The decision to prescribe a drug is based on the best interest of the patient, taking into account reasonable medical evidence. The physician who prescribes the drug must weigh the benefits and risks of using the drug, regardless of whether the drug has received approval from the FDA for the specific indication and age of the patient. Consultation with infectious diseases and pulmonology specialists is often indicated for severe cases.

The major focus of this chapter is on the ambulatory patient. Parenteral antibiotics are included because, increasingly, children with illnesses or diseases requiring these antibiotics are managed outside the hospital setting.

Choice of Antibiotic and Dosage

Multiple factors guide the choice of antibiotic and are included in **Box 58-1**. Dosages listed in this chapter are for the typical patient and should be considered as guidance and individualized for the patient who is being treated (**Table 58-1**). The dosages are for patients who are adequately hydrated and have normal renal and hepatic function. The duration of treatment should be individualized. The dosages are based on the literature, common practice, and experience.

Updates for treatment of SARS-CoV-2 are at www.aap.org/Nelsons.

Box 58-1

Considerations for the Choice of Antibiotic

- Condition to be treated
- Specific illness suspected or proven
- Proven efficacy in clinical trials
- Degree of potency for a particular pathogen
- Age of the child
- Immune status of the child
- Weight of the child
- Tolerance
- Degree of hydration
- Renal function
- Liver function
- Cost
- Transportation
- Access to antibiotics and follow-up care

Table 58-1. Antibiotic Choices

UPPER AIRWAY INFECTIONS		
Clinical Diagnosis	**Therapy (evidence grade)**	**Comments**
Epiglottitis (supraglottitis) *H influenzae* type b in an *unimmunized* child; rarely pneumococcus, *S aureus*	Ceftriaxone 50 mg/kg/day IV, IM q24h for 7–10 days	Emergency: provide airway. For suspected *S aureus* infection (causes only 5% of epiglottitis), consider adding clindamycin to ceftriaxone or using ceftaroline single-drug therapy.
Tracheitis, bacterial *S aureus,* including CA-MRSA; group A streptococcus; pneumococcus; *H influenzae* type b, rarely *Pseudomonas*	Clindamycin 40 mg/kg/day IV div q8h or vancomycin 40 mg/kg/day IV div q8h AND ceftriaxone 50 mg/kg/day q24h OR ceftaroline single-drug therapy: 2 mo–<2 y, 24 mg/kg/day IV div q8h; ≥2 y, 36 mg/kg/day IV div q8h (max single dose 400 mg); >33 kg, either 400 mg/dose IV q8h or 600 mg/dose IV q12h	For suspected susceptible *S aureus,* oxacillin/nafcillin or cefazolin. May represent bacterial superinfection of viral laryngotracheobronchitis , including influenza.
LOWER RESPIRATORY TRACT INFECTIONS		
Clinical Diagnosis	**Therapy (evidence grade)**	**Comments**
Abscess, lung		
• Primary (a complication of severe, necrotizing community-acquired pneumonia caused by pneumococcus; *Staphylococcus aureus*, particularly CA-MRSA; group A streptococcus, rarely *Mycoplasma pneumoniae*)	Empiric therapy with ceftriaxone 50–75 mg/kg/day q24h AND clindamycin 40 mg/kg/day div q8h or vancomycin 45 mg/kg/day IV div q8h for ≥14–21 days (AIII) OR (for MRSA) ceftaroline single-drug therapy: 2–<6 mo, 30 mg/kg/day IV div q8h (each dose given over 2 h); ≥6 mo, 45 mg/kg/day IV div q8h (each dose given over 2 h) (max single dose 600 mg) (BII)	For presumed *Mycoplasma*, add a fluoroquinolone (levofloxacin) or macrolide. Bronchoscopy may be necessary if abscess fails to drain; surgical excision is rarely necessary for pneumococcus but may be important for CA-MRSA and MSSA. Focus antibiotic coverage based on culture results. For MSSA: oxacillin/nafcillin or cefazolin.

(continued)

Table 58-1. Antibiotic Choices *(continued)*

LOWER RESPIRATORY TRACT INFECTIONS		
Clinical Diagnosis	**Therapy (evidence grade)**	**Comments**
Abscess, lung *(continued)*		
• Secondary to aspiration (ie, foul smelling; polymicrobial infection with oral aerobes and anaerobes)	Clindamycin 40 mg/kg/day IV div q8h or meropenem 60 mg/kg/day IV div q8h for ≥10 days (AIII)	Alternatives: ceftriaxone AND metronidazole OR imipenem IV OR pip/tazo IV (BIII) Oral step-down therapy with clindamycin or amox/clav (BIII)
Allergic bronchopulmonary aspergillosis	Prednisone 0.5 mg/kg qd for 1–2 wk and then taper (BII) for mild, acute stage illness AND (for more severe disease) voriconazole 18 mg/kg/day PO div q12h load followed by 16 mg/kg/day div q12h (AIII) OR itraconazole 10 mg/kg/day PO div q12h (BII). Voriconazole and itraconazole require trough concentration monitoring.	Not all allergic pulmonary disease is associated with true fungal infection. Larger steroid dosages to control inflammation may lead to tissue invasion by *Aspergillus*. Corticosteroids are the cornerstone of therapy for exacerbations, and itraconazole and voriconazole have a demonstrable corticosteroid-sparing effect.
Aspiration pneumonia (polymicrobial infection with oral aerobes and an aerobes)	Clindamycin 40 mg/kg/day IV div q8h; ADD ceftriaxone 50–75 mg/kg/day q24h for additional *Haemophilus* activity OR, as a single agent, meropenem 60 mg/kg/day IV div q8h; for ≥10 days (BIII).	Alternatives: ceftriaxone AND metronidazole OR imipenem IV OR pip/tazo IV (BIII) Oral step-down therapy with clindamycin or amox/clav (BIII)
Atypical pneumonia (See *Mycoplasma pneumoniae* and Legionnaires disease later in this table under Pneumonias of other established etiologies.)		
Bronchitis (bronchiolitis), acute	For bronchitis/bronchiolitis in children, no antibiotic needed for most cases, as disease is usually viral	With PCR multiplex diagnosis now widely available, a nonbacterial diagnosis will allow clinicians to avoid use of antibiotics, but viral/bacterial coinfection can still occur.

LOWER RESPIRATORY TRACT INFECTIONS		
Clinical Diagnosis	**Therapy (evidence grade)**	**Comments**
Community-acquired pneumonia (See Community-acquired pneumonia: empiric therapy later in this table.)		
Cystic fibrosis: Seek advice from experts in acute and chronic management. Larger than standard dosages of beta-lactam antibiotics have been required in the past to achieve the same blood concentrations as those in children without CF, but in the current era of maximal pulmonary and nutritional support of CF, it seems that most antibiotics eliminated by the kidney can be administered at typical doses to achieve adequate blood concentrations. However, we do not know whether the concentrations of antibiotics achieved at the deep sites of infection in the CF lung are adequate, particularly with advanced CF disease. The Cystic Fibrosis Foundation posts guidelines (www.cff.org/Care/Clinical-Care-Guidelines/Respiratory-Clinical-Care-Guidelines/Pulmonary-Exacerbations-Clinical-Care-Guidelines; reviewed July 2021; accessed September 21, 2022). Dosages of beta-lactams should achieve their pharmacokinetic/pharmacodynamic goals to increase the chance of response.		
• Acute exacerbation (*Pseudomonas aeruginosa* primarily; also *Burkholderia cepacia*, *Stenotrophomonas maltophilia*, *S aureus* [including CA-MRSA], nontuberculous mycobacteria)	Cefepime 150–200 mg/kg/day div q8h or meropenem 120 mg/kg/day div q6h AND tobramycin 6–10 mg/kg/day IM, IV div q6–8h for treatment of acute exacerbation (AII); many alternatives: imipenem IV, ceftazidime IV, or ciprofloxacin 30 mg/kg/day PO, IV div tid May require vancomycin 60–80 mg/kg/day IV div q8h for MRSA, OR ceftaroline 45 mg/kg/day IV div q8h (each dose given over 2 h) (max single dose 600 mg) (BIII) Duration of therapy not well-defined: 10–14 days (BIII)	Monitor concentrations of aminoglycosides, vancomycin. Insufficient evidence to recommend routine use of inhaled antibiotics for acute exacerbations. Cultures with susceptibility will help select antibiotics, as multidrug resistance is common, but synergy testing is not well standardized. Combination therapy may provide synergistic killing and delay the emergence of resistance (BIII). Attempt at early eradication of new-onset *Pseudomonas* may decrease progression of disease. Failure to respond to antibacterials should prompt evaluation for appropriate drug doses and for invasive/allergic fungal disease as well as maximization of pulmonary hygiene.

(continued)

Table 58-1. Antibiotic Choices *(continued)*

LOWER RESPIRATORY TRACT INFECTIONS		
Clinical Diagnosis	**Therapy (evidence grade)**	**Comments**
Cystic fibrosis *(continued)*		
• Chronic inflammation in CF: impact of inhaled antibiotics and azithromycin to minimize long-term damage to lung	Inhaled tobramycin 300 mg bid, cycling 28 days on therapy, 28 days off therapy, is effective adjunctive therapy between exacerbations, with new data suggesting a benefit of alternating inhaled tobramycin with inhaled aztreonam (AI). Azithromycin adjunctive chronic therapy, greatest benefit for those colonized with *Pseudomonas* (AII).	Alternative inhaled antibiotics: colistin (BIII). Two newer powder preparations of inhaled tobramycin are available. Azithromycin does not decrease the benefit of improved pulmonary function with inhaled tobramycin in those with *Pseudomonas* airway colonization.
Pertussis	Azithromycin: for those ≥6 mo, 10 mg/kg/day for day 1, then 5 mg/kg/day for days 2–5; for those <6 mo, 10 mg/kg/day for 5 days; OR clarithromycin 15 mg/kg/day div bid for 7 days; or erythromycin (estolate preferable) 40 mg/kg/day PO div qid for 7–10 days (AII) Alternative: TMP/SMX 8 mg/kg/day of TMP div bid for 14 days (BIII)	Azithromycin and clarithromycin are better tolerated than erythromycin; azithromycin is preferred in young infants to reduce pyloric stenosis risk. Provide prophylaxis to family members. Unfortunately, no adjunctive therapy has been shown to be beneficial in decreasing the cough.
Community-acquired pneumonia: empiric therapy for bronchopneumonia, lobar consolidation, or complicated pneumonia with pleural fluid/empyema		
• Mild to moderate "chest cold"–like illness (overwhelmingly viral, especially in preschool children)	No antibiotic therapy unless epidemiologic, clinical, or laboratory reasons to suspect bacterial coinfection, or *Mycoplasma*	Broad-spectrum antibiotics may increase risk of subsequent infection with antibiotic-resistant pathogens.

LOWER RESPIRATORY TRACT INFECTIONS		
Clinical Diagnosis	**Therapy (evidence grade)**	**Comments**
Community-acquired pneumonia: empiric therapy for bronchopneumonia, lobar consolidation, or complicated pneumonia with pleural fluid/empyema *(continued)*		
• Moderate to severe illness (pneumococcus; group A streptococcus; *S aureus,* including CA-MRSA; *M pneumoniae;* for those with aspiration and underlying comorbidities, *Haemophilus influenzae,* nontypeable; and for unimmunized children, *H influenzae* type b)	Empiric therapy For most regions now with high PCV13 vaccine use or low pneumococcal resistance to penicillin: ampicillin 150–200 mg/kg/day div q6h. For regions with low rates of PCV13 use or high pneumococcal resistance to penicillin: ceftriaxone 50–75 mg/kg/day q24h (AI). For suspected CA-MRSA: ceftaroline: 2–<6 mo, 30 mg/kg/day IV div q8h (each dose given over 2 h); ≥6 mo, 45 mg/kg/day IV div q8h (each dose given over 2 h) (max single dose 600 mg) (BII), OR vancomycin 40–60 mg/kg/day (AIII). For suspected *Mycoplasma*/atypical pneumonia agents, particularly in school-aged children, ADD azithromycin 10 mg/kg IV, PO on day 1, then 5 mg/kg qd for days 2–5 of treatment (AII).	Tracheal aspirate or BAL for Gram stain/culture for severe infection in intubated children. For CA-MRSA: if vancomycin is being used rather than ceftaroline, check vancomycin serum concentrations and renal function, particularly at the higher dosage needed to achieve an AUC:MIC of 400. Alternatives to azithromycin for atypical pneumonia include erythromycin IV, PO, or clarithromycin PO, or doxycycline IV, PO for children >7 y, or levofloxacin IV, PO. Benefits of combination empiric therapy with a beta-lactam and a macrolide conflict and may apply only to certain populations. Duration of therapy is still not well-defined in prospective, controlled trials in pediatric community-acquired pneumonia. Retrospective data with diagnosis based only on clinical examination and radiograph suggested that 10 days may be unnecessary for all children (5 days may be sufficient). Empiric oral outpatient therapy for less severe illness: high-dosage amoxicillin 80–100 mg/kg/day PO div tid (NOT bid, which is used for otitis) (BIII).

(continued)

Table 58-1. Antibiotic Choices *(continued)*

LOWER RESPIRATORY TRACT INFECTIONS		
Clinical Diagnosis	**Therapy (evidence grade)**	**Comments**
Community-acquired pneumonia: empiric therapy for bronchopneumonia, lobar consolidation, or complicated pneumonia with pleural fluid/empyema *(continued)*		
• **Pleural fluid/empyema** (same pathogens as for community-associated bronchopneumonia) (Based on extent of fluid and symptoms, may benefit from chest tube drainage with fibrinolysis; rarely from video-assisted thoracoscopic surgery.)	Empiric therapy: ceftriaxone 50–75 mg/kg/day q24h AND vancomycin 40–60 mg/kg/day IV div q8h (BIII) OR ceftaroline single-drug therapy: 2–<6 mo, 30 mg/kg/day IV div q8h; ≥6 mo, 45 mg/kg/day IV div q8h (each dose given over 2 h) (max single dose 600 mg) (BII)	Initial therapy based on Gram stain of empyema fluid; typically, clinical improvement is slow, with persisting but decreasing "spiking" fever for 2–3 wk. Concerns about the effectiveness of vancomycin monotherapy in influenza-associated MRSA pneumonia. Combination therapy with agents added to vancomycin, or monotherapy with other agents like ceftaroline, may provide a better option.
• **Interstitial pneumonia syndrome of early infancy**	If *Chlamydia trachomatis* suspected, azithromycin 10 mg/kg on day 1, followed by 5 mg/kg/day qd days 2–5 OR erythromycin 40 mg/kg/day PO div qid for 14 days (BII)	Most often respiratory viral pathogens, CMV, or chlamydial; role of *Ureaplasma* uncertain
Pneumonia: definitive therapy for pathogens of community-acquired pneumonia		
• **Pneumococcus** (may occur with non-PCV13 serotypes)	Empiric therapy For regions with high PCV13 vaccine use or low pneumococcal resistance to penicillin: ampicillin 150–200 mg/kg/day div q6h For regions with low rates of PCV13 use or high pneumococcal resistance to penicillin: ceftriaxone 50–75 mg/kg/day q24h (AI) Empiric oral outpatient therapy for less severe illness: high-dosage amoxicillin 80–100 mg/kg/day PO div tid (NOT bid, which is used for otitis)	Change to PO after improvement (decreased fever, no oxygen needed); treat until patient clinically asymptomatic and chest radiograph significantly improved (7–21 days) (BIII). No reported failures of ceftriaxone for pen-R pneumococcus; no need to add empiric vancomycin for this reason (CIII). Oral therapy for pneumococcus may also be successful with amox/clav, cefdinir, cefixime, cefpodoxime, or cefuroxime, particularly for fully pen-S strains. Levofloxacin is an alternative, particularly for those with severe allergy to beta-lactam antibiotics (BI), but, due to theoretical cartilage toxicity concerns for humans, should not be first-line therapy.

LOWER RESPIRATORY TRACT INFECTIONS		
Clinical Diagnosis	**Therapy (evidence grade)**	**Comments**
Pneumonia: definitive therapy for pathogens of community-acquired pneumonia		
• Pneumococcal, pen-S	Penicillin G 250,000–400,000 U/kg/day IV div q4–6h for 10 days (BII) OR ampicillin 150–200 mg/kg/day IV div q6h	After improvement, change to amoxicillin 50–75 mg/kg/day PO div tid OR penicillin V 50–75 mg/kg/day div qid.
• Pneumococcal, pen-R	Ceftriaxone 75 mg/kg/day q24h for 10–14 days (BIII)	Addition of vancomycin has not been required for treatment of pen-R strains. Ceftaroline is more active against pneumococcus than ceftriaxone, but with no current ceftriaxone resistance, ceftaroline is not required. For oral convalescent therapy, high-dosage amoxicillin (100–150 mg/kg/day PO div tid), clindamycin (30 mg/kg/day PO div tid), linezolid (30 mg/kg/day PO div tid), or levofloxacin PO.
• ***Staphylococcus aureus*** (including CA-MRSA) is a rare (1%) cause of pediatric community-acquired pneumonia.	For MSSA: oxacillin/nafcillin 150 mg/kg/day IV div q6h or cefazolin 100 mg/kg/day IV div q8h (AII) For suspected CA-MRSA: ceftaroline: 2–<6 mo, 30 mg/kg/day IV div q8h (each dose given over 2 h); ≥6 mo, 45 mg/kg/day IV div q8h (each dose given over 2 h) (max single dose 600 mg) (BII), OR vancomycin 40–60 mg/kg/day (AIII); may need addition of rifampin, clindamycin, or gentamicin (AIII)	Check vancomycin serum concentrations and renal function, particularly at the higher dosage designed to attain an AUC:MIC of 400, or serum trough concentrations of 15 mcg/mL for invasive CA-MRSA disease. For life-threatening disease, optimal therapy for CA-MRSA has not been studied and remains poorly defined: consider adding gentamicin and/or rifampin for combination therapy (CIII). Linezolid 30 mg/kg/day IV, PO div q8h is another option, more effective in adults than vancomycin for MRSA nosocomial pneumonia (follow platelet and WBC counts weekly). For influenza-associated MRSA pneumonia, vancomycin monotherapy was inferior to combination therapies. Do NOT use daptomycin for pneumonia. Oral convalescent therapy for MSSA: cephalexin PO; for CA-MRSA: clindamycin or linezolid PO. Total course for ≥21 days (AIII).

(continued)

Table 58-1. Antibiotic Choices *(continued)*

LOWER RESPIRATORY TRACT INFECTIONS		
Clinical Diagnosis	**Therapy (evidence grade)**	**Comments**
Pneumonia: definitive therapy for pathogens of community-acquired pneumonia *(continued)*		
• **Group A streptococcus**	Penicillin G 250,000 U/kg/day IV div q4–6h for 10 days (BII)	Change to amoxicillin 75 mg/kg/day PO div tid or penicillin V 50–75 mg/kg/day div qid to tid after clinical improvement (BIII).
Pneumonia: immunosuppressed, neutropenic host		
• **Immunosuppressed, neutropenic host** (*P aeruginosa*, other community-associated or nosocomial gram-negative bacilli, *S aureus*, fungi, AFB, *Pneumocystis*, viral [adenovirus, CMV, EBV, influenza, RSV, others])	Cefepime 150 mg/kg/day IV div q8h (AII), OR meropenem 60 mg/kg/day div q8h (AII) (BIII), OR pip/tazo 240–300 mg/kg/day div q6h; AND if *S aureus* (including MRSA) is suspected clinically, ADD vancomycin 40–60 mg/kg/day IV div q8h (AIII) OR ceftaroline: 2–<6 mo, 30 mg/kg/day IV div q8h; ≥6 mo, 45 mg/kg/day IV div q8h (max single dose 600 mg) (BIII).	Biopsy/BAL for histology/cultures or serum/BAL for cell-free next-generation sequencing testing helps determine need for antifungal, antiviral, antimycobacterial treatment. Antifungal therapy usually started if no response to antibiotics in 48–72 h (AmB, voriconazole, or caspofungin/micafungin). For septic patients, the addition of tobramycin will increase coverage for most gram-negative pathogens. For those with mucositis, anaerobic coverage may be needed, as provided by carbapenems and pip/tazo (or with the addition of clindamycin or metronidazole to other agents). Consider use of 2 active agents for definitive therapy for *Pseudomonas* for neutropenic hosts to assist clearing the pathogen and potentially decrease risk of resistance, but there is no evidence to support better outcomes (BIII).

LOWER RESPIRATORY TRACT INFECTIONS		
Clinical Diagnosis	**Therapy (evidence grade)**	**Comments**
Pneumonia: nosocomial (health care–associated/ventilator-associated)		
• **Nosocomial (health care–associated/ventilator-associated)** (*P aeruginosa,* gram-negative enteric bacilli [*Enterobacter, Klebsiella, Serratia, Escherichia coli*], *Acinetobacter, Stenotrophomonas,* and gram-positive organisms including CA-MRSA and *Enterococcus*)	Commonly used regimens Meropenem 60 mg/kg/day div q8h, OR pip/tazo 240–300 mg/kg/day div q6–8h, OR cefepime 150 mg/kg/day div q8h; ± gentamicin 6.0–7.5 mg/kg/day div q8h (AIII); ADD vancomycin or ceftaroline for suspected CA-MRSA (AIII).	Empiric therapy should be institution specific, based on your hospital's nosocomial pathogens and susceptibilities. Pathogens that cause nosocomial pneumonia often have multidrug resistance. Cultures are critical. Empiric therapy also based on child's prior colonization/infection. Do not treat colonization, though. For MDR gram-negative bacilli, available IV therapy options include ceftazidime/avibactam (now FDA approved for children), tol/taz, meropenem/vaborbactam, cefiderocol, plazomicin, or colistin. Aerosol delivery of antibiotics may be required for MDR pathogens, but little high-quality controlled data are available for children.
Pneumonias of other established etiologies		
• *Chlamydophila pneumoniae, Chlamydophila psittaci,* or *Chlamydia trachomatis*	Azithromycin 10 mg/kg on day 1, followed by 5 mg/kg/day qd days 2–5 or erythromycin 40 mg/kg/day PO div qid; for 14 days	Doxycycline (patients >7 y). Levofloxacin should also be effective.
• CMV (immunocompromised host)	Ganciclovir IV 10 mg/kg/day IV div q12h for 2 wk (BIII); if needed, continue at 5 mg/kg/day q24h to complete 4–6 wk total (BIII).	Bone marrow transplant recipients with CMV pneumonia whose ganciclovir therapy alone fails may benefit from therapy with IV CMV hyperimmunoglobulin and ganciclovir given together (BII). Oral valganciclovir may be used for convalescent therapy (BIII). Foscarnet for ganciclovir-resistant isolates.

(continued)

Table 58-1. Antibiotic Choices *(continued)*

LOWER RESPIRATORY TRACT INFECTIONS		
Clinical Diagnosis	**Therapy (evidence grade)**	**Comments**
Pneumonias of other established etiologies *(continued)*		
• *E coli*	Ceftriaxone 50–75 mg/kg/day q24h (AII)	For cephalosporin-R strains (ESBL producers), use meropenem, imipenem, or ertapenem (AIII). Use high-dose ampicillin if susceptible.
• *Enterobacter* spp	Cefepime 100 mg/kg/day div q12h or meropenem 60 mg/kg/day div q8h; OR ceftriaxone 50–75 mg/kg/day q24h AND gentamicin 6.0–7.5 mg/kg/day IM, IV div q8h (AIII)	Addition of aminoglycoside to third-generation cephalosporins (ceftriaxone, ceftazidime) may retard the emergence of ampC-mediated constitutive high-level resistance, but concern exists for inadequate aminoglycoside concentration in airways; not an issue for ampC-stable beta-lactams (cefepime, meropenem, imipenem, or pip/tazo).
• *Francisella tularensis*	Gentamicin 6.0–7.5 mg/kg/day IM, IV div q8h for ≥10 days for more severe disease (AIII); for less severe disease, ciprofloxacin or levofloxacin (AIII)	Other alternative for oral therapy for mild disease: doxycycline PO for 14–21 days (but watch for relapse). See www.cdc.gov/tularemia/clinicians/index.html (reviewed July 5, 2022; accessed September 21, 2022).
• Fungi Community-associated pathogens, which vary by region (eg, *Coccidioides, Histoplasma*) *Aspergillus*; mucormycosis; other mold infections in immunocompromised hosts	For suspected endemic fungi or mucormycosis in an *immunocompromised* host, treat empirically with a lipid AmB and not voriconazole; biopsy needed to guide therapy. Posaconazole and isavuconazole have in vitro activity and clinical efficacy data against some *Rhizopus* spp. For suspected invasive aspergillosis, treat with voriconazole (AI) (load 18 mg/kg/day div q12h on day 1, then continue 16 mg/kg/day div q12h).	For immunocompetent hosts, triazoles (fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole) are better tolerated than AmB and equally effective for many community-associated pathogens. Check voriconazole trough concentrations; need to be at least >2 mcg/mL. For *Coccidioides* infection refractory to fluconazole therapy, consider increasing the dose, switching to other azoles, or switching to AmB.

LOWER RESPIRATORY TRACT INFECTIONS		
Clinical Diagnosis	**Therapy (evidence grade)**	**Comments**
Pneumonias of other established etiologies *(continued)*		
– Influenza virus. – Recent seasonal influenza A and B strains continue to be resistant to adamantanes.	Empiric therapy, or documented influenza A or B Oseltamivir (AII): <12 mo: Full-term infants 0–8 mo: 3 mg/kg/dose bid 9–11 mo: 3.5 mg/kg/dose bid ≥12 mo: ≤15 kg: 30 mg PO bid >15–23 kg: 45 mg PO bid >23–40 kg: 60 mg PO bid >40 kg: 75 mg PO bid Zanamivir inhaled (AII): for those ≥7 y, 10 mg (two 5-mg inhalations) bid Peramivir (BII): 6 mo–12 y: single IV dose of 12 mg/kg, up to 600 mg max 13–17 y: single IV dose of 600 mg Baloxavir (BI): ≥5 y: <20 kg: single dose PO of 2 mg/kg 20–79 kg: single dose PO of 40 mg ≥80 kg: single dose PO of 80 mg	Check for antiviral susceptibility each season at www.cdc.gov/flu/professionals/antivirals/index.htm (reviewed by the CDC September 8, 2022; accessed September 21, 2022). For children 12–23 mo, the unit dose of oseltamivir of 30 mg/dose may provide inadequate drug exposure. 3.5 mg/kg/dose PO bid has been studied for pharmacokinetics, but sample sizes were limited. Limited data for oseltamivir in preterm neonates: <38 wk of PMA (gestational plus chronologic age): 1.0 mg/kg/dose PO bid 38–40 wk of PMA: 1.5 mg/kg/dose PO bid The adamantanes (amantadine and rimantadine) had activity against influenza A before the late 1990s, but all circulating A strains of influenza have been resistant for many years. Influenza B is intrinsically resistant to adamantanes.

(continued)

Table 58-1. Antibiotic Choices *(continued)*

LOWER RESPIRATORY TRACT INFECTIONS		
Clinical Diagnosis	**Therapy (evidence grade)**	**Comments**
Pneumonias of other established etiologies *(continued)*		
• *Klebsiella pneumoniae*	Ceftriaxone 50–75 mg/kg/day IV, IM q24h (AIII); for ceftriaxone-resistant strains (ESBL strains), use meropenem 60 mg/kg/day IV div q8h (AIII) or other carbapenem.	For *K pneumoniae* that contain ESBLs, other carbapenems, pip/tazo, and fluoroquinolones are other options. Data in adults suggest that outcomes with pip/tazo are inferior to those with carbapenems. For KPC-producing strains that are resistant to meropenem, alternatives include ceftazidime/avibactam (FDA approved for adults and children), fluoroquinolones, or colistin (BIII).
• Legionnaires disease (*Legionella pneumophila*)	Azithromycin 10 mg/kg IV, PO q24h for 5 days (AIII)	Alternatives: clarithromycin, erythromycin, ciprofloxacin, levofloxacin, doxycycline
• Mycobacteria, nontuberculous (*Mycobacterium avium* complex most common)	In a normal host with pneumonia that requires therapy, 3 drugs are now recommended: azithromycin PO (or clarithromycin PO) AND ethambutol, AND rifampin, given 3 times/wk to prevent macrolide/azalide resistance. Duration of treatment is not well-defined; consider 12 mo, or 6–12 wk if susceptible. For more extensive cavitary or advanced/severe bronchectatic disease, ADD amikacin or streptomycin (AIII).	Highly variable susceptibilities of different nontuberculous mycobacterial spp. Culture and susceptibility data are important for success. Check if immunocompromised: HIV or interferon-γ receptor deficiency. Consider consulting an ID physician.
• *Mycobacterium tuberculosis* (See Tuberculosis later in this table.)		

LOWER RESPIRATORY TRACT INFECTIONS		
Clinical Diagnosis	**Therapy (evidence grade)**	**Comments**
Pneumonias of other established etiologies *(continued)*		
• *M pneumoniae*	Azithromycin 10 mg/kg on day 1, followed by 5 mg/kg/day qd days 2–5, OR clarithromycin 15 mg/kg/day div bid for 7–14 days, OR erythromycin 40 mg/kg/day PO div qid for 14 days	*Mycoplasma* often causes self-limited infection and does not routinely require treatment (AIII). Little prospective, well-controlled data exist for treatment of documented mycoplasma pneumonia, specifically in children. Doxycycline (patients >7 y) or levofloxacin. Macrolide-resistant strains have recently developed worldwide but may respond to doxycycline or levofloxacin. Studies have been difficult without better diagnostic techniques, but respiratory tract PCR testing is now available to assist in early identification of possible infections.
• *Pneumocystis jiroveci* (formerly *carinii*); disease in immunosuppressed children and those with HIV	Severe disease: preferred regimen is TMP/SMX, 15–20 mg/kg/day of TMP IV div q8h for 3 wk (AI). Mild to moderate disease: may start with IV therapy, then after acute pneumonitis is resolving, TMP/SMX 20 mg/kg/day of TMP PO div qid for 21 days (AII). Use steroid adjunctive treatment for more severe disease (AII).	Alternatives for TMP/SMX intolerant, or clinical failure: pentamidine 3–4 mg IV qd, infused over 60–90 min (AII); TMP AND dapsone; OR primaquine AND clindamycin; OR atovaquone. Prophylaxis: TMP/SMX as 5 mg/kg/day of TMP PO, div in 2 doses, q12h, daily or 3 times/wk on consecutive days (AI); OR TMP/SMX 5 mg/kg/day of TMP PO as a single dose, qd, given 3 times/wk on consecutive days (AI); once-weekly regimens have also been successful; OR dapsone 2 mg/kg (max 100 mg) PO qd, or 4 mg/kg (max 200 mg) once weekly; OR atovaquone: 30 mg/kg/day for infants 1–3 mo, 45 mg/kg/day for infants 4–24 mo, and 30 mg/kg/day for children >24 mo.

(continued)

Table 58-1. Antibiotic Choices *(continued)*

LOWER RESPIRATORY TRACT INFECTIONS		
Clinical Diagnosis	**Therapy (evidence grade)**	**Comments**
Pneumonias of other established etiologies *(continued)*		
• *P aeruginosa*	Cefepime 150 mg/kg/day IV div q8h ± tobramycin 6.0–7.5 mg/kg/day IM, IV div q8h (AII). Alternatives: meropenem 60 mg/kg/day div q8h, OR pip/tazo 240–300 mg/kg/day div q6–8h (AII) ± tobramycin (BIII).	Ciprofloxacin IV, or colistin IV for MDR strains of *Pseudomonas*.
• RSV infection (bronchiolitis, pneumonia)	For immunocompromised hosts, the only FDA-approved treatment is ribavirin aerosol: 6-g vial (20 mg/mL in sterile water), by SPAG-2, over 18–20 h daily for 3–5 days, although questions remain regarding efficacy.	Treat only for severe disease, immunocompromised, severe underlying cardiopulmonary disease, as aerosol ribavirin provides only a small benefit. Airway reactivity with inhalation precludes routine use. We have not personally used inhaled ribavirin for the past several years. Palivizumab (Synagis) is not effective for treatment of an active RSV infection but cost-effective for prevention of hospitalization in high-risk patients. RSV antivirals and more potent monoclonal antibodies are currently under investigation.

LOWER RESPIRATORY TRACT INFECTIONS		
Clinical Diagnosis	**Therapy (evidence grade)**	**Comments**
Tuberculosis		
• Primary pulmonary disease	INH 10–15 mg/kg/day (max 300 mg) PO qd for 6 mo AND rifampin 15–20 mg/kg/day (max 600 mg) PO qd for 6 mo AND PZA 30–40 mg/kg/day (max 2 g) PO qd for first 2 mo of therapy only (AII). Twice-weekly treatment, particularly with DOT, is acceptable. If risk factors present for multidrug resistance, ADD ethambutol 20 mg/kg/day PO qd OR streptomycin 30 mg/kg/day IV, IM div q12h initially.	Obtain baseline LFTs. Consider monthly LFTs for at least 3 mo or as needed for symptoms. It is common to have mildly elevated liver transaminase concentrations (2–3 times normal) that do not further increase during the entire treatment interval. Children with obesity may have mild elevation when therapy is started. New recommendations on short-course (4-mo) daily therapy for children with non-severe TB may soon be made for the United States, following new World Health Organization guidelines (www.who.int/publications/i/item/9789240046764; accessed September 21, 2022). Contact TB specialist for therapy for drug-resistant TB. Fluoroquinolones may play a role in treating MDR strains. Bedaquiline, in a new drug class for TB therapy, is approved for adults and children >5 y with MDR TB when used in combination therapy. Delamanid is not FDA approved as of July 2022. DOT preferred; after 2 wk of daily therapy, can change to twice-weekly dosing double dosage of INH (max 900 mg), PZA (max 2 g), and ethambutol (max 2.5 g); rifampin remains same dosage (15–20 mg/kg/day, max 600 mg) (AII). LP ± CT of head for children ≤2 y to rule out occult, concurrent CNS infection; consider testing for HIV infection (AIII). *Mycobacterium bovis* infection from unpasteurized dairy products is also called "tuberculosis" but rarely causes pulmonary disease; all strains of *M bovis* are PZA resistant. Treat 9–12 mo with INH and rifampin.

(continued)

Table 58-1. Antibiotic Choices *(continued)*

LOWER RESPIRATORY TRACT INFECTIONS		
Clinical Diagnosis	**Therapy (evidence grade)**	**Comments**
Tuberculosis *(continued)*		
• Latent TB infection (skin test conversion; more recently just called "TB infection" in contrast to "TB disease" for symptomatic TB infection)	Many options now INH/rifapentine: For children 2–11 y: *once-weekly* DOT for *12 wk:* INH 25 mg/kg/dose (max 900 mg), AND rifapentine: 10.0–14.0 kg: 300 mg 14.1–25.0 kg: 450 mg 25.1–32.0 kg: 600 mg 32.1–49.9 kg: 750 mg ≥50.0 kg: 900 mg (max) For children 2–11 y: INH 25 mg/kg, rounded up to nearest 50 or 100 mg (max 900 mg), AND rifapentine (See above.) Rifampin alone (all ages): 15–20 mg/kg/dose *daily* (max 600 mg) for *4 mo* INH/rifampin (all ages): INH 10–15 mg/kg/day (max 300 mg)/rifampin 15–20 mg/kg/day (max 600 mg) *daily* for *3 mo* INH 10–15 mg/kg/day (max 300 mg) PO daily for *6–9 mo (12 mo for immunocompromised patients*) (AIII); treatment with INH at 20–30 mg/kg twice weekly for *9 mo* also effective (AIII)	Obtain baseline LFTs. Consider monthly LFTs or as needed for symptoms. Stop INH/rifapentine if AST or ALT ≥5 times the ULN even in the absence of symptoms or ≥3 times the ULN in the presence of symptoms. For children <2 y: INH and rifapentine may be used, but there are less data on safety and efficacy. For exposure to known INH-resistant but rifampin-susceptible strains, use rifampin 6 mo (AIII).

LOWER RESPIRATORY TRACT INFECTIONS		
Clinical Diagnosis	**Therapy (evidence grade)**	**Comments**
Tuberculosis *(continued)*		
• Exposed child <4 y, or immunocompromised patient (high risk for dissemination)	Prophylaxis for possible infection for 2–3 mo after last exposure with rifampin 15–20 mg/kg/dose PO qd OR INH 10–15 mg/kg PO qd; for at least 2–3 mo (AIII), with repeated skin test or interferon-γ release assay test (AIII). Also called "window prophylaxis."	Alternative regimens INH 10–15 mg/kg PO qd AND rifampin 15–20 mg/kg/dose qd (max 600 mg) for up to 3 mo. If PPD or interferon-γ release assay test remains negative at 2–3 mo and child appears well, consider stopping empiric therapy. PPD may not be reliable in immunocompromised patients. Not much data to assess reliability of interferon-γ release assays in very young infants or immunocompromised hosts, but not likely to be much better than the PPD skin test.

AFB, acid-fast bacilli; ALT, alanine transaminase; AmB, amphotericin B; amox/clav, amoxicillin/clavulanate; ampC, amphotericin C; AST, aspartate transaminase; AUC:MIC, area under the curve (the mathematically calculated area below the serum concentration-versus-time curve) to minimum inhibitory concentration; BAL, bronchoalveolar lavage; bid, twice daily; CA-MRSA, community-associated methicillin-resistant *Staphylococcus aureus;* CF, cystic fibrosis; CMV, cytomegalovirus; CNS, central nervous system; CT, computed tomography; div, divided; DOT, directly observed therapy; EBV, Epstein-Barr virus; ESBL, extended-spectrum beta-lactamase; FDA, US Food and Drug Administration; ID, infectious disease; IM, intramuscular; INH, isoniazid; IV, intravenous; KPC, *Klebsiella pneumoniae* carbapenemase; LFT, liver function test; LP, lumbar puncture; max, maximum; MDR, multidrug resistant; MRSA, methicillin-resistant *S aureus*; MSSA, methicillin-susceptible *S aureus;* PCR, polymerase chain reaction; PCV13, Prevnar 13-valent pneumococcal conjugate vaccine; pen-R, penicillin-resistant; pen-S, penicillin-susceptible; pip/tazo, piperacillin/tazobactam; PMA, postmenstrual age; PO, orally; PPD, purified protein derivative; PZA, pyrazinamide; q, every; qd, once daily; qid, 4 times daily; RSV, respiratory syncytial virus; SPAG-2, small particle aerosol generator-2; spp, species; TB, tuberculosis; tid, 3 times daily; TMP/SMX, trimethoprim/sulfamethoxazole; tol/taz, ceftolozane/tazobactam; ULN, upper limit of normal; WBC, white blood cell.

Adapted from Bradley JS, Nelson JD, eds. *2023 Nelson's Pediatric Antimicrobial Therapy 2022*. 29th ed. American Academy of Pediatrics; 2023.

(continued)

Classes of Antibiotics

Oral Cephalosporins

The oral cephalosporins (**Box 58-2**) have an advantage over oral penicillins of somewhat greater spectrum of activity. The serum half-lives of cefpodoxime, ceftibuten, and cefixime are greater than 2 hours, which allows for twice-daily dosing. There is varying activity against *Haemophilus influenzae* and *Streptococcus pneumoniae.*

Box 58-2

Oral Cephalosporins

- Cephalexin
- Cefadroxil
- Cefaclor
- Cefprozil
- Cefuroxime
- Cefixime
- Cefdinir
- Cefpodoxime
- Cefditoren (≥12 years)
- Ceftibuten

First-generation cephalosporins (**Box 58-3**) are used mainly for treatment of gram-positive infections. Cefazolin is well tolerated on intramuscular or intravenous injection.

Second-generation cephalosporins (**Box 58-3**) provide increased activity against many gram-negative organisms. Cefoxitin has additional activity against up to 80% of strains of *Bacteroides fragilis.* In empiric therapy for mild to moderate infections at low risk of being caused by *B fragilis*, cefoxitin can be considered for use in place of the more active agents such as metronidazole or carbapenems. Cefotetan has a spectrum similar to cefoxitin with a longer half-life, so it can be given every 12 hours. Cefuroxime is given as a single injection in many countries for pneumonia that is caused by gram-positive cocci or *H influenzae* type b, or *H influenzae* nonencapsulated strains in children with underlying lung diseases.

Box 58-3

Parenteral Cephalosporins

First Generation
- Cefazolin

Second Generation
- Cefamandole
- Cefuroxime
- Cephamycins
  - Cefoxitin
  - Cefotetan

Third Generation
- Ceftriaxone
- Ceftazidime

Fourth Generation
- Cefepime

Fifth Generation
- Ceftaroline

Third-generation cephalosporins (**Box 58-3**) have enhanced potency against gram-negative bacilli but lack activity against inducible amphotericin C (AmpC) β-lactamases and extended-spectrum β-lactamases. They are inactive against enterococci and *Listeria* and have variable activity against *Pseudomonas* and *Bacteroides.* Ceftazidime has the unique property of activity against *Pseudomonas aeruginosa* and is widely used in patients with cystic fibrosis (CF).

The fourth-generation cephalosporin cefepime has antipseudomonal activity as well as activity

against gram-positive organisms and inducible AmpC β-lactamase–producing gram-negative bacilli, such as *Enterobacter* and *Serratia*.

The fifth-generation cephalosporin ceftaroline is the first of the β-lactam antibiotics to demonstrate activity against methicillin-resistant *Staphylococcus aureus* (MRSA). In addition, it provides activity against the gram-negative enteric bacilli similar to the third-generation cephalosporins, lacking activity against inducible AmpC β-lactamase–producing pathogens, extended-spectrum β-lactamase–producing pathogens, and *Pseudomonas aeruginosa*.

Penicillinase-Resistant Penicillins

The penicillinase-resistant penicillins (**Box 58-4**) were specifically formulated to address stability against the β-lactamase produced by *S aureus.* These compounds are not stable to the β-lactamases produced by gram-negative bacteria. They are active against methicillin-sensitive *S aureus* (MSSA) but not MRSA. Nafcillin is excreted primarily by the liver rather than the kidneys, compared with the others in this group, which may explain the relative lack of nephrotoxicity when this penicillin is compared with methicillin, which is no longer available in the United States.

Box 58-4

Penicillinase-Resistant Penicillins

- Dicloxacillin
- Nafcillin
- Oxacillin

The oral antibiotics cloxacillin, dicloxacillin, and oxacillin are equivalent in activity but virtually unpalatable.

Antipseudomonal β-lactams

Piperacillin/tazobactam (Zosyn) and ceftazidime/avibactam (Avycaz) (both FDA approved for children), and, still under investigation in children, ceftolozane/tazobactam (Zerbaxa), imipenem/relebactam (Recarbrio), and meropenem/vaborbactam (Vabomere), represent combinations of a β-lactam and a β-lactamase inhibitor. The antibiotic binds effectively to the target site in the bacteria, resulting in death of the organism, whereas the second β-lactamase inhibitor binds irreversibly to and neutralizes the β-lactamase enzyme the organism produced to degrade the original antibiotic. The antipseudomonal intracellular binding activity of the combination is no different than the original; in addition, there is increased protection by these β-lactamase inhibitors for other β-lactamase–positive bacteria, including *S aureus* (MSSA strains only) and *B fragilis.*

Box 58-5

Antipseudomonal β-lactams

- Piperacillin and tazobactam
- Aztreonam
- Ceftazidime
- Cefepime
- Meropenem
- Imipenem
- Ertapenem

Pseudomonas has an intrinsic capacity to develop resistance to β-lactam antibiotics by many mechanisms (β-lactamases, efflux pumps, cell wall changes to decrease drug entry into the bacteria). Particularly for ceftazidime, β-lactamase induction may lead to resistance with single-drug therapy, so combination with an aminoglycoside (or other active antibiotic) is advisable. Cefepime, meropenem, and imipenem are less likely to develop resistance from β-lactamases and can be used as single therapy. However, in patients who are immunocompromised, have CF, or have life-threatening infections, these antibiotics should be used in combination with an aminoglycoside or other active antibiotic.

Aminopenicillins

Ampicillin, an aminopenicillin (**Box 58-6**), is more likely than the other aminopenicillins to cause diarrhea and to cause overgrowth of *Candida*. Amoxicillin is well absorbed, good tasting, and associated with very few side effects. Amoxicillin and clavulanic acid (Augmentin) is available in the United States in oral form and for parenteral use in many other countries; it has activity against many β-lactamase–producing bacteria, including *H influenzae* and *S aureus* (MSSA strains only).

Carbapenems

Carbapenems (**Box 58-7**) have a broader spectrum of activity than any other β-lactams currently available. They are active against streptococci and *S aureus* (MSSA strains only), *Pseudomonas*, most coliform bacilli (including ceftriaxone-resistant strains), and anaerobes, including *B fragilis.* Ertapenem does not have activity against *Pseudomonas*.

Macrolides

Erythromycin is the prototype macrolide antibiotic, and the 3 shown in **Box 58-8** are the only commercial macrolide antibiotics available in the United States. Azithromycin is more accurately called an azalide but is structurally very similar to macrolides. Azithromycin and clarithromycin have activity against certain nontuberculous mycobacteria but should not be used as monotherapy because of the potential to develop resistance. The macrolides are usually active against the "atypical pneumonia" pathogens *(Mycoplasma, Legionella, Chlamydia, Chlamydophila).*

Box 58-6

Aminopenicillins

- Amoxicillin
- Amoxicillin and clavulanate
- Ampicillin
- Ampicillin and sulbactam

Box 58-7

Carbapenems

- Meropenem
- Imipenem
- Ertapenem

Box 58-8

Macrolides

- Erythromycin
- Azithromycin
- Clarithromycin

Aminoglycosides

Amikacin, gentamicin, and tobramycin (**Box 58-9**) are widely used for systemic therapy of aerobic gram-negative infections and for synergy in the treatment of certain gram-negative and gram-positive infections. It is advisable to monitor levels because of potential toxicity to the kidneys and the eighth cranial nerve. The desired peak concentrations of amikacin are 20 to 35 mcg/mL, and the optimal trough concentration should be less than 10 mcg/mL; for gentamicin and tobramycin, peak concentrations should be 5 to 10 mcg/mL and trough concentrations less than 2 mcg/mL. Children with CF usually require significantly higher dosages of these medications. Aminoglycosides demonstrate concentration-dependent killing of organisms, and the peak serum concentrations when given once daily are greater than those achieved with dosing 3 times daily with less associated toxicity. Once-daily dosing of tobramycin is increasingly being prescribed, with doses of 5 to 7.5 mg/kg and, in patients with CF, doses of 9 to 10 mg/kg. When using high doses given less frequently, peak levels are often not measured and typically are 20 to 30 mcg/mL, but it is important that the trough level is less than 1.0 mcg/mL to avoid renal toxicity and ototoxicity. There are sufficient prospectively collected comparative data for the Cystic Fibrosis Foundation to recommend once-daily treatment, compared with 8-hourly dosing in children with CF.[1]

Box 58-9

Aminoglycosides

- Amikacin
- Gentamicin
- Tobramycin
- Streptomycin[a]
- Kanamycin[a]

[a]Not commonly used.

Fluoroquinolones

Ciprofloxacin usually has very good gram-negative activity against enteric bacteria (*Escherichia coli, Klebsiella, Enterobacter, Salmonella,* and *Shigella,* as well as coverage against *P aeruginosa*) but has minimal coverage for gram-positive organisms, so if *S aureus* or pneumococcus is suspected, additional coverage should be added. The newer quinolones, such as levofloxacin, have improved coverage against these organisms but should not be considered optimal therapy for staphylococcal infections.

There are theoretical concerns regarding toxicity of fluoroquinolones to cartilaginous weight-bearing joints, so the fluoroquinolones (**Box 58-10**) should be used cautiously in children.

Box 58-10

Fluoroquinolones

- Ciprofloxacin
- Levofloxacin
- Moxifloxacin

Antifungal Agents

Amphotericin B

Amphotericin B is a polyene antifungal antibiotic that has been available since 1958 for the treatment of invasive fungal infections. It remains the most broad-spectrum antifungal available for clinical use, with a mechanism of action against the fungal cell membrane in which pores are created, compromising the integrity of the membrane and creating a fungicidal effect. The toxicity of the conventional formulation, amphotericin B deoxycholate, can be substantial from the standpoints of systemic reactions (eg, fever, rigors) and renal toxicity. Premedication with acetaminophen, diphenhydramine, and meperidine is often required to prevent systemic reactions during infusion. Renal dysfunction develops primarily as decreased glomerular filtration with a rising serum creatinine concentration, but substantial tubular nephropathy is associated with potassium and magnesium wasting, requiring supplemental potassium for many neonates and children, regardless of clinical symptoms associated with infusion. Newer lipid preparations decrease toxicity with no apparent decrease in clinical efficacy and should be used because they are far better tolerated than amphotericin B deoxycholate.

Azoles

The azoles were first approved in 1981. All the azoles work by inhibition of ergosterol synthesis (fungal cytochrome P450 sterol 14-demethylation) that is required for fungal cell membrane integrity. In general, the azoles are fungistatic in vivo, in contrast to polyenes like amphotericin and echinocandins, which are fungicidal.

Primarily active against *Candida* species, ketoconazole is available for systemic treatment in an oral formulation. Fluconazole is active against a broader range of fungi than ketoconazole and includes clinically relevant activity against *Cryptococcus, Coccidioides,* and *Histoplasma*. Fluconazole remains one of the most active and safest systemic antifungal agents for the treatment of most *Candida* infections, although some resistance is present in many non-*albicans Candida* species as well as in *Candida albicans* in children repeatedly exposed to fluconazole. Fluconazole is available in parenteral and oral formulations, and toxicity is unusual and primarily hepatic.

Itraconazole is active against an even broader range of fungi and molds, including *Aspergillus*. However, pediatric clinical data are limited. Voriconazole was approved for adults in 2002 and is FDA approved for children 2 years and older. It is the treatment of choice for *Aspergillus* infections. Voriconazole is active against *Candida* species, including some that are fluconazole resistant, but fluconazole is preferred if the *Candida* is susceptible. Voriconazole produces some unique transient visual field abnormalities in about 10% of adults and children. There are an increasing number of reports, seen in as high

as 20% of patients, of a photosensitive sunburn-like erythema that is not aided by sunscreen (only sun avoidance). In some rare long-term (mean of 3 years of therapy) cases, this voriconazole phototoxicity has developed into cutaneous squamous cell carcinoma. Discontinuing voriconazole is recommended in patients experiencing chronic phototoxicity. Hepatotoxicity is uncommon, occurring in 2% to 5% of patients. Voriconazole is cytochrome P450 metabolized, interacts with any similarly metabolized drugs, and may produce profound changes in serum concentrations of many concurrently administered drugs.

Posaconazole is the most recently FDA-approved triazole for children. It has activity against *Candida* and *Aspergillus* but, importantly, it has substantial activity against *Rhizopus* species and *Mucor* species, as well as *Coccidioides, Histoplasma,* and *Blastomyces,* with a more clinically acceptable drug-drug interaction profile when compared with voriconazole.

Echinocandins

The echinocandin class of antifungals was approved in 2001. Echinocandins inhibit cell wall formation by inhibiting glucan synthesis. They are fungicidal against yeasts like *Candida,* and fungistatic against molds like *Aspergillus.* Caspofungin was the first to be approved. Active in vitro against most *Candida* and *Aspergillus* species, published data suggest that the echinocandins produce equivalent outcomes in the therapy of invasive *Candida* infections compared with amphotericin but with fewer side effects. Caspofungin has received FDA approval for children aged 3 months to 17 years for the following:

- Empiric therapy of presumed fungal infections in febrile neutropenic children
- Treatment of candidemia (including esophagitis, peritonitis, and empyema)
- Salvage treatment of invasive *Aspergillus*

Micafungin was recently FDA approved for pediatric patients 4 months and older for the treatment and prophylaxis of a wide range of *Candida* infections. Anidulafungin is a similar echinocandin agent, approved for adults but not officially approved for pediatric patients. The echinocandins are highly protein bound (>95%), but, unlike some of the triazole antifungals, they are not metabolized by the P450 system.

Adverse Reactions to Antibiotics

Adverse drug reactions to antibiotics should be considered whenever there is a symptom that is associated with the side-effect profile of the drug or when unexpected symptoms and signs arise. The most common of these is a rash, often with itching, but more severe reactions can occur, including anaphylaxis. These reactions may require discontinuation of the drug or further supportive treatment.

Drug Interactions

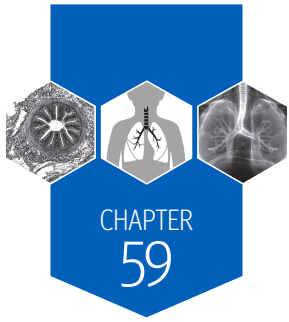
Infectious diseases consultants and pharmacists should be consulted whenever there is a potential for drug interaction. There are also sources on the internet that provide extensive information concerning drug interactions.

Acknowledgment

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Nutritional Aspects of Pulmonary Conditions

Ellen K. Bowser, MS, RDN, LDN, RN, FAND
Mary H. Wagner, MD

Pulmonary disorders such as cystic fibrosis (CF), bronchopulmonary dysplasia (BPD), and asthma may compromise a child's growth and acquisition of specific nutrients, and nutritional deficiencies may adversely affect the overall course of these conditions. On the other hand, overnutrition plays a role in the development or severity of pulmonary disorders, such as obstructive sleep apnea (OSA) or Prader-Willi syndrome. Thus, understanding nutritional issues is important in the care of children with pulmonary disorders.

General Nutritional Evaluation

Nutritional assessment of children with pulmonary conditions can be accomplished using the ABCDEF method (**Table 59-1**). Anthropometric data determine the child's growth and body composition in comparison to their peers. Biochemical indices assist the pediatrician in determining hematologic, protein, and vitamin and mineral status. Clinical examination helps in the determination of nutritional status, while dietary, elimination, and feeding information assist in the formulation of a diagnosis. Dietary intake data provide an accurate depiction of daily intake and meal patterns. Elimination patterns help identify bowel and bladder issues. Feeding history illuminates oral motor skills acquisition and timing of meals and snacks.

Anthropometric Evaluation

Anthropometric data include growth plotted on standard growth charts, as well as head circumference (up to 3 years of age) and skinfold measurements. The Centers for Disease Control and Prevention recommendations are to use the World Health Organization international growth charts for children younger than 24 months and the Centers for Disease Control and Prevention growth charts for individuals 2 to 19 years of age.[3] Genetics play a major role in each child's growth potential. Evaluation of the parents' height (midparental height calculation) provides an estimate of the child's potential for height. Well-nourished children with CF and asthma are able to meet their genetic potential for growth. Children with BPD who were born preterm are often shorter and

weigh less than their peers.[4] Body mass index (BMI, [weight in kg]/[height in m^2]) is an overall assessment of the child's weight for their height. Children's BMI values change as they grow. Body mass index *percentiles* provide a better assessment of the child's weight for height compared to peers. Normal or healthy BMI percentiles for children are between the 5th and 85th percentiles. Optimal nutrition for children with CF is a BMI greater than the 50th percentile for age.

Table 59-1. ABCDEF Nutritional Assessment in Children With Pulmonary Conditions: Components of Interest for Specific Conditions

Assessment	All Children	CF	Asthma/OSA	BPD
Anthropometric data[a]	Weight percentile Height percentile Weight/height percentile (< 3 years) BMI percentile (> 3 years) Head circumference (< 3 years)	Midparental height	Neck size (OSA)	Correction for prematurity (up to 2 years of corrected age)[1,2]
Biochemical indices	Prealbumin Hemoglobin Hematocrit	Serum vitamin A, 25-hydroxy vitamin D, vitamin E, PT/INR (a marker for vitamin K status)	25-Hydroxy vitamin D	—
Clinical examination	Appearance Skin turgor Wasting or excess weight	Increased cough, frequent respiratory infections	Acanthosis, striae	Increased work of breathing, pulse oximetry
Dietary information	24-hour dietary recall	3-day diet record	3-day diet record Portion sizes, consumption of sugary beverages	Formula preparation Solid foods
Elimination patterns	Bladder, bowel habits Emesis	Detailed stooling history, constipation or distal intestinal obstruction syndrome?	—	—
Feeding history	Location and timing of meals and snacks	Enzyme dosing	Skipping meals or overeating	Oral motor feedings/ skills

Abbreviations: BPD, bronchopulmonary dysplasia; BMI, body mass index; CF, cystic fibrosis; INR, international normalized ratio; OSA, obstructive sleep apnea; PT, prothrombin time.
[a] See information on growth charts under Anthropometric Evaluation in main text.

Growth for infants who are born preterm should be corrected for their gestational age.[1] Health care providers usually correct for weight and length for up to 2 years on standard growth charts.[2]

Biochemical Evaluation

Biochemical indices most commonly used for nutritional assessment include prealbumin, hemoglobin and hematocrit, and vitamin levels. Prealbumin is a serum protein synthesized by the liver that is an indicator of protein status. Prealbumin reflects protein status of the preceding 2 to 3 days. Prealbumin can be decreased in various circumstances, including liver disease and acute illness.[5]

Hemoglobin and hematocrit are indicators of anemia. Anemia in children with lung conditions can be caused by poor dietary intake of iron, folate, vitamin B_{12}, or vitamin E. Malabsorption can also contribute to anemia in children with CF. Anemia of chronic disease also may be found in children with CF.

Serum fat-soluble vitamin levels are routinely measured in children with CF. Serum 25-hydroxy vitamin D levels have been found to be decreased in children with obesity, asthma, and OSA.[6,7]

Clinical Evaluation

Clinical examination of the child with a pulmonary condition includes evaluation of overall appearance, skin turgor, and evidence of wasting or excess weight. Acanthosis or striae may be found in children with obesity. In children undergoing evaluation for OSA, neck circumference should be measured because those with a higher neck circumference have an increased risk of OSA.[8]

Dietary Evaluation

Dietary information is essential in assessing the nutritional status of a child with a pulmonary condition. A 24-hour dietary recall is useful in obtaining a general indicator of a child's caloric and protein intake. However, this is often inaccurate and may not reflect usual intake. A 3-day diet record is the most accurate means to assess intake, but this may be difficult and should be done in consultation with a registered dietitian. Specific instructions need to be given to the caregivers and child on estimating portion size and providing details, such as product brands and restaurant names. It is also important to evaluate portion sizes and timing of meals and snacks. The amount of beverages containing added sugar (sodas, sports drinks, etc) should also be evaluated because the consumption of these is associated with overweight and obesity in children.[9]

Elimination Evaluation

Elimination patterns include bladder and bowel habits as well as emesis. In addition to determining current patterns, it is important to assess if there are any recent changes. The number and consistency of stools should be established. In children with CF, pancreatic insufficiency (PI) is associated with steatorrhea with malodorous, greasy stools. Distal intestinal obstruction syndrome should be considered in a child with CF with abdominal pain, cramping, nausea/vomiting, and lack of bowel movements.[10]

Feeding Evaluation

Feeding history should include location and timing of meals and snacks. Length of meals and oral motor and feeding skills are also important to assess. Children with BPD often have a delay in normal oral motor skill development due to their prematurity, delay in oral feedings, and/or length of time on a ventilator. The calorie intake should be assessed and, as recall is often poor, a prospective 3-day dietary record of intake is useful. Meal skipping (usually breakfast) and compensatory overeating should be evaluated. Infants and children with a history of choking or coughing with feedings should receive a swallowing evaluation.

Nutritional Management of Respiratory Conditions Associated With Undernutrition

Cystic Fibrosis

Nutrition plays a key role in the management of persons with CF. Adequate nutrition is important in maintaining health, fighting infection, and avoiding deficiencies that may accompany the disorder. Assessment of nutritional parameters is an important part of routine care of persons with CF. (See Chapter 45, Cystic Fibrosis.) A decline in growth may herald worsening pulmonary status, onset of CF-related diabetes, or CF-related liver disease. The Cystic Fibrosis Foundation (CFF) recommends that children with CF maintain normal weight and height for age, as normal growth has been associated with better lung function and survival.[11] The CFF suggests that children (those >2 years, including adolescents) should achieve energy intake at levels of 110% to 200% above the usual requirements in healthy children to achieve age-appropriate weight gain.[10] This may require a combination of approaches, including calorie boosting, nutritional supplements, and behavioral interventions.

Nutritional intervention begins when a diagnosis of CF is established. Approximately 85% to 90% of persons with CF will have exocrine PI. This most often presents at birth or shortly thereafter, but, in some children, it develops after the first year.[12] The diagnosis of PI may be confirmed by finding a low level of

fecal elastase.[12] Persons with PI have malabsorption of fat, protein, and other nutrients, including the fat-soluble vitamins (A, D, E, and K).

Anthropometric measurements, including height, weight, and weight for length or BMI, should be obtained at each clinic visit. A goal of maintaining BMI at the 50th percentile or greater is suggested because this level of growth is associated with a forced expiratory volume in 1 second near 80% of predicted.[10] All persons with CF should have additional monitoring of their nutritional status by yearly laboratory evaluation, including complete blood cell count, differential, liver function tests, clotting studies, and vitamin levels (A, E, and D 25-hydroxy vitamin D).[13]

Enzyme Replacement Therapy

Patients with PI should be given pancreatic enzyme replacement therapy with all meals and snacks, including human milk and predigested formulas. The microsphere tablet preparations are enteric-coated to avoid degradation in the acidic gastric environment, so the enzymes are released in the proximal small intestine to optimize nutrient absorption. Some patients may benefit from the addition of a histamine type-2 receptor blocker or proton pump inhibitor because gastric acid passing into the duodenum, unbuffered by pancreatic bicarbonate secretion, may decrease the effectiveness of pancreatic enzymes.[13]

Enzymes should be taken before every meal or snack unless the snack is exclusively carbohydrate, such as fruit or fruit juice. Patients usually take half of the typical meal dose before a snack. The dose of enzymes for a meal may need to be distributed throughout the meal for patients who take an extended period to eat or who are snacking throughout the day. The family and patient need to learn how to adjust the enzyme dose depending on the size, content, and duration of the meal. All caregivers, including in child care and school environments, need to be educated about the need for enzymes with all snacks and meals.

Enzyme doses should be in the range of 1,500 to 2,500 units of lipase per kilogram of body weight per meal, with an upper limit of 10,000 units of lipase per kilogram per day.[10] These dose ranges are formulated to avoid risk of fibrosing colonopathy. Patients with persistent malabsorption need further evaluation for other conditions, such as small bowel bacterial overgrowth, celiac disease, or lactase deficiency.

Infants With Cystic Fibrosis

Infants with CF may be identified by either newborn screening or clinical history. For most infants, the major form of nutrition in the first year after birth should be human milk. Formulas with a caloric density greater than 20 kcal/oz or human milk are often necessary to maintain the desirable level of weight gain. The caloric density of formula or human milk can be augmented by

concentrating the formula or adding fat or carbohydrate. Solid foods can be added at age 4 to 6 months per recommendations of the American Academy of Pediatrics.[14] However, the primary source of caloric intake should remain formula or human milk, especially if adequate growth is an issue. Infant cereal should be mixed with formula or human milk rather than juice or water. Whole milk can be used after 1 year of age for children who are growing well.[12]

For patients with PI, enzymes can be administered in a small amount of formula or baby food. Infants should receive vitamin supplementation, including vitamins A, D, E, and K. The adequacy of dietary iron and fluoride should be evaluated and supplements should be added if necessary. Those infants with suboptimal growth may need supplementation of their caloric intake by addition of carbohydrate or fat.[12]

Due to the extra sodium and chloride losses in sweat, infants with CF should be supplemented with 1/8 teaspoon of salt daily for infants up to age 6 months and 1/4 teaspoon of salt daily for infants older than 6 months.[12,13] This can be given in 1 or 2 doses mixed with formula or expressed human milk or given in the applesauce and enzyme mixture for infants who are breastfed. The CFF developed guidelines for the care of the infant with CF, which are available at www.cff.org.

Toddlers and Preschool-Aged Children With CF

Families with toddlers and preschool children with CF may experience more mealtime difficulties (ie, more feeding resistance, longer mealtimes) than families who do not have children with CF.[15] This can lead to mealtime battles and dysfunctional eating behaviors. Clinical or behavioral psychology services can be useful to enhance positive feeding behaviors and consistent weight gain.[15]

The CFF developed clinical practice guidelines for the preschool child with CF, available at www.cff.org.

School-Aged Children With CF

Children with CF who are of school age may experience decreased growth[16] because of the number of activities that limit time for meals and snacks. Disease progression may also affect growth velocity. Diets high in protein and fat should be encouraged, and vitamin supplementation should continue. Behavioral interventions may be required if mealtime problems are identified. Children with PI should understand the need for enzyme supplementation.

A plan should be developed so that enzymes can be taken at school or childcare. School staff education is necessary so that enzymes are given immediately prior to eating. Educational materials are available for caregivers, teachers, and coaches who work with children with CF.[17]

Adolescents With CF

Calorie and nutrient requirements increase in adolescents for several reasons, including pubertal growth spurt, increased activity, and disease progression in some children. Girls are at greater risk of underweight primarily because of gender-specific social norms and expectations regarding weight.[18] Some patients may develop CF-related diabetes as the incidence and prevalence of this condition increases after age 10 years.[19] Decreased growth or delayed sexual maturation may occur in those with severe disease.[13] Additional issues that may be encountered with adolescents with CF include loss of parental control over medication administration and intentional weight loss. The adolescent should understand the link between good nutrition, good lung health, and avoiding hospitalization. Adolescents experiencing weight loss should be questioned about their perspective on their body image and if any weight loss is intentional. Adolescents with CF can develop eating disorders with potentially severe consequences.[20] Adolescents should be involved with their own treatment plan to improve adherence and results.

Nutritional Supplements and Calorie Boosters

Children and adolescents with chronic pulmonary conditions may benefit from strategies to increase the caloric density of their usual diet. This can be accomplished using milkshakes or calorie boosters with their daily foods (**Box 59-1**). Other children and adolescents with suboptimal growth may benefit from the use of commercial formulas. These preparations can be useful and convenient but entail additional expense and may be difficult for the families to obtain. Dietary intake should be monitored so that these preparations are used to supplement rather than replace meals. They can be delivered orally or enterally if a feeding tube is present. Nutritional supplement of the child's choice is best. Most will benefit from a rotation of different supplements because they may tire of the same one if used repeatedly. Patients and families should be questioned about what over-the-counter supplements they may be using to avoid excess intake of specific nutrients. Herbal or other over-the-counter supplements are not regulated by the Food & Drug Administration and may contain harmful ingredients.[13]

Cystic Fibrosis Transmembrane Conductance Regulator Modulation Therapy and Growth

New medications designed to correct the cystic fibrosis transmembrane conductance regulator mutation defect have shown improvements in lung function and growth. (See Chapter 45, Cystic Fibrosis). A 2022 systematic review found some improvements in weight gain and growth in children with CF depending on cystic fibrosis transmembrane conductance regulator mutation class and specific modulator(s) examined.[21]

Box 59-1

Tips to Help a Child Gain Weight

Feeding Suggestions

Stick to a regular meal schedule (for example, 3 meals and 3 snacks each day).

Offer solid foods first and then liquids.

Limit juice to 4 oz per day.

Praise positive behavior and ignore negative behavior.

Do not force a child to eat; this can be counterproductive.

Avoid the TV and other distractions during mealtimes.

Limit meals and snacks to 20 to 30 minutes.

Calorie Boosters

Adding extra calories to a child's diet may help them gain weight. There are many ways to add extra calories to common foods. Following are some examples:

Sour cream: Put on baked potatoes, add to burritos and tacos, stir into cream soups.

Cheese dip: Eat with pretzels, apples, or celery. Melt over broccoli or cauliflower.

Nut butters: Spread on breads, crackers, apples, bananas, and celery.

Cream cheese: Spread on bagels; use flavored cream cheese as a dip for fruits.

Vegetable oil: Drizzle over noodles and vegetables. Use to make scrambled eggs or as a dipping oil for breads and rolls.

Salad dressings: Use as dip for vegetables or as a sandwich spread.

Recipes

Power milk: 1 cup whole milk, 2 tbsp heavy whipping cream, 2 tbsp chocolate or strawberry syrup.

Nachos: 15 tortilla chips, 1/4 cup cheese, 2 tbsp sour cream, 2 tbsp black olives, 2 tbsp guacamole or avocado dip.

Chocolate peanut butter shake: 1/2 cup heavy whipping cream, 3 tbsp creamy peanut butter, 3 tbsp chocolate syrup, 1½ cups chocolate ice cream. Mix in blender and top with crushed sandwich cookies.

Apple pie a la mode shake: 1 cup apple pie filling, 1/2 cup whole milk, 1 cup vanilla ice cream, dash of cinnamon. Mix in blender and top with caramel and crushed graham crackers.

French toast sandwich: Spread 2 tbsp of peanut butter and 1 tbsp of jelly between 2 slices of French toast.

No bake chocolate cookies: Mix 1/4 cup softened margarine, 1/4 cup peanut butter, 1/2 cup instant sweet cocoa mix, 1 cup oatmeal. Form into 1-inch balls and chill in refrigerator for 10 minutes.

Cooked carrots: 2 tbsp apricot preserves and brown sugar, or 2 tbsp honey added to buttered, cooked carrots.

Chocolate pudding: Use 1 can (12–14 oz) sweetened condensed milk instead of regular milk when making pudding and sprinkle white chocolate chips on top.

Tube Feedings

Children who are unable to consume adequate calories during their daily intake may benefit from tube feedings. This approach should be considered in those who are unable to attain growth/weight maintenance goals.[22] Feedings can be administered via tubes placed nasally (nasogastric [NG]) or percutaneously (gastrostomy tubes). Some children who are unable to consume adequate calories will appreciate the option of being able to supplement their intake with NG feedings delivered during sleep; however, NG tubes are generally considered for a short-term (<3 months) basis due to the risks of tube displacement and aspiration. Longer-duration feedings will require a more permanent gastrostomy tube placement in those children who are unable to attain weight goals by exclusively oral intake. Pancreatic enzymes are usually given prior to the start of the feeding and again in the morning. Some children require additional enzyme administration during the midpoint of the feeding period. Patient response to these feedings should be carefully monitored, including weight gain, symptoms of malabsorption, and daytime appetite. Other strategies include using predigested formulas with and without enzymes. These formulas incur additional expense and have not been shown to be better absorbed, but they may be preferred in those who have had small intestine resection.[23] Tube feedings may need to end 2 hours prior to the usual wake-up time for the child to feel hungry for breakfast. The CFF has developed guidelines for the use of enteral feedings in children with CF, which are available at www.cff.org.

Vitamins

Persons with CF are at risk for deficiencies of fat-soluble vitamins, including A, D, E, and K. The CFF has specific recommendations for supplementation of fat-soluble vitamins.[13] These preparations are available in a variety of forms (soft gels, chewable tablets, and drops). Vitamin levels should be monitored at least annually with supplementation if adequate levels cannot be achieved despite intake of recommended formulations.[13]

All patients should receive the dietary reference intake suggested for calcium based on age. Calcium supplementation may be required for those on oral corticosteroids or those with decreased dietary calcium intake or decreased bone density. Suboptimal serum levels of vitamin D (<74.88 nmol/L [<30 ng/mL] of 25-hydroxy vitamin D) are seen commonly in children with CF. This is thought to be a combination of inadequate intake, decreased storage, and decreased synthesis.[24] There is a higher incidence of osteopenia and osteoporosis in children with CF than in those without CF.[24]

Salt

Children with CF experience increased losses of sodium and chloride through their sweat. Salt requirements in older children and adolescents can be met with liberal use of high-salt foods or adding table salt to meals. They may require

additional salt supplementation at times of increased salt losses, such as with fever, hot weather exposure, vigorous physical activity, or diarrheal illnesses.[13]

Bronchopulmonary Dysplasia

Infants with BPD are often of extremely low or very low birth weight due to their prematurity. Weight gain in the neonatal intensive care unit (NICU) early in the disease process may be poor, and these infants tend to remain small for their gestational age. Upon discharge from the NICU, they may continue to experience growth faltering. Adequate nutrition to allow normal growth and development is key to the resolution of BPD.[4] Growth of new lung tissue can occur in humans up to 8 years of age; therefore, it is important to continue to encourage good nutrition.

Numerous factors need to be considered when evaluating and managing the nutritional needs of children with BPD. These include increased metabolic rate, increased work of breathing, need for catch-up growth, volume intolerance, feeding issues, frequent respiratory infections, and fluid restrictions.

The effects of increased metabolic rate and increased work of breathing may increase energy expenditure by 25% for infants with BPD.[25] Human milk is considered the optimal form of nutrition for all infants. Exclusive breastfeeding until age 4 months, and partial breastfeeding thereafter, is associated with significant reduction of respiratory and gastrointestinal morbidity rates in infants up to 1 year of age. For infants with BPD, the increase in caloric expenditure along with the need for catch-up growth often mandate the use of human milk fortifiers or the addition of concentrated formula to human milk. Human milk can be enhanced to reach a caloric density of 24 to 30 kcal/oz. If human milk is not available, special infant formulas designed for the preterm or low birth weight infant can be used. These formulas have higher caloric and nutrient density. Nutrient-enriched formulas are also available for the preterm neonate after discharge from the NICU.[4] When using high–caloric density formulas, caution should be taken due to the dilution of protein, vitamins, and minerals in the formula. These infants may also need additional free water. A registered dietitian/nutritionist familiar with the nutritional care of the child with BPD should be consulted if an increased caloric density formula is required. Infants with BPD are often fluid restricted and given diuretics to improve lung function and prevent pulmonary edema.[26]

Volume intolerance can be caused by hyperinflation of the lungs and compression of the diaphragm and stomach. This can lead to limited intake of the nutrient-enriched formula. Gastroesophageal reflux can make feeding the infant with BPD more challenging. Evaluation for gastroesophageal reflux

may be appropriate, as medical or even surgical treatment may be necessary to ensure adequate oral intake and prevent aspiration.

Feeding issues for the infant or toddler with BPD may include uncoordinated suck, swallow, and breathing; oral motor difficulties; and adverse feeding behaviors. If these issues are suspected, a feeding evaluation should be considered by a speech-language or occupational therapist. Ongoing therapy for oral motor difficulties may be required to allow the child with BPD to achieve adequate oral intake for growth.

Feeding Challenges

Most children with pulmonary conditions such as CF or asthma will have normal oral motor skill development. However, children with a history of prematurity are at increased risk for delayed development of oral motor skills. Children who were born preterm are at increased risk for impairments in swallowing and feeding disruptions.[27]

Chronic lung disease may be associated with uncoordinated suck, swallow, and breathing patterns, which increase the risk of aspiration. Infants who were mechanically ventilated for an extended period may develop oral motor defensiveness. Those who remain on supplemental oxygen may experience fatigue with feeding and tolerate only small volumes of formula. Infants and children with neuromuscular, genetic, and craniofacial disorders may also experience feeding difficulties. Infants and older children with feeding difficulties should receive treatment from a speech-language pathologist or occupational therapist.

Children with tracheostomies can feed orally once it is ascertained that the child is not aspirating. Children who receive exclusive tube feedings should receive oral motor stimulation during feedings to help associate the sensations of fullness with oral involvement. Failure to cough or clear the throat in response to aspiration is common in children with complex medical conditions.

Parental feeding behaviors and the feeding environment are also vital for appropriate feeding skills. A calm, non-stimulating setting (TV and other distractions turned off) is important. Scheduled meals and snacks, parental role modeling, and the use of positive reinforcement should be encouraged.

Gastrostomy tube feedings are often used when a child with a pulmonary disorder is unable to maintain adequate oral intake over time. These feedings may be either bolus or continuous. Gastrostomy tube feedings may be used to supplement inadequate oral intake or as a substitute for oral intake in children who may be at significant risk for aspiration. Oral motor stimulation should be encouraged if the child is receiving exclusive tube feedings.

Nutritional Aspects of Respiratory Conditions Associated With Obesity

The overall prevalence of pediatric obesity in the US population was 19.3% in 2017 to 2018.[28] The prevalence has been increasing in all age groups over recent years.[29] Obesity is associated with a variety of pulmonary disorders including OSA, asthma, and restrictive lung disease. (See Chapter 43, Asthma and Other Respiratory Disorders Associated With Obesity.)

Children with obesity may have restricted chest wall movement and a restrictive pattern on their pulmonary function tests; if obesity is severe, they may have obesity hypoventilation syndrome with impaired response to carbon dioxide.

The Endocrine Society clinical practice guidelines for the prevention and treatment of pediatric obesity, published in 2017,[30] recommend that treatment for overweight and obesity include appropriate lifestyle changes, including diet, physical activity, and behavioral counseling for the patient and the family. This panel recommended physical activity, including moderate-to-vigorous exercise for 60 minutes per day, and restriction of sedentary activities, including TV viewing, video gaming, and use of computers. Lifestyle modification that included family involvement was emphasized. Many of these recommendations are mirrored by the Academy of Nutrition and Dietetics, suggesting multi-component programs, including diet, physical activity, nutritional counseling, and parent participation, for the intervention to be successful.[31]

Asthma

An association between overweight and asthma has been reported in the literature, but a cause-and-effect relationship has not been clear.[32] One group concluded that school-aged children with BMI at the 85th percentile or greater had a 50% higher risk of developing asthma than their normal-weight peers. They also found neonates with a birth weight of 3.8 kg or higher had a 20% higher risk of future asthma than their peers.[32] A recent systematic review found improvement in quality of life and, in some cases, asthma control in children with overweight and asthma who participated in weight loss programs.[33]

Children and adolescents with asthma are often discouraged from drinking milk or other calcium-rich dairy products due to the ongoing belief by some individuals that milk or dairy consumption increases mucus production.

Although this theory has been disproved, the "milk-mucus connection" myth remains widespread.[34] Parents of children with asthma often report avoiding dairy in their children's diets.[34] This is an important topic to discuss with families, as some children who receive inhaled corticosteroids have been found to have decreased bone density and growth velocity.[35] Children with asthma should be encouraged to consume adequate amounts of calcium and vitamin D for bone growth and mineralization. Pediatricians should inquire about calcium and vitamin D intakes when working with children with asthma. Parents who remain hesitant to give their children dairy products should be encouraged to give their children calcium and vitamin D supplements to meet the Institute of Medicine Food and Nutrition Board's dietary reference intake levels.[36]

Several dietary interventions have been proposed for reducing the incidence or severity of asthma, including supplementation with fish oils, antioxidants, vitamins C and E, and beta-carotene, and reduction in dietary sodium. However, recent analyses do not support these interventions.[37]

Obstructive Sleep Apnea

Obstructive sleep apnea is estimated to occur in 2% to 3% of the general pediatric population.[38] Obesity is a risk factor for the development of OSA.[39] However, young children may present with failure to thrive. Many children will have no growth issues. Weight loss has been shown to result in an improvement in sleep-related breathing disorders[40]; thus, assessment of nutritional status is important in children with OSA. Nutritional intervention is an important component of the multifaceted management plan for children with OSA.

Prader-Willi Syndrome

Prader-Willi syndrome has an estimated prevalence of 1 in 10,000 to 1 in 25,000 live births.[41] Initial nutritional symptoms include poor suck, hypotonia, and poor growth. Patients with Prader-Willi syndrome evolve to a pattern of food-seeking behavior and insatiable appetite with subsequent development of obesity.[42] Pulmonary manifestations can include restrictive lung disease and sleep-related breathing disorders, including OSA, central apnea, and excessive daytime sleepiness.[43] Dietary management is very important to deal with the different nutritional phases these patients experience and should be under the direction of a registered dietitian experienced in the care of these patients. Strategies for dietary management include environmental management of food intake, a calorically controlled diet, and constant supervision.

key points

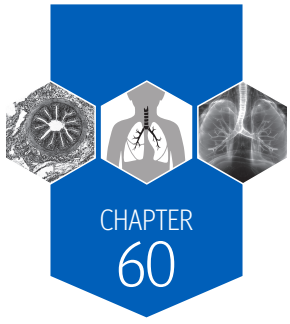
- One method to evaluate nutritional status in children with pulmonary conditions is the ABCDEF method (**Table 59-1**).
- Nutritional status is linked to lung function and survival in CF.
- Children with CF and PI should receive pancreatic enzymes before all snacks and meals.
- All children with CF should be supplemented with additional vitamins, with a focus on the fat-soluble vitamins.
- The stepwise approach to increase caloric intake in children with CF includes calorie boosters added to meals/snacks, oral nutritional supplements, and tube feedings.
- The CFF is an excellent resource for age-specific dietary recommendations.
- Children with BPD with inadequate weight gain should be evaluated by a pediatric registered dietitian/nutritionist.
- Obesity in children is increasing, and successful weight management programs incorporate the family and lifestyle changes, including physical activity and moderation in caloric intake.
- Weight loss can improve asthma symptoms and quality of life in children with asthma and obesity.
- Weight management is important in the treatment of children with OSA and obesity.

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CHAPTER 60

Oxygen Therapy

Shyall Bhela, MD
Sankaran Krishnan, MD, MPH

Introduction

Oxygen is a gas that is essential for human life and cellular metabolism. Conditions that are associated with diminished partial pressure of oxygen (Po_2) in the blood result in a decreased oxygen content, which, if not corrected, can lead to organ damage and eventually death. Oxygen is administered as a medical therapy in these situations.

Definitions

- **Hypoxemia:** Decreased partial pressure of oxygen in the blood
- **Hypoxia:** Decreased oxygen content in the tissues
- **Normobaric oxygen therapy:** Administration of oxygen under atmospheric pressure (760 mm Hg at sea level)
- **Hyperbaric oxygen:** Delivery of oxygen under pressures that exceed the atmospheric pressure
- **High-flow oxygen:** Delivery of oxygen at significantly higher flow rates using specialized cannula as compared to traditional flow rates used for oxygen therapy

Determinants of Oxygen Delivery to Tissues

Oxygen-carrying capacity is the sum of the amount of oxygen dissolved in blood plus oxygen bound to hemoglobin (which provides ~98% of the oxygen delivered to tissue). The oxygen dissociation curve (**Figure 60-1**) describes the relationship between the Po_2 and the oxygen saturation as measured by pulse oximetry (Spo_2, often referred to as 'percentage of hemoglobin saturated with oxygen').

The relationship between Po_2 and Spo_2 is not linear but rather S-shaped. The curve flattens out at higher Po_2 levels, indicating that, at these levels, there is little incremental increase in Spo_2 for a given increase in Po_2. For example,

when the hemoglobin is 90% saturated, the arterial partial pressure of oxygen (P_{AO_2}) is 60 mm Hg. Above this value, further increases in the P_{AO_2} result in only a small increase in the Spo_2. Below 60 mm Hg, however, a small change in P_{AO_2} level results in a large change in the Spo_2. Certain conditions, such as elevated partial pressure of carbon dioxide (P_{CO_2}), increased temperature, and acidosis, decrease hemoglobin's affinity for oxygen, which results in an increase in the unloading of oxygen at the tissue level with a shifting of the curve rightward. In contrast, lower P_{CO_2}, decreased temperature, and alkalosis increase hemoglobin's affinity for oxygen and facilitate oxygen uptake by red blood cells, thus shifting the curve leftward.[1]

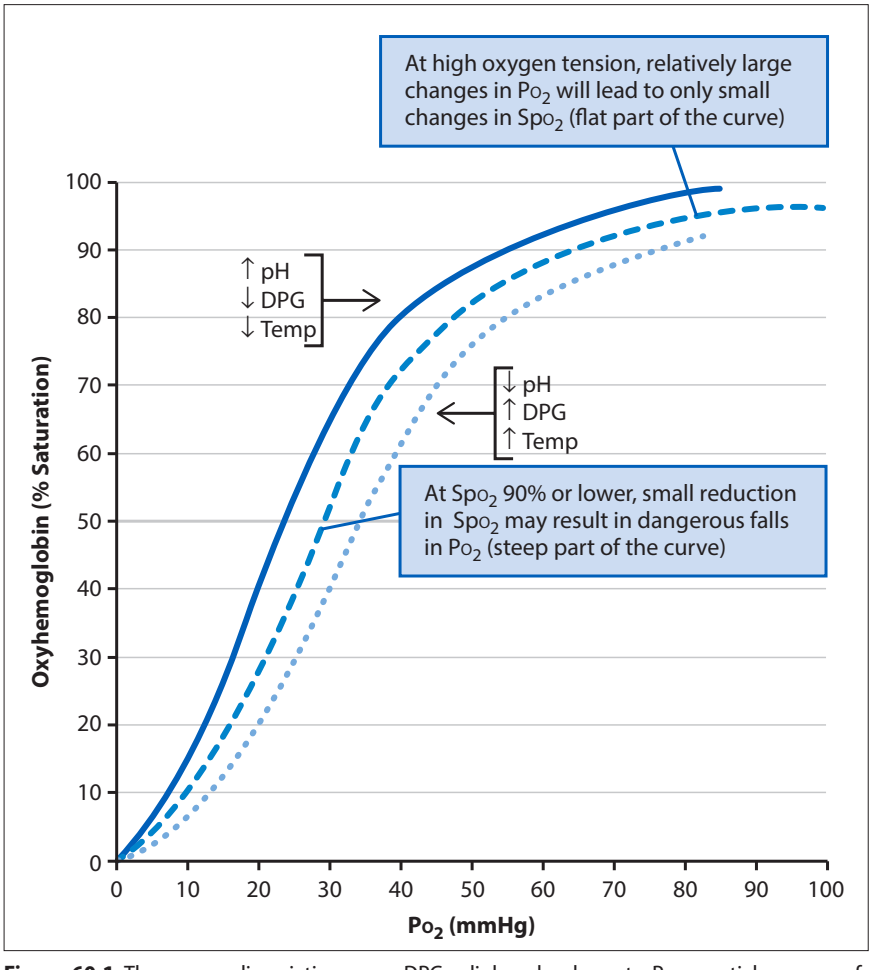


Figure 60-1. The oxygen dissociation curve. DPG = diphosphoglycerate, Po_2 = partial pressure of oxygen, Spo_2 = oxygen saturation as measured by pulse oximetry (percentage of hemoglobin saturated with oxygen).

From Krishnan S. Oximetry and capnography. In: Stokes DC, Dozor AJ, eds. *Pediatric Pulmonology, Asthma, and Sleep Medicine: A Quick Reference Guide.* American Academy of Pediatrics; 2018: 63–67.

The Alveolar Gas Equation and the Alveolar-Arterial Gradient

The alveolar gas equation is used to calculate the alveolar partial pressure of oxygen (P_{AO_2}), which is required to calculate the alveolar-arterial oxygen gradient (A-a gradient).

$P_{AO_2} = P_{IO_2} - P_{ACO_2}$ (where P_{IO_2} is the partial pressure of inspired air).

P_{IO_2} (in room air) = $F_{IO_2} \times (P_B - 47$ mm Hg), where P_B is barometric pressure (760 mm Hg at sea level), 47 mm Hg is the partial pressure of water vapor or humidified air as it reaches the alveoli, and F_{IO_2} (fraction of inspired oxygen) is 0.21 at sea level. At sea level, P_{IO_2} is 150 mm Hg.

Assuming a P_{ACO_2} of 40 mm Hg, the P_{AO_2} would be 110 mm Hg. With an arterial O_2 (Pao_2) of 100 mm Hg, therefore, the normal A-a gradient is approximately 10 mm Hg.

Conditions that affect the ventilation-perfusion relationships in the lung or those that affect the alveolar-capillary membrane will be associated with an abnormal (increased) A-a gradient.

Causes of Hypoxia and Hypoxemia

The causes of hypoxia and hypoxemia can be broadly grouped into 6 categories:

1. Ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch: Resulting from differential ventilation and perfusion of the lungs, observed in conditions that impair either of these functions.
2. Hypoventilation:
   a. Central/neurogenic conditions (eg, central hypoventilation syndromes, encephalopathies, opioid/sedative overdose).
   b. Neuromuscular conditions (eg, spinal muscular atrophy, muscular dystrophies, myopathies, myasthenia gravis).
3. Diffusion defect: Diseases and conditions that affect the alveolar-capillary barrier (eg, interstitial lung disease).
4. Shunting: Occurs when blood returns to the systemic circulation after passing through areas not being ventilated. Can be classified as physiologic (eg, the Thebesian vessels of the heart) or pathologic (eg, congenital cyanotic heart defects or pulmonary arteriovenous malformations).
5. Alteration in oxygen-carrying capacity: Diseases and conditions that disrupt the structure or function of the hemoglobin molecule, thereby altering the oxygen-carrying capacity (eg, carboxyhemoglobinemia, methemoglobinemia, and cyanide toxicity).
6. Decreased inspiratory concentration of oxygenation as seen at high altitudes.

Ventilation-Perfusion Mismatch

This term refers to an imbalance between ventilation ($\dot{V}$) (gas flow into the lungs) and blood flow ($\dot{Q}$) through the lung. Blood flow and ventilation vary according to region of the lung and the patient's position. In healthy individuals, pulmonary blood vessels are regulated such that if a particular gas exchange unit is not receiving adequate ventilation, the vascular supply to that unit will correspondingly decrease. This compensation, however, may not be seen in disease conditions such as pneumonia, bronchiolitis, atelectasis, pulmonary edema, asthma, and acute lung injury/acute respiratory distress syndrome. In these conditions, blood flow continues into areas of the lung that are under-ventilated, leading to less oxygen uptake and resultant hypoxemia.

Hypoventilation

Hypoventilation (insufficient ventilation) is a result of either a decreased central respiratory drive to breathe or weak respiratory neuromuscular apparatus. Apart from the disease states listed in the previous paragraph, sedation or anesthesia as well as certain drugs may present with hypoxemia due to hypoventilation. A hallmark of hypoxemia due to hypoventilation is a normal A-a gradient.[2]

Supplemental oxygen should be administered with caution when hypoxemia is due to hypoventilation. The application of supplemental oxygen may correct the Spo_2 but may place the patient at greater risk because of blunting of the hypoxic drive. Patients who have hypoventilation may require ventilatory support rather than supplemental oxygen alone.

Diffusion Defect

A diffusion defect usually occurs when there is a thickening or disruption of the normal surface area available for gas exchange in the lung. In otherwise healthy individuals, the space across which oxygen passes from the alveolus to the blood is less than 1 micron thick. At baseline, the red blood cells have more than a sufficient amount of time to traverse the pulmonary capillary and receive oxygen from the alveolus. In the healthy individual, this arrangement accommodates states of increased demand, such as exercise, during which the cardiac output increases up to fivefold and the capillary transit time decreases. In children with defects in diffusion, there may be insufficient time for the blood to be fully oxygenated (especially when the system is stressed), resulting in hypoxemia. Diffusion defects are rare in children, occurring in conditions such as interstitial lung diseases and pulmonary hemosiderosis.

Shunts

Cardiac and intrapulmonary shunts cause blood to bypass functional alveoli and result in hypoxemia. This hypoxemia cannot be completely corrected by administering oxygen. Oxygen saturation in patients with intracardiac right-to-left shunts does not improve even when 100% oxygen is administered.

Alteration in Oxygen-Carrying Capacity

Dyshemoglobinemias are a collection of diseases and conditions where the structure and/or function of the hemoglobin molecule has been altered, affecting the oxygen-carrying capacity and resulting in tissue hypoxia.[3] Dyshemoglobinemias include carboxyhemoglobinemia, methemoglobinemia, and cyanide toxicity.

Carboxyhemoglobinemia results from carbon monoxide (CO) exposure in which the CO binds to hemoglobin with a higher affinity than oxygen, resulting in a left shift of the oxygen disassociation curve and causing tissue hypoxia. Sources of CO poisoning include smoke inhalation, idling cars in closed garages, gas grills, kerosene heaters, and camp stoves in enclosed spaces.[3]

Methemoglobinemia results when iron species in the hemoglobin is converted from a ferrous (2+) to ferric (3+) state, which leads to an inability of the hemoglobin to bind oxygen. Methemoglobinemia may be congenital or acquired. Congenital methemoglobinemia is secondary to mutations of the cytochrome-B^3-reductase enzyme and can either be type 1 (normal life expectancy) or type 2 (decreased life expectancy). Acquired methemoglobinemia occurs after exposures to agents that oxidize the iron species on the hemoglobin. Common exposures include well water that may be contaminated with nitrites from fertilizer runoff, topical anesthetics (lidocaine and benzocaine), and foods rich in nitrites.[3]

Cyanide toxicity occurs due to inhibition of cytochrome C oxidase that interferes with oxidative phosphorylation, halting cellular respiration. Cyanide exposures most commonly occur secondary to structural fires; other etiologies include industrial accidents and, occasionally, medical exposure to sodium nitroprusside.

Changes in Oxygenation at High Altitude

Hypoxemia also can result from inspiration of a lower partial pressure of ambient oxygen (ie, F_{IO_2}), which can occur at high altitude or during air travel. Certain individuals who are normoxic at sea level (whether on room air or supplemental oxygen) may require an increased amount of oxygen during air travel or at altitude. The body's normal compensatory response in the presence of a decreased $F_{IO_2}$is to increase the ventilatory drive. A child with neuromuscular weakness with decreased chest wall compliance may not be able to

sufficiently produce the required sustained respiratory muscle force to compensate for the hypoxemia.

High-Altitude Simulation Test

This test is advisable for persons with known risk of hypoxemia prior to taking a flight in commercial jets. This involves the patient breathing air with a known, decreased F_{IO_2} (usually 0.15, which simulates 8,000 feet), calibrated to approximate a pressurized aircraft cabin. These settings are because commercial aircraft cabins are pressurized to simulate conditions at 8,000 feet, irrespective of the flight altitude. Though a person would be breathing room air, the P_{O_2} at this altitude would approximate breathing 15% F_{IO_2} at sea level. This test is performed with the patient breathing via a mask, with continual monitoring of Sp_{O_2}, respiratory rate, and heart rate. The body's normal response is to increase minute ventilation to maintain adequate oxygenation. Once it is established that the patient is unfit for air travel on room air, the testing session may be used to calibrate the flow needed by the patient.[4] The cutoff value for initiating supplemental oxygen during air travel remains controversial.[5]

Use of Oxygen While Flying

Current Federal Aviation Administration rules do not permit travelers to carry their own oxygen tanks or liquid oxygen aboard commercial aircraft because they are defined as hazardous materials. Instead, patients may use a Department of Transportation-approved battery-powered portable oxygen concentrator. A prescription is necessary.

Portable oxygen concentrators are available for rent from most durable medical equipment suppliers; however, they must be approved by the airline, with a 48-hour advance notice, along with completed approval forms. Different portable oxygen concentrators are available, including conserving devices, which are flow triggered and deliver oxygen only in response to a patient's inhalation. These are sufficient for older children and adults; however, the infant or young child with neuromuscular weakness may not be able to actively trigger this delivery. Therefore, for these children, it is best to procure a portable concentrator with continuous flow.

Travelers are expected to bring enough 12-cell batteries for 1½ times the anticipated duration of the flight. Specific battery approval forms must be completed as per airline policy.

The clinician should be aware that commercial aircraft are typically pressurized up to an altitude of 8,000 feet only, beyond which there may be a drop in oxygen saturations.

Clinical Features of Hypoxemia

Signs on Physical Examination

Acutely, hypoxemia will manifest with signs of respiratory distress, such as tachypnea, tachycardia, and evidence of efforts to increase ventilation, including the use of accessory muscles of respiration (such as supraclavicular, suprasternal, intercostal, and subcostal retractions) as well as thoraco-abdominal asynchrony and nasal flaring. Cyanosis of the mucus membranes is seen late and constitutes a medical emergency. If the patient has been chronically hypoxemic, digital clubbing may be seen late in the course of the disease.

Evaluation of Hypoxemia

Pulse Oximetry

First described in the 1940s, pulse oximetry is now considered the "fifth vital sign" and has evolved to be the method of choice to monitor the oxygenation status of a patient.[6]

Pulse oximetry measures oxygen saturation (ie, Spo_2) by relying on the differential absorption spectra of deoxyhemoglobin (red light, 660 nm) and oxyhemoglobin (infrared light, 940 nm) (**Figure 60-2**).

The comparative ratio of light absorbance at these 2 wavelengths is calculated and calibrated against direct measurements of arterial oxygen saturation

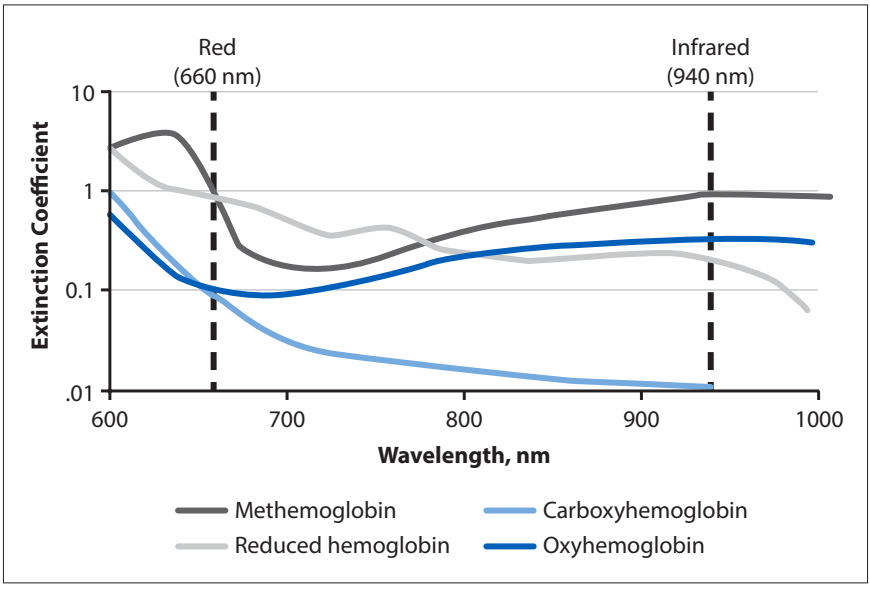


Figure 60-2. The oxygen dissociation curve. DPG = diphosphoglycerate, Po_2 = partial pressure of oxygen, Spo_2 = oxygen saturation as measured by pulse oximetry (percentage of hemoglobin saturated with oxygen).

Adapted from Krishnan S. Oximetry and capnography. In: Stokes DC, Dozor AJ, eds. *Pediatric Pulmonology, Asthma, and Sleep Medicine: A Quick Reference Guide.* American Academy of Pediatrics; 2018: 63–67.

(SaO_2) by blood gas measurements. This establishes the Spo_2. Pulse oximeters typically consist of 2 light-emitting diodes (LEDs), one emitting at the red spectrum and the other at the infrared spectrum. At the other end of the diodes, a detector measures non-absorbed energy. A microprocessor subtracts absorption by constant sources like bone and tissue and displays the final signal electronically as a waveform. The waveform reflects the pulsatile nature of blood flow and thus is a marker of pulse or heart rate. Spo_2 is calculated by converting the absorption ratios using dedicated calibration algorithms stored in the microprocessor of the device. These algorithms are derived from blood gas measurements in healthy volunteers breathing standard oxygen concentrations. They are not useful below Spo_2 of 75% because it is unethical to expose volunteers to oxygen concentrations to test the algorithm in these conditions. In most pulse oximeters, displayed Spo_2 represents the mean of the measurements obtained during the previous 3 to 6 seconds. Typical measuring sites include the finger, toe, pinna, and lobe of the ear. Newer technology uses a patented signal extraction technique to smooth out motion artifacts. Pulse oximeters equipped with this technology tend to reflect Spo_2 more accurately in infants and young children.

Blood Gas Measurements

Arterial blood gas provides direct measurement of PAO_2 and $PACO_2$, as well as pH. Venous blood gas is less useful because the values obtained may be variable and inconsistent and may not adequately represent oxygenation status. Capillary blood gas may be more reliable than venous blood gas, due to proximity to the arterial circulation, and relatively easier to obtain than arterial blood gas, especially in young infants. Mixed venous saturation, obtained directly from a central line or during cardiac catheterization, can provide a measure of oxygen extraction at the tissue level. Because of the potential for error in blood gas measurement, proper collection of the specimen is paramount. The sample should be of sufficient quantity and collected directly into a heparinized syringe that is quickly placed on ice. Increased quantity of heparin may adversely affect the pH measurement, when not using prefilled syringes. Care must also be taken not to introduce air into the syringe; an air bubble may falsely elevate the PAO_2 or depress the $PACO_2$.

Co-oximetry

Co-oximetry is useful in determining the cause of a discrepancy between percent saturation and Po_2, as may be seen in CO poisoning or methemoglobinemia.[1,2] Co-oximetry uses technology that is similar to pulse oximetry but evaluates absorbance using multiple wavelengths; thus, the co-oximeter determines not only the percent saturation of hemoglobin by oxygen (oxyhemoglobin), but also carboxyhemoglobin and methemoglobin. An individual with CO poisoning will often present with bright red or cherry red mucous

membranes; the blood similarly is bright red. The pulse oximeter will display a normal Spo_2 in the face of a low Pao_2. In contrast, those with methemoglobinemia will appear cyanotic, and the blood specimen will appear chocolate brown; Pao_2 can be normal, but the Spo_2 is low. Anemic patients will often not appear cyanotic despite a low Pao_2, whereas patients with polycythemia will appear cyanotic at more mild levels of desaturation. Pulse oximetry results are not completely accurate in patients with hemoglobinopathies.[1,2]

Use of Home Oxygen Therapy

In general, the clinical goals of home oxygen therapy include maintaining saturations within an appropriate range based on the underlying medical condition (usually > 92%; possibly higher in children with pulmonary hypertension and lower for children with congenital heart disease), limiting potential complications of hypoxemia, improving symptoms associated with hypoxemia, and promoting sustained adequate growth.[7–9] Optimal somatic growth is crucial for children with lung disease because there is a finite window, usually up to 6 to 8 years of age, in which to grow new alveoli.

The most important consequences of chronic hypoxemia are due to reflex increases in pulmonary vascular resistance leading to acute pulmonary hypertension and, ultimately, chronic pulmonary hypertension and cor pulmonale, increased right-to-left shunting through a patent foramen ovale, and poor growth.[9,10]

Specific Clinical Conditions

Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia (BPD) is defined by the need for supplemental oxygen at 36 weeks' postmenstrual age in the preterm neonate. Some studies suggest that the incidence of supplemental oxygen dependence in infants with BPD is decreasing,[11] but this may reflect changed practices and new definitions of BPD.[12] In general, prescribing supplemental oxygen in the infant with BPD results in a quicker discharge, improvement in growth, and reduced episodes of desaturation. In addition, prevention of hypoxemia reduces the risk of development of pulmonary hypertension.

Optimal target oxyhemoglobin saturations in BPD continue to be debated. Saturation targets of 90% to 92% are well tolerated in the nursery setting and are associated with similar rates of infant growth and development over time. To promote adequate growth and help prevent pulmonary hypertension, American Thoracic Society guidelines recommend that in-home oxygen saturation levels be 95% to 99% for children no longer at risk for oxygen-induced retinopathy. These saturations should be maintained while the child is awake and asleep.[8,9]

Home oxygen is often prescribed for infants with other lung diseases and malformations, such as congenital diaphragmatic hernia.[13] These infants may experience a component of BPD as well because of exposure to high pressures and oxygen concentration while receiving mechanical ventilation.

Cyanotic Congenital Heart Disease

Children with cyanotic congenital heart disease usually do not require supplemental oxygen. An exception is the child with cyanotic congenital heart disease and pulmonary hypertension. Supplemental oxygen therapy is used as supportive therapy, to alleviate symptoms, and to promote good growth.

Pulmonary Hypertension

Pulmonary hypertension may develop secondary to persistent hypoxemia in the context of lung disease, may be idiopathic in nature, or may develop in those with long-standing congenital heart disease. In individuals with lung disease, hypoxemia leads to smooth muscle contraction in pulmonary arteries with possible endothelial remodeling. Hypoxic crises may be episodic, and the severity of hypoxemia often worsens with stressors such as illness or exercise.

Interstitial Lung Disease

The conditions that cause interstitial lung disease in childhood are heterogeneous, with a variable age of onset and prognosis, and are quite different from the conditions causing interstitial lung disease in adults. Primary childhood interstitial lung diseases are broadly classified as diffuse developmental disorders like alveolar capillary dysplasias, lung growth abnormalities like pulmonary hypoplasia, surfactant protein deficiency syndromes, and specific conditions of uncertain etiology like neuroendocrine cell hyperplasia of infancy.[14] Interstitial lung disease may also be secondary to infectious etiologies, malignancies, rheumatologic disorders, and posttransplant syndromes, including bronchiolitis obliterans.

Children with these conditions often require long-term oxygen supplementation throughout infancy, and sometimes through childhood. The goals are similar to oxygen supplementation in infants with BPD: good growth, decreasing the risk of pulmonary hypertension, and alleviating the dyspnea and increased respiratory work associated with hypoxemia.[9]

Use of Oxygen in the Setting of Obstructive Sleep Apnea

Supplemental oxygen is generally not indicated in obstructive sleep apnea, in which hypoxemia, when it occurs, is due to episodic periods of airway obstruction leading to intermittent hypoxia.

Supplemental oxygen may depress the respiratory drive, especially in those children who have hypoventilation as a component of their disease. Positive-pressure ventilation, such as continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP), is more physiologically

appropriate in these patients. However, some children may not tolerate the interface necessary for delivery of positive pressure. In those cases, it is necessary to weigh the risks of worsened hypoventilation with the benefits of normalizing oxygenation, such as augmented growth and decreased likelihood of developing pulmonary hypertension. Careful titration of optimal supplemental oxygen and monitoring for induced hypoventilation by polysomnogram is necessary.[9,14]

Discharge From Hospital With Supplemental Oxygen

Before discharge home with supplemental oxygen, the child must maintain stable oxygen levels within the targeted saturation goal. The child's family must be familiar and comfortable with the care plan and have suitable resources in place (eg, for reliable access to electrical sources). Family members should receive training in the care of a child receiving supplemental oxygen, and they must feel secure in providing this care.[7–9,15] **Table 60-1**, excerpted from the American Thoracic Society statement on care of children with chronic lung disease of infancy, describes the considerations and planning for the child discharged on home oxygen (see rows on assessment, nutrition, oxygen, emergency management, anticipatory guidance, and travel).

Table 60-1. Topics for Discharge Teaching

Topic	Teaching Component
Chronic lung disease of infancy	Disease process, sequelae, management
Assessment	Vital signs (temperature, pulse, respirations) Evaluation of color Breathing pattern Lung auscultation Fluid balance, skin turgor Neurologic status Changes in appetite, behavior Use of cardiorespiratory monitor (if needed)
Well-child care	Bathing, diapering, skin care Immunizations Development and stimulation Car, home safety
Nutrition	Feeding schedule, importance of weight gain Formula preparation Methods of feeding Techniques to maximize oral feeding Nasogastric/gastrostomy tube feedings Use of enteral feeding pumps Antireflux measures

(continued)

Table 60-1. Topics for Discharge Teaching *(continued)*

Topic	Teaching Component
Medications	Name, purpose Dosage, route, frequency Method of administration Side effects Omitting or repeating a dose Storage, safety Indications for as-needed medications
Oxygen	Purpose, flow rate Method of administration Reading the flow meter Maintenance and cleaning of equipment Weaning procedure Oximetry technique and interpretation Safety considerations
Pulmonary treatments	Purpose, frequency of treatments Methods to clear secretions, bulb syringe, suction Nebulizer technique Chest physical therapy
Infection control	Minimize exposure, day care issues Handwashing technique Care providers to receive influenza vaccine
Tracheostomy care	Suctioning technique Humidification Changing the tracheostomy tube Skin care Techniques to facilitate speech Care, cleaning of the tracheostomy tube Safety considerations, emergency management
Mechanical ventilation	Principles of operation Settings Operation, maintenance, cleaning of equipment Troubleshooting equipment Schedule for ventilation, weaning Response to alarms Safety considerations, emergency management
Emergency management	Who and when to call for symptoms Procedure for emergency assistance Cardiopulmonary resuscitation technique Telephone numbers posted near phone

Table 60-1. Topics for Discharge Teaching *(continued)*

Topic	Teaching Component
Anticipatory guidance	Emotional and social needs of family Sibling rivalry Rehospitalization Alternatives to home care
Travel	Transport bag with emergency supplies Portable suction machine Air travel with oxygen

Reprinted with permission of the American Thoracic Society. Copyright © 2003 American Thoracic Society. All rights reserved. Allen J, Zwerdling R, Ehrenkranz R, et al. Statement on the care of the child with chronic lung disease of infancy and childhood. *Am J Respir Crit Care Med*. 2003;168:356–396. The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society.

Monitoring

A pulse oximeter or cardiorespiratory monitor should be used to monitor the child on oxygen at home. Monitoring patterns should be based on the patient's needs, including during awake and/or sleeping states, as well as with feeding and activity. A pulse oximeter provides immediate heart rate and oxygen saturation data, but its use can be fraught with difficulty in the home, as movement artifacts can lead to inaccurate readings and false alarms. The American Thoracic Society recommends home monitoring for infants with BPD as well as other chronic lung diseases since these children may develop apnea or bradycardia should the flow of oxygen become disrupted and hypoxemia ensue.[8,9] Parameters for heart rate, respiratory rate, apnea delay, or saturation for the monitoring equipment should be determined based on the needs of the child, in conjunction with the pulmonary specialist. Caregivers should be proficient in the use of this equipment and should be aware that most alarms are false alarms, resulting from poor lead placement, shallow respirations, or, in the case of pulse oximetry, movement artifact.

Successful discharge planning requires a team approach. Often, this begins with a multidisciplinary meeting, including the durable medical equipment company, a social worker, the child's physician, nursing, the discharge care management team, and the family. The child's family (and the child, if developmentally appropriate) should be educated regarding use and maintenance of all equipment.

The family should be comfortable assessing the causes of equipment alarms. In addition, caregivers should be able to recognize the signs and symptoms of hypoxia and any worsening of the child's baseline pulmonary status and have a written care plan to follow for such problems. Education should be ongoing until the caregivers feel comfortable with their child's needs and can demonstrate competency in managing both the child's disease and the accompanying technology.

Special attention should be paid to precautions and safety measures. There should be no smoke exposure in the home. The electrical system should be functional, safe, and able to provide the power necessary to maintain equipment. This assessment should be performed by personnel from the medical equipment company prior to discharge.

Equipment for Oxygen Therapy

Delivery interface and oxygen source must be considered in light of patient size, disease process, and patient and family preference when selecting equipment for an individual patient, in both the inpatient and ambulatory settings.[16–18]

Box 60-1 provides a list of equipment that is typically necessary for home oxygen delivery.

Delivery Interfaces

Fraction of inspired oxygen is determined by individual patient characteristics, such as size, tidal volume, and breathing pattern (slow or fast, deep or shallow), and by characteristics of the delivery device (flow, oxygen concentration, amount of room air entrained).

Table 60-2 describes the different delivery devices, accompanying maximal flow rates, and achievable F_{IO_2}.

Low-Flow Devices

Nasal prongs or cannulae sit directly in the anterior nares. They are available in several sizes that are appropriate for infants, children, and adults. Typically, infants can tolerate flows up to 2 L/min, whereas an older child or adult can tolerate higher flows, up to 4 L/min. The prongs must be held in place in infants and young children, typically by using an adhesive to affix tubing to the cheeks. For short-term administration, tape is often sufficient, but for long-term home use, it is often irritating to infant skin. There are tapes made especially for sensitive skin and several different types of gentle adhesives that are

Box 60-1

Typical Equipment for Delivery of Supplemental Oxygen at Home

- For portable use: concentrator, small liquid portable unit, or lightweight compressed gas cylinder
- For home: concentrator, liquid oxygen reservoir, or large compressed gas tank
- Low-flow meter
- Humidification system, if needed
- Appropriately sized cannulae/mask/tubing
- Adhesive to keep cannula in place (tape, "tender grips")
- Stroller with necessary structure to transport concentrator or cylinders
- Pulse oximeter with extra probes

Table 60-2. Oxygen Delivery Devices, Maximal Flow Rates, and Maximal Fraction of Inspired Oxygen Achievable.

Device	Maximal flow rate	Maximal F_{IO_2} achievable	Flow	Entrainment of room air
Nasal cannula	1–2 L/m	Variable	Variable	Yes
Simple face mask	6–10 L/m	30%–60%	Variable	Yes
Partial rebreather mask	10–12 L/m	50%–60%	Variable	Yes
Non-rebreather mask	10–12 L/m	Up to 95%	Relatively fixed	No
Oxyhood	10–15 L/m	80%–90%	Relatively fixed	No
Oxygen tent	10–15 L/m	30%–50%	Variable	Yes
Venturi mask	Variable	Variable, predictable	Fixed	Yes

From Krishnan S. Oxygen therapy. In: Stokes DC, Dozor AJ, eds. *Pediatric Pulmonology, Asthma, and Sleep Medicine: A Quick Reference Guide.* American Academy of Pediatrics; 2018:805–811.

applied to the skin that may remain in place for several days. Parents should be cautioned to be especially careful during sleep because prongs may dislodge from the nares and infants may become entangled in long cords.

High-Flow and Reservoir Devices

There are several mask interfaces that may be used to deliver oxygen therapy, mostly in the inpatient setting but now being increasingly used as a home oxygen delivery system for patients who require additional support but are unable to tolerate CPAP or BiPAP. Standard masks have apertures on either side to allow for exhalation and room air entrainment. Venturi masks allow for oxygen to be administered at a set concentration, at high flows. The high flows create a shearing effect, entraining a specific proportion of room air; because the flow often exceeds an individual's peak inspiratory flow, the F_{IO_2} is more predictable. A non-rebreather mask administers 100% oxygen using 2 one-way valves to prevent mixing of delivered supplemental oxygen with both expired gas and entrained room air. This mask achieves the highest F_{IO_2} in a non-intubated patient.

Delivery Methods

Oxygen may be stored and delivered in several ways: compressed gas, in tanks of several sizes; liquid oxygen, contained in a large central reservoir to distribute to smaller tanks for portability; and concentrating devices (which extract oxygen from the air). Each of these systems has its own advantages and disadvantages and a patient's prescription may include more than one modality, accounting for cost, convenience, and portability.[19,20] **Table 60-3** describes various available delivery methods for home use.

Table 60-3. Delivery Methods for Home Oxygen Use

Features	Concentrator	Compressed gas	Liquid
Availability	Common	Common	Limited
Reliability	Good with regular service	Good but gauges may become inaccurate	Generally good, but connector may freeze
Cost	Low, but cost of electricity borne by patient	Moderate	High
Power: wall current	Required	Not required	Not required
Stationary weight	35–50 lb Portable 2–4 lb (Deliver continuous or pulsed oxygen)	H cylinder 200 lb, E cylinder 22 lb with cart, M6 cylinder 4.5 lb	Reservoir 120 lb, 6 lb with no conserver, portable 3.4 lb with conserver
Use time at 2 L/min^{-1}	Continuous. Variable on portable devices, based on battery life/ charging.	2.5 days for "H," 5 hours for "E ," and 12 hours for "M6" type	8.9 days, 4 hours, and 10 hours

Derived from Jacobs SS, Krishnan JA, Lederer DJ, et al. Home oxygen therapy for adults with chronic lung disease. An official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med.* 2020;202(10):e121–e141.

Monitoring and Weaning

A pulse oximeter is a useful tool for families to use to become familiar with a child's normal baseline Spo_2, heart rate, and oxygen saturation. Often, tachycardia may be the first sign of distress. Tracking the child's normal values, especially resting heart and respiratory rates, in conjunction with oxygen saturation, provides trends that may be used to begin the weaning process. In conjunction with the child's medical equipment company, downloads of pulse oximeter data over a night of sleep can provide oxygen saturation and heart rate. The quality of data is variable, however, and must be interpreted with caution. In special situations, polysomnography, in a laboratory familiar with pediatric patients, may provide a more accurate record of overnight oxygenation and a full picture of the child's respiratory status with sleep, including variation in heart and respiratory rates, end-tidal carbon dioxide levels, and differences with sleep stages.

There is significant variability in practice, monitoring, and assessment during the weaning process.[8,9,19] Oxygen needs during wakefulness are often less than during sleep. As a first step in the weaning process, a trial of weaning supplemental oxygen may be performed with the child awake in a monitored setting, such as during a prolonged visit to a physician's office. When gradually decreasing oxygen flow rates, it is practical to wean by halving because conventional home oxygen delivery devices easily allow for this (1 L/min to 0.5 L/min then 0.25 L/min, and so forth) before room air challenges.[8,9] Weaning flow rate should be done gradually over the course of weeks while

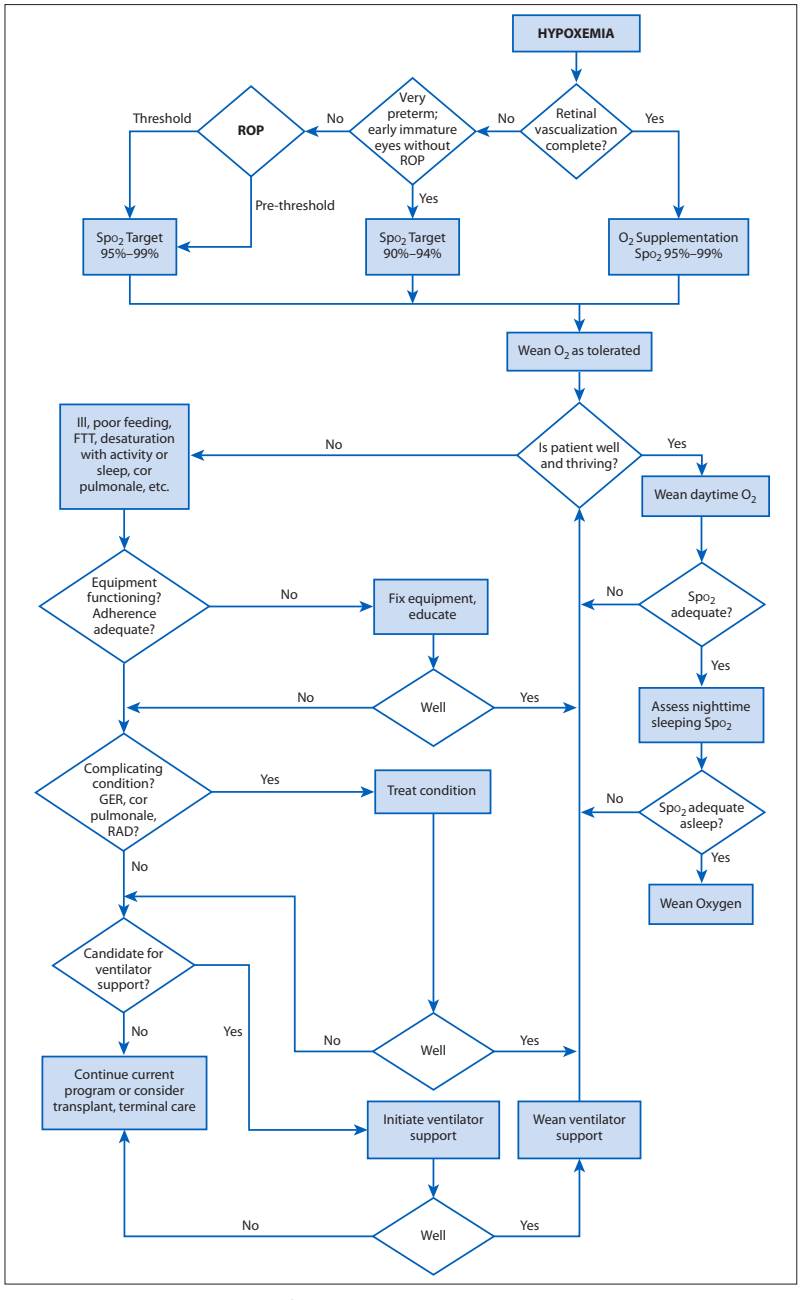


Figure 60-3. The bottom portion of this decision tree shows an approach to weaning supplemental oxygen in the child with chronic lung disease. GER, gastroesophageal reflux; RAD, reactive airway disease; Spo_2, oxygen saturation as measured by pulse oximetry.

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frequently monitoring for adverse effects. Regular (weekly to monthly) visits with the physician are needed to assess the child's progress.[8,9] Once the child has been weaned to room air while awake and has tolerated this well for a period at home by demonstrating continued good growth and acceptable oxygen saturations, then oxygen weaning during sleep can be attempted. Oxygen levels while awake do not accurately reflect oxygen levels during sleep. Nighttime weaning may require a review of downloadable readings from overnight pulse oximeter monitoring or a formal polysomnography.[8,9]

Failure to progress successfully with weaning, in conditions such as BPD, should prompt a diagnostic workup for confounding conditions, including aspiration of gastric or oral contents, gastroesophageal reflux, airway malformations, sleep-disordered breathing, pulmonary hypertension, and congenital heart disease. **Figure 60-3** suggests an approach to weaning oxygen in children with chronic lung disease.

Adverse Effects of Oxygen Therapy

Oxygen therapy should be treated as any drug therapy, with the physician and the patient/caregiver aware of risks associated with it. Some adverse effects reported include

- Retinopathy of prematurity in infants born preterm.
- Carbon dioxide narcosis. Oxygen administration only corrects hypoxemia and not ventilatory failure with elevated carbon dioxide. It is particularly important in those who have hypoventilation from neuromuscular weakness where injudicious oxygen therapy can mask impending respiratory failure or arrest.
- Possible increase of pulmonary blood flow, which can be deleterious in patients with certain cardiac pathologies.
- Oxygen therapy is associated with free radical production and subsequent damage to lung tissue, even with relatively short durations of oxygen therapy.
- Persistent oxygen therapy, especially at high inspired concentrations, can lead to pulmonary fibrosis.

High-Flow Oxygen Therapy

High-flow oxygen therapy (HFOT), delivered via a variety of devices, is a relatively new noninvasive ventilation therapy. Current literature suggests that HFOT is a relatively safe, well-tolerated, and feasible method for delivering oxygen to children, with few adverse events reported. High flow is usually

defined as flow rate 4 L/min or higher but ranging from 4 to 20 L/m, with some studies reporting flows as high as 70 L/m. High-flow oxygen therapy may reduce the need for less-tolerated and more invasive respiratory supports, such as CPAP or BiPAP and mechanical ventilation. Among children, HFOT has been most frequently used for infants and young children who were hospitalized with bronchiolitis. There are reports of HFOT use in congenital heart disease, obstructive sleep apnea, and pulmonary edema. Even though there is no conclusive evidence for the safety, effectiveness, or relative cost analysis of HFOT, use in clinical practice continues to increase.[21–23]

The mechanisms of action of HFOT are incompletely understood as the flow rates delivered are greater than the normal minute ventilation of patients.[21–23]

Possible effects of HFOT include

- Nasopharyngeal dead space washout.
- Reduction of inspiratory resistance and work of breathing.
- Providing positive end-expiratory pressure to the lungs.
- Improvement of airway conductance and pulmonary compliance by providing adequate heating and humidification, thereby reducing the effects of dry air.

Pressures Generated by HFOT

The amount of pressure generated by HFOT is variable depending on the flow rate, the diameter of the nasal cannula compared to the nares, the weight and size of the patient, and whether or not the mouth is closed. Recent studies have suggested limited pressure delivery as measured in the pharynx and esophagus, ranging from 2 to 4 cm H_2O in both children and adults.

Patient Comfort With HFOT

Studies in children outside the neonatal period and adults report HFOT to be more comfortable and associated with less dyspnea and mouth dryness compared to oxygen delivered via face mask. Improved patient tolerance may be one of the reasons for the increasing use of HFOT despite lack of conclusive evidence for clinical effectiveness.

Adverse Effects and Safety of HFOT

Most studies report no adverse events. There are anecdotal reports of pneumothorax in younger infants with flows exceeding 10 L/m, abdominal distention, and nasal bleeding. Unlike CPAP, there is no regulatory pressure-relief valve; pressure effects may be seen if there is minimal or no leak.

When to Refer

- Documented persistent hypoxemia or frequent episodes of subnormal oxyhemoglobin saturation
- Most children requiring chronic supplemental oxygen
- Intermittent desaturations during a polysomnogram
- Poor growth despite adequate caloric intake

When to Admit

- Documented persistent significant increase in supplemental oxygen requirement despite additional airway clearance methods (see Chapter 55, Airway Clearance Techniques) and other measures to treat the underlying disease process.
- Significant signs and symptoms of respiratory distress, such as accessory muscle use and tachypnea.
- For children receiving supplemental oxygen at home, the threshold for hospitalization may be individualized. In certain circumstances, particularly if the patient has only a mild illness or there is significant nursing support in the home, then pulmonary care, including increased oxygen administration and airway clearance, may escalate safely without hospitalization. In these cases, there must be close communication between the child's home care provider and pulmonary specialist or pediatrician. If there is any concern about the patient's stability, then it is best to err on the side of caution and hospitalize the patient for closer evaluation.

Resources for Physicians

- Pulse oximetry (American Thoracic Society). www.thoracic.org/patients/patient-resources/resources/pulse-oximetry.pdf
- Using the Pulse Oximeter (World Health Organization). www.who.int/patientsafety/safesurgery/pulse_oximetry/who_ps_pulse_oxymetry_tutorial2_advanced_en.pdf

Parts of this chapter are adapted from Krishnan S. Oxygen therapy. In: Stokes DC, Dozor AJ, eds. Pediatric Pulmonology, Asthma, and Sleep Medicine: A Quick Reference Guide. *American Academy of Pediatrics; 2018:805–811.*

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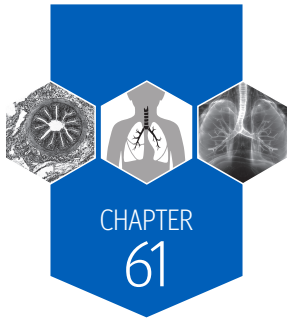
key points

- The number of children with complex respiratory care provided in the home setting is increasing, so the general pediatrician must be familiar with equipment such as supplemental oxygen and home monitoring requirements.
- Etiologies of hypoxemia include $\dot{V}/\dot{Q}$ mismatch, hypoventilation, diffusion defects, shunts, alterations in oxygen-carrying capacity, and high-altitude ascent. Ventilation-perfusion mismatch is the most common etiology.
- Administering supplemental oxygen without investigating the cause may mask hypoventilation; the alveolar gas equation helps differentiate hypoventilation from other causes of hypoxemia.
- A patient's required F_{IO_2} is determined by their size, tidal volume, underlying lung disease, and mode of supplemental oxygen delivery.
- Oxygen therapy, while generally safe, is not without potential complications and should only be prescribed when all risks and benefits are considered, with adequate supervision and monitoring.
- High-flow oxygen therapy is a relatively new approach, predominantly used in hospitals, but recently finding its place in the home of selected patients.
- Family education is vital.
- Close collaboration between the primary care provider, medical equipment company, nursing agency, pulmonary specialist, and family is essential for the success of home supplemental oxygen therapy.

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CHAPTER
61

Nicotine and Tobacco

Harold J. Farber, MD, MSPH, FAAP
Marianna Martin Sockrider, MD, DrPH, FAAP

Introduction

Tobacco dependence is one of the most important preventable causes of premature death and disability. It is a severe chronic illness with serious consequences for smokers and individuals close to them. The 2006 US Surgeon General Report found, "Massive and conclusive scientific evidence documents adverse effects of involuntary smoking on children and adults, including cancer and cardiovascular diseases in adults, and adverse respiratory effects in both children and adults."[1] Involuntary smoking is the tobacco smoke exposure of nonusers. Tobacco smoke is a complex mixture of more than 4,000 substances, including respiratory irritants, toxins, and carcinogens. The greatest contribution to the tobacco smoke exposure of children is from their parents and caregivers.[2] Addressing tobacco dependence in parents and other caregivers is important for achieving and maintaining their children's respiratory health.

There is currently an epidemic of electronic nicotine delivery systems (ENDS) use among middle and high school students, with rates of current electronic cigarette use skyrocketing from 1.5% in 2011 to 27.5% in 2019 among high school students in the United States.[3,4] With the COVID-19 pandemic and increase of age for sale of tobacco products to 21 years in 2020, current electronic cigarette use in high school students dipped to 19.6% in 2020 and 11.3% in 2021; however, with the end of the pandemic lockdown, e-cigarette use among high school students has started to rise again, with a rate of current e-cigarette use among high school students reported as 14.[1]% in 2022.[5,7] Use of 2 or more different tobacco products is common among youth (11.3% in 2018).[3] Survey data may underestimate true usage rates both because young people may use different terms for the tobacco product than those used in the surveys and because they may consider a positive response not socially acceptable. As ENDS use becomes more popular, involuntary exposure to ENDS emissions by nonusers is a growing concern. It is not uncommon for high school students to report the fruity odor of ENDS emissions in their school bathrooms.

Parents and caregivers who are tobacco dependent are an important source of involuntary smoke and ENDS emission exposure, as well as important role models for their children. It is important for pediatricians and pediatric pulmonologists to address both prevention and treatment of tobacco and nicotine dependence in their patients, parents, and caregivers. Pediatric patients should be screened for tobacco product use and exposure. Anticipatory guidance to prevent tobacco and nicotine product use initiation should start as soon as a child is able to understand the concepts. Tobacco and nicotine dependence most commonly start before the completion of adolescence.

Tobacco Products

Cigarettes

A cigarette is a tube-shaped roll of tobacco wrapped in thin paper. The most commonly used tobacco product worldwide, cigarettes are commonly taxed at a higher rate than other tobacco products. In the United States, most flavoring of cigarettes is prohibited, with the significant exception of menthol. Menthol decreases the natural harshness of tobacco smoke. Menthol cigarette smokers are less likely to stop smoking compared to non-menthol cigarette smokers.[8] Adolescents who initiate tobacco use with menthol cigarettes are more likely to go on to become regular smokers.[9]

Innovations in cigarette design have increased their addictiveness and toxicity. The tobacco industry has repeatedly misled the public about purported harm reduction of innovative tobacco products. Flue-curing of the tobacco allowed the smoke to be inhaled more deeply into the lungs. Filters reduced the large particles but allowed the small particles that would penetrate deeply into the lungs to pass. Addition of ammonia increased the amount of nicotine in the free-base form, increasing its addictiveness. The Kent Micronite filter in the 1950s, reported to have "proof of greatest health protection," contained asbestos.[10,11] "Low tar," "natural," and "organic" cigarettes are no less deadly.[12,13]

Electronic Nicotine Delivery Systems

Electronic nicotine delivery systems are referred to by many terms, including *electronic cigarettes, e-cigarettes, vape pens, vapes, vaporizers, e-hookah,* and *mechanical mods*, as well as brand names such as JUUL and Puff Bar. Some of these devices are marketed for use with substances of abuse other than nicotine (eg, "favorite herb," a euphemism for marijuana). Many popular electronic cigarette products are optimized for stealth use—to enable the user to discretely use the product in places (such as schools and airplanes) where its use is prohibited. Stealth ENDS devices have been designed to resemble a USB drive, writing pen, key fob, cell phone, candy container, hoodie zipper, and even an asthma inhaler.[14,15] ENDS are available in a wide variety of

youth-appealing flavors. Fruit-, candy-, mint-, and menthol-flavored ENDS products are popular among adolescents.[5]

ENDS produce an aerosol for inhalation from a solution that typically contains nicotine, propylene glycol, vegetable glycerin, and flavoring chemicals. Propylene glycol and vegetable glycerin adversely impact cell viability in cell culture assays in a dose-dependent manner.[16] Many commonly used flavoring agents have irritant and/or cytotoxic effects.[17] Volatile organic compounds, metallic nanoparticles (including nickel, tin, cadmium, and lead), and tobacco-related carcinogens, including nitrosamines and polycyclic aromatic hydrocarbons, have been identified in ENDS emissions. Heating the liquid to create the aerosol generates additional toxicants and carcinogens, including formaldehyde, acetaldehyde, and acrolein.[18]

The Centers for Disease Control and Prevention (CDC) reported a large series of patients with severe lung injury and death from ENDS use (referred to as *electronic cigarette, or vaping, product use-associated lung injury* [EVALI]), with 2,807 cases of severe lung injury requiring hospitalization and 68 deaths reported as of February 18, 2020. Although most of the cases reported "vaping" of tetrahydrocannabinol (THC) containing products alone or in combination with nicotine (with lung injury suspected to be from vitamin E acetate contaminating those products), 14% of the cases report exclusive use of nicotine-containing products.[19,20] There have been multiple published case reports and case series of severe injuries from ENDS, including reports of burns and facial and eye injuries from product explosions,[21–23] acute nicotine acute poisoning (from ingestion or dermal exposure),[24] eosinophilic pneumonia,[25,26] diffuse alveolar hemorrhage,[27] hypersensitivity pneumonitis,[28] organizing pneumonia,[29] lipoid pneumonia,[30,31] and severe asthma.[32] Population health studies have found ENDS use to be associated with increased risk of cough, phlegm, bronchitis, asthma, and emphysema.[33,34] ENDS use is associated with increased risk for myocardial infarction,[35,36] with biologic plausibility supported by laboratory studies that have found evidence of endothelial damage, DNA damage, and oxidative stress from electronic cigarette aerosols, as well as increased atherosclerotic plaque in mice exposed to ENDS emission.[37–39] Laboratory mice that are chronically exposed to nicotine-containing electronic cigarette aerosols develop changes in lung structure and function typical of emphysema.[40] ENDS aerosols dampen innate immune responses and impair mucociliary clearance.[41] Murine models show ENDS emission exposure to be associated with decreased defenses against bacterial and viral pathogens as well as increased risk for lung cancer.[42,43] Most smokers who use ENDS remain dual users of ENDS and combustible tobacco products. This exposes the user to both the toxins in combustible tobacco and additional toxins unique to ENDS. Evidence from population health studies suggests higher rates of incident respiratory disease, worse general health scores, and increased stroke risk in

dual users compared to those using combustible cigarettes only.[44–46] A 2019 European Respiratory Society task force report concluded that there is "no evidence that electronic cigarettes are safer than tobacco in the long term."[47]

Compared to nonusers, ENDS use among adolescent and young adult nonsmokers is associated with greater rates of progression to combustible tobacco smoking[48] and progression from intermittent to regular combustible tobacco use.[49] Among adult smokers, electronic cigarette use is associated with decreased rates of stopping combustible tobacco use.[50,51] Among former smokers, electronic cigarette use is associated with a greater rate of relapse to combustible cigarette smoking.[52] The World Health Organization (WHO) advises, "Unlike the tried and tested nicotine and non-nicotine pharmacotherapies that are known to help people quit tobacco use, WHO does not endorse electronic cigarettes as cessation aids."[53]

The JUUL product has been aggressively promoted to young people. This ENDS product is designed to look like a USB drive for a computer. A high school student was quoted about JUUL in a 2018 news article as saying, "The vapor cloud is so small and dissipates so quickly that teachers are usually none the wiser."[54] JUUL's advertising imagery in its first 6 months on the market was patently youth oriented, including aggressive use of social media and "influencers." After JUUL claimed to have stopped social media promotion, JUUL hashtags on Instagram surged.[55,56] JUUL uses a nicotine salt (nicotine benzoate) that does not have the aversive properties of free-base nicotine and very rapidly goes to the brain after inhalation.[57] The JUUL product uses a high concentration of nicotine (59 mg/mL—higher than most other ENDS products when it was introduced). Although all nicotine products are highly addictive, the pro-ducts using nicotine salts in high concentration, such as JUUL, appear to be particularly addictive.[58] Since JUUL was introduced to the market in 2015, it surged to a 76% market share by December 2018 and became very popular among youth.[59,60] Reacting to the popularity of JUUL among youth, the US Food & Drug Administration (FDA) Center for Tobacco Products took action in January 2020 to ban flavors other than tobacco and menthol in cartridge-based ENDS devices (such as JUUL); subsequent to that action, JUUL market share dropped. Other ENDS products have stepped in to fill the void. Discreet disposable ENDS devices using nicotine salts, high nicotine concentrations, youth-appealing flavors, and youth-targeted online marketing (such as Puff Bar) have become popular, overtaking JUUL in relative search volume on Google by February 2020.[61,62] The 2021 National Youth Tobacco Survey reports that Puff Bar has become the most commonly used ENDS product among middle and high school students.[6] The adverse environmental impact of disposable ENDS products is of increasing concern.

ENDS are considered "tobacco products" for regulatory purposes in the United States. Several cities and states have banned sale of flavored ENDS

products as a public health measure.[63] The FDA Center for Tobacco Products is mandated to conduct premarket reviews on tobacco products introduced to the market after February 2007 and reject products if their introduction is not appropriate for the protection of the public health.[64] The FDA has begun premarket reviews and has authorized for marketing a high-nicotine electronic cigarette product (Vuse Solo), although it has limited available flavors. Vuse is the second-most popular electronic cigarette brand among middle and high school students.[6] The American Academy of Pediatrics (AAP) has expressed significant concern that children will access these products, and the FDA's decision is a departure from policies in other countries that prohibit high-nicotine electronic cigarette products. The AAP is also concerned that the FDA is considering authorizing menthol flavors, which are popular among youth.[65]

Heat-Not-Burn Tobacco

The IQOS brand of heat-not-burn tobacco product, marketed by Philip Morris International, was authorized by the FDA for marketing in the United States in 2019.[66] This product heats a tobacco-filled stick sufficiently to generate an aerosol but not to combust. The smoke released by IQOS contains elements from pyrolysis and thermogenic degradation that are the same harmful constituents of conventional tobacco cigarette smoke.[67] There is no evidence to demonstrate that heated tobacco products are less harmful than conventional tobacco products. There is substantial concern that these products appeal to young people. Analyses of 2019 National Youth Tobacco Survey data found 3% of US high school students reported having used heated tobacco products.[68] Despite promises to the FDA not to market to young people, Philip Morris International has been found to be doing so on social media.[69,70]

Hookah

A hookah (water pipe, also called *narghile, argileh, shisha, hubble-bubble*, and *goza)* is used to smoke tobacco that is moist, shredded, mixed with sweeteners such as honey or molasses, and often fruit or candy flavored. Charcoal is used to heat the tobacco to generate the smoke, with the smoke from the tobacco and charcoal combining to produce high levels of toxins, carcinogens, and carbon monoxide.

Hookah smoking has many of the same health risks as cigarette smoking. Inhaling the smoke through water lowers the temperature of the smoke but does not reduce the concentration of toxins and carcinogens. Because of the way a hookah is used, with prolonged sessions and inhaling deeply, a typical hookah session involves inhaling much more smoke and tobacco-related toxins than a typical smoker would inhale from a cigarette.[71] Flavors, misperception of safety, and social aspects of use increase the appeal of the hookah for young people.

Cigars and Little Cigars

What differentiates a cigar from a cigarette is that a cigar is wrapped in tobacco leaf and a cigarette is wrapped in paper. In the United States, cigars are not subject to the same level of taxes and restrictions on flavorings as cigarettes. Inexpensive fruit- and candy-flavored cigars, which appeal to young people, are commonly marketed in the United States and are available in many supermarkets, gas stations, and convenience stores.

Other Tobacco Products

Chewing tobacco is loose leaves, plugs, or twists of tobacco that are placed between the cheek and gum. Snuff is finely ground tobacco. Moist snuff is placed between gum and lower lip or cheek. Dry snuff can be sniffed. Snus is similar to snuff but is usually not fermented. Youth-appealing fruit and candy flavors are common. A former US Tobacco (now a subsidiary of Altria) sales representative was quoted as saying, "Cherry Skoal is for somebody who likes the taste of candy, if you know what I'm saying."[72]

Bidis (or beedis), popular in South Asia, are tobacco (often with added flavors) wrapped in a tendu leaf and tied with a string at one end. Kreteks are cigarettes made with tobacco, cloves, and other flavors. Cloves contain eugenol, whose local anesthetic effect allows deeper inhalation of the smoke.

Tobacco and Nicotine Initiation

Risk Factors for Initiation

Marketing

Marketing that is accessible and appeals to youth increases rates of tobacco and ENDS initiation. Conversely, anti-tobacco media campaigns are effective in reducing tobacco product initiation. The 2014 US Surgeon General Report concluded, "The evidence is sufficient to conclude that advertising and promotional activities by the tobacco companies cause the onset and continuation of smoking among adolescents and young adults" and "The evidence is sufficient to conclude that mass media campaigns, comprehensive community programs, and comprehensive statewide tobacco control programs prevent initiation of tobacco use and reduce the prevalence of tobacco use among youth and adults."[12] Tobacco marketing disproportionately targets communities of color; a meta-analysis of 7 studies found 2.6 times more smoking-related billboards in predominantly Black communities compared to predominantly white communities.[73]

Exposure to point-of-sale marketing, such as in convenience stores, markets, and gas stations, is associated with increased rates of smoking initiation among youth.[74,75] Therefore, marketing of tobacco products should be prohibited in proximity to schools, playgrounds, sports facilities, and other areas accessible to children.

Cost matters when it comes to tobacco use. Low-priced products facilitate tobacco use initiation. Increasing excise taxes on tobacco products reduces both tobacco use and tobacco product initiation.[76]

Flavors

Most youth who are current tobacco smokers started smoking with a flavored product.[77] Perceptions of "fun" and having "great flavorings" and "fun tricks" increase the appeal for electronic cigarettes among youth.[78]

Social Influences

Adolescents whose family and friends smoke are more likely to initiate smoking and progress to regular smoking.[79] Similarly, report of observation of ENDS use at school is associated with increased risk for initiation of ENDS use.[80] Adolescents who perceive strong parental disapproval of smoking are less likely to become smokers. Teens who attend religious activities and those who feel it is important to contribute to their community are less likely to smoke.[81–83]

Lesbian, gay, bisexual, transgender, and questioning youth, as well as Native American youth, have significantly higher rates of smoking.[84,85] Lower levels of educational attainment and lower family income are associated with greater rates of cigarette smoking.[12,84,86] ENDS use impacts adolescents of all socioeconomic strata. Adolescents who begin using ENDS, as well as those who progress to use of combustible tobacco, often do not have the socioeconomic and psychosocial risk factors (rebelliousness, lack of parental support, willingness to smoke) as those who begin tobacco product use with combustible tobacco products.[87,88]

Emotional/Mental Health

Mental health disorders are a risk factor for smoking initiation and current smoking among adolescents.[89,90] Teens with mental health problems are more likely to become tobacco and/or ENDS users.[91,92] Psychiatric comorbidities and other substance use are common among adolescents who are dependent on tobacco.

Preventing Initiation of Nicotine and Tobacco Use

Nicotine and tobacco dependence does not occur if use is not initiated. Opportunities for intervention to prevent nicotine and tobacco use initiation are present for both individual clinicians and public policy decision makers and advocates.

Clinician Interventions

Counseling from a health care provider reduces the risk of smoking initiation.[93] Messages should be clear, personally relevant, and age appropriate. The AAP recommends that anticipatory guidance should start as early as children are developmentally ready, generally around 5 years of age.[94] Ask children and adolescents to identify their own reasons for being tobacco free and to make a

commitment to be tobacco free. The clinician can help the young person to expand on those reasons. Messages that may resonate include the effects of tobacco and nicotine product use on appearance, breath, and sports performance; how much money they would have to spend; and how the tobacco industry deceives them. Encourage the child to value good health. Correct misperceptions about how fast tobacco dependence develops and the severity of tobacco addiction. With ENDS use rapidly rising in popularity among adolescents, messages should also include a focus on ENDS. Teens may incorrectly believe that ENDS are safe or that nicotine is not highly addictive.[95] Help them develop skills to resist peer pressure to use tobacco and nicotine products. Counsel parents on signs that their child may be using ENDS (**Table 61-1**).

Table 61-1. Signs of Vaping (Electronic Nicotine Delivery Systems Use) That a Parent Should Look For

Sign	Guidance for Parents
Equipment	You may find devices that look like flash (USB) drives, e-liquid bottles, pods/cartridges (that contain the liquid used in electronic nicotine delivery systems [ENDS] devices) or product packaging.
Online purchases/ packages in the mail	Look for purchases made online and charged to your credit card, and unexpected packages that arrive in the mail.
Scent	The scent of flavors, such as bubble gum, chocolate cake, fruit, candy, mint, or menthol, might be from a vaping product.
Increased thirst/ nosebleeds/interest in stronger flavors	Some of the chemicals used in ENDS dry out the mouth and nose. This may lead to drinking more liquids, having nosebleeds, and/or a desire for stronger flavors (when the mouth is dry, flavor perception is reduced).
Vaping slang	You may see vaping slang in text messages such as "atty" for an atomizer, "VG" for vegetable glycerin found in the liquids used in ENDS device or "sauce" referring to the liquids used in ENDS devices. Getting "nicked" refers to the euphoria experienced with high doses of nicotine and feeling "nic sick" refers to heart palpitations, nausea/vomiting or light-headedness associated with the overuse of nicotine vapes.
Social media and online references	Kids often brag about their vaping exploits on social media. Look for pictures or references on their social media accounts. Take note of popular vaping terms in their online searches.
Appearance and behavior changes	Vaping nicotine may lead to anxiety, irritability, difficulty concentrating, and loss of appetite.
Physical symptoms	Physical side effects of vaping may include trouble breathing, headaches, cough, dizziness, sore throat, and/or chest pain.

Adapted from Partnership to End Addiction (2018). *Vaping: What Families Need to Know to Help Protect Children, Teens and Young Adults*. See original at: https://drugfree.org/wp-content/uploads/2018/11/What-You-Need-to-Know-and-How-to-Talk-to-Your-Kids-About-Vaping-Guide-Partnership-for-Drug-Free-Kids.pdf.

Public Policy Interventions

Pediatric health care providers also have important responsibilities to advocate for public policies to eliminate children's tobacco smoke and ENDS emission exposure and to protect youth from becoming tobacco dependent. The AAP recommends the following evidence-based public policies be implemented[96]:

- Prohibit all tobacco product advertising and promotion in forms that are accessible to children and youth.
- Ban point-of-sale tobacco product advertising and product placement that can be viewed by children, including in proximity to schools, playgrounds, sports facilities, and other areas where children congregate.
- Restrict depictions of tobacco products in movies and other media that can be viewed by youth. Tobacco control programs should change the image of tobacco by telling the truth about tobacco and ENDS.
- Increase the price of all tobacco products to reduce youth tobacco-use initiation.
- Increase the minimum age for sale of tobacco products to 21 years. Enforce regulations on age for sale of tobacco. While the age for sale of tobacco was increased to 21 years in the United States. on December 20, 2019, most other countries still have 18 years as the legal age for sale. Age-for-sale regulations are not consistently enforced.
- Prohibit use of all flavoring agents, including menthol in all tobacco and ENDS products.
- Ensure adequate funding of tobacco control programs.
- Comprehensive smoking bans should be enacted and include any tobacco product that produces an emission. Prohibit smoking in workplaces, restaurants, bars, and other public venues. Prohibit smoking in or near schools, parks, playgrounds, sports facilities, entertainment venues, and other areas where young persons congregate. Prohibit smoking in multiunit housing. Make tobacco-dependence treatment resources available to people who are dependent on tobacco products.

Tobacco and Nicotine Dependence

Development of Nicotine Dependence

Nicotine dependence most commonly starts in the pediatric years; close to 90% of adult smokers started smoking before the age of 18 years.[12] The rapidly developing adolescent brain is particularly susceptible to nicotine; nicotinic acetylcholine receptors regulate critical facets of brain maturation during

adolescence.[97] Symptoms of nicotine dependence can develop rapidly after smoking initiation and are present even among low-level and intermittent smokers. Progression from intermittent use to daily use is driven by progression in number and severity of nicotine dependence symptoms and shortening of latency to withdrawal.[98,99] Inhaled nicotine moves quickly via the arterial circulation from the lungs to the brain, where it binds to nicotinic cholinergic receptors, which release a variety of neurotransmitters, including dopamine. The dopamine is released in the mesolimbic area, the corpus striatum, and the frontal cortex. The stimulation of dopamine release is critical for the pleasurable experience and reinforcing effects of nicotine use. Neuroadaptation (tolerance) develops, leading to the craving and withdrawal symptoms associated with tobacco dependence.[100]

DiFranza et al describe severity of compulsion to smoke as wanting, craving, and needing. Wanting is a mild desire to smoke that is short-lived and easily ignored. Craving is a stronger urge to smoke that is more persistent and difficult to ignore. Needing is an intense and urgent desire to smoke that is unpleasant and unremitting.[101]

Nicotine withdrawal is not just craving or compulsion to use tobacco products. Withdrawal symptoms include anxiety, depression, irritability, frustration, anger, insomnia, anhedonia, difficulty concentrating, increased appetite, constipation, nausea, and tremors.[102] Nicotine withdrawal can lead to mood disturbances of similar intensity to those seen in psychiatric outpatients.[103]

Assessment of Nicotine Dependence

Tobacco dependence in adults can be assessed with the Fagerström Test for Nicotine Dependence. Adolescent-specific instruments include the Modified Fagerström Tolerance Questionnaire and the Hooked on Nicotine Checklist.[104–106] As non-cigarette tobacco products become increasingly popular, cigarette-based assessments of nicotine dependence become problematic. A modification to the Fagerström Test for Nicotine Dependence for electronic cigarettes has been proposed.[107]

Treatment of Tobacco and Nicotine Dependence

Treatment of tobacco and nicotine dependence involves suppression of nicotine withdrawal symptoms with medications and learning skills to manage or cope with nicotine withdrawal symptoms. The most effective methods for tobacco-dependence treatment for adults include both counseling and pharmacotherapy. Patients with more severe addiction or less ability to cope with withdrawal

symptoms (such as patients with psychiatric comorbidities) often need more intensive pharmacotherapy to better control the withdrawal symptoms.

Non-pharmacologic Approaches to Tobacco Dependence

Commonly recommended counseling approaches are described in **Box 61-1**. Counseling approaches start with helping the patient or parent to appreciate the importance of stopping tobacco use and then building confidence in their ability to stop. To build confidence in ability to stop tobacco use, help the patient identify nicotine withdrawal symptoms, develop skills to cope with nicotine withdrawal symptoms, develop strategies to anticipate and manage difficult periods (such as times or situations at risk for smoking), and organize needed social supports. Counseling approaches include counseling about the ability of pharmacotherapy to control withdrawal or reduce it to a manageable level. If the patient or parent has had prior experience in stopping smoking, build on that as a success that provided important insight and experience. Telephone "quit lines" (such as 1-800-QUIT-NOW) and online support (see smokefree.gov and quitSTART app) can help adults and teenagers with strategies, motivational messages, and support. (See **Box 61-2**.)

Box 61-1

Tobacco-Dependence Counseling Approaches

Counseling to Facilitate Smoking Cessation: 6 As

Anticipate risk of tobacco use.

Ask about tobacco use and exposure history.

Advise about the harm of active smoking and secondhand exposure.

Assess readiness to change, and severity of, nicotine dependence.

Assist in developing a tobacco-dependence treatment plan.

Arrange follow-up.

Not Ready to Stop Smoking: 5 Rs

Relevance of smoking cessation.

Risks of tobacco use.

Rewards of smoking cessation.

Roadblocks to smoking cessation.

Repetition at every office visit follow-up.

Facilitate Behavior Change: ASK NOW

Assess the health behavior.

Determine the **Stage** of change.

Keep in mind **Key** facts.

Jointly **Negotiate** an action plan.

Observe outcome in follow-up.

Work toward the next stage.

Box 61-2

Telephone and Online Tobacco-Dependence Resources

1-800-QUIT-NOW: Connects caller to their state quitline for free telephone counseling.

Smokefree.gov: Hosts the National Cancer Institute's tobacco prevention and cessation resources with support, tools, and advice for stopping smoking.

Teen.Smokefree.gov: Hosts the National Cancer Institute's tobacco prevention and cessation resources for teenagers, including the following:

- **SmokefreeTXT: A mobile text messaging program from the National Cancer Institute that provides tips, advice, and encouragement for stopping smoking**
- **quitSTART: A smartphone-based app from the National Cancer Institute made for teens that provides tailored tips, inspiration, and challenges to help smokers become smoke free.**
- **1-877-44U-QUIT: Telephone smoking cessation support from National Cancer Institute counselors. Support is available in English and Spanish.**

A Smoking Prevention Interactive Experience (https://aspire.mdanderson.org/aspirestudent): An internet-based program from MD Anderson Cancer Center that delivers an individually tailored interactive smoking prevention and cessation curriculum that can be used by individuals or in the school setting.

Smoke Out: Tobacco Pirates: A smartphone- or tablet-based game designed in consultation with the American College of Chest Physicians Tobacco Dependence Treatment Toolkit Committee to help people to learn about tobacco addiction and its treatment, and become more conscious of their tobacco use as they defeat the tobacco bosses to rule the seven seas. It is free for download from Google Play and the Apple App Store.

Partnership to End Addiction: How to Talk to Your Child About Vaping: A motivational interviewing–based guide to assist parents in counseling their adolescent child about ENDS (https://drugfree.org/article/how-to-talk-with-your-kids-about-vaping/).

The American Academy of Pediatrics has collected resources for Behavioral Tobacco and ENDS Cessation Supports for Youth and Young Adults at https://www.aap.org/en/patient-care/tobacco-control-and-prevention/youth-tobacco-cessation/behavioral-cessation-supports-for-youth/

Pharmacotherapy of Tobacco and Nicotine Dependence

The FDA-approved medications for the treatment of tobacco dependence in adults 18 years and older include the prescription medications varenicline, bupropion, nicotine nasal spray, nicotine oral inhaler, and over-the-counter medications (nicotine patch, nicotine gum, and nicotine lozenge). Varenicline is the most effective single medication for tobacco dependence treatment.[108] Combination of varenicline with nicotine replacement therapy is more effective than either alone.[109] The combination of nicotine patch plus nicotine gum has greater efficacy than either treatment alone.[110] Sustained smoking

cessation is improved by extended courses (more than 12 weeks) of pharmacotherapy, with supporting evidence best for varenicline.[111]

Varenicline, bupropion, and nicotine patch are long-acting medications. Nicotine gum, nicotine lozenge, nicotine oral inhaler, and nicotine nasal spray are shorter-acting medications. As such, they can be combined with the longer-acting medications to use "as needed" for withdrawal symptoms. They are not as rapid acting as a cigarette. Nicotine from a cigarette achieves peak levels in the brain in as little as 8 seconds and can saturate close to 90% of the nicotine receptors. The nicotine is absorbed through oral mucosae for the nicotine gum, lozenge, and oral inhaler, and thus takes about 30 minutes to reach peak levels. The nicotine nasal spray has a more rapid time to peak (about 8 minutes) but is still not as rapid as a cigarette. It is likely that the slower onset of action is what makes these products effective for treating tobacco dependence.

Which medications to choose will depend on the severity of the patient's nicotine dependence, ability or motivation to cope with withdrawal symptoms, and medication that the patient is willing to accept. Parents may not have adequate health insurance or may have limited ability to pay for medications, in which case over-the-counter nicotine replacement therapy (nicotine patch, nicotine gum, and/or nicotine lozenge) can be recommended. If an individual is ready to reduce but not stop tobacco product use within the next month, use of nicotine patch and/or varenicline can help the person reduce smoking and get ready to stop.[112,113] Electronic cigarettes should *never* be recommended because of substantial safety and efficacy concerns.

Nausea is common with varenicline and usually improves or resolves with continued use. Bupropion can lower seizure threshold; having a seizure disorder is considered a relative contraindication. Vivid dreams or nightmares are common with use of the nicotine patch and can be managed by removing the patch before going to sleep. Swallowed nicotine from the gum or lozenge can cause nausea or hiccups; this can be managed by chewing the gum a little to release the bitter-tasting nicotine, then parking it between the cheek and gums and chewing a little again when the taste goes away. The nicotine lozenge can be simply parked between the cheek and gums rather than being sucked on like a candy; this allows the nicotine to be absorbed through the oral mucosae and not swallowed. Varenicline, bupropion, and nicotine patch do not increase risk for suicide, suicidal ideation, or other psychiatric comorbidities over placebo.[108] Inadequately controlled nicotine withdrawal can lead to psychiatric symptoms.[103]

On follow-up, the health care provider should assess both tobacco product use and control of nicotine-withdrawal symptoms. If the patient is not using tobacco products *and* withdrawal is well controlled, medications for tobacco-

dependence treatment can be stepped down. If withdrawal is not well controlled or the patient is using tobacco products, consider whether medications need to be stepped up. Use of pharmacotherapy may need to extend beyond the time frames recommended on package inserts.

Tobacco-Dependence Treatment in Adolescents

Tobacco-dependence treatment in adolescents can be challenging. Counseling strategies include reaching an agreement on the importance of stopping tobacco and nicotine use and building confidence in the adolescent's ability to stop. For the adolescent to invest in making a behavior change, belief in the importance of the change and having confidence in being able to accomplish it are key building blocks. Helping the adolescent explore the pros and cons can help them consider change by highlighting discrepancies between their values and their current behavior. To build confidence, review lessons learned from previous attempts to stop smoking, anticipate challenges, and plan coping strategies. Teens may need assistance in developing refusal skills and managing peer pressure.[114] Provide concrete and readily accessible support and resources such as stop smoking support offered by telephone, text message, smartphone app, or the internet (see **Box 61-2**) and/or referral to local community or school-based resources (if available). Multi-session, school-based group interventions, including Project EX and Not On Tobacco, help adolescents to stop smoking. Cessation rates in these programs are greater for those with mild nicotine dependence compared with those with more severe nicotine dependence.[115–117]

In contrast to research in adults with tobacco dependence, the literature on pharmacotherapy of tobacco dependence in adolescents is limited. Achieving adherence to therapy is challenging, and relapse after cessation of medication is common. Poorly controlled nicotine withdrawal has been associated with lapses of smoking in adolescents on tobacco-dependence treatment.[118] A clinical trial among adolescents with moderate to severe tobacco dependence who were motivated to stop smoking found that use of nicotine patches combined with cognitive behavioral therapy improved smoking cessation rates at 3 months after the 12-week intervention concluded (20.6% vs 5%, $P = .06$).[119] A study of bupropion 150 mg twice a day given for 6 weeks demonstrated benefit only during the active treatment period (29% vs 16% abstinence at 6 weeks, $P = .02$); there was not a sustained benefit compared to the control group after bupropion was discontinued.[120] A 12-week clinical trial of varenicline vs placebo in adolescents aged 14 to 21 years with tobacco dependence was limited by large loss to follow-up (55% of varenicline group, 39% of placebo group lost to follow-up). The study found increased cotinine-confirmed tobacco abstinence with varenicline during the trial; however, there was no

between-group difference by the end of treatment. Importantly, there were no medication-related serious adverse events in either the varenicline or placebo group; the rates of non-severe adverse events were not significantly different.[121]

Acknowledging the low quality of the evidence in adolescents, the AAP recommends that tobacco-dependence pharmacotherapy can be considered as an option for adolescents with moderate to severe tobacco dependence who want to stop tobacco products.[94] There is no biological or cognitive rationale to have age 18 years as the minimum for offering pharmacotherapy of tobacco dependence. Treatment should be appropriate to the adolescent's level of tobacco dependence, readiness to change, and treatments they are ready to accept.[94] Counseling should address the behavioral, social, and motivational factors that contribute to continued tobacco product use in adolescents. Keep in mind that other substance use may complicate tobacco-dependence treatment.

For teens who are not ready to stop tobacco use, focus on the "5 Rs": **R**elevance, **R**isks, **R**ewards, **R**oadblocks, **R**epetition (see **Box 61-1**).[110] Give messages that are age appropriate and personally relevant.

Impact of Exposure on the Non-user

Involuntary Tobacco Smoke and ENDS Emission Exposure

The harms of tobacco smoke and ENDS are not restricted to the user. Involuntary exposure to tobacco smoke and ENDS emissions includes secondhand exposure (from breathing in the smoke and aerosols generated by the device and/or exhaled by the user) and thirdhand exposure (from the toxins and carcinogens absorbed into walls, furniture, carpeting, etc, and exposing the nonuser by either dermal absorption, ingestion, or off-gassing and inhalation). Although research on the harms of involuntary exposure to ENDS emissions is limited, we do know that exposure to ENDS product emissions leads to increased levels of nicotine, tobacco-related carcinogens, and exposure to respiratory irritant chemicals in the nonuser.[122,123]

Children living in rented homes are more than twice as likely to be exposed to tobacco smoke compared to children who live in homes that are owned.[124] Smoking in multiunit housing is an important source of involuntary tobacco smoke exposure among nonsmokers.[125] In July 2018, the US Department of Housing and Urban Development (HUD) implemented a rule prohibiting the use of tobacco in, and within 25 feet of, HUD housing. To ensure equity, as part of implementation of smoke-free multiunit housing policies, it is important to have tobacco dependence treatment resources available to the residents.

The National Health and Nutrition Examination Survey (NHANES) data show that non-Hispanic Black children are 1.85 times more likely to have evidence of tobacco smoke exposure than non-Hispanic white children.[124] A survey of children in a Medicaid managed care program serving a diverse low-income population in southeast Texas found that children who self-identified as white were more likely to have a smoker in the home compared to other ethnic groups.[126] These findings, which may appear contradictory on the surface, suggest that the National Health and Nutrition Examination Survey finding of increased tobacco smoke exposure in children of color reflects economic disparities rather than a racial/ethnic characteristic.

Tobacco Use by Parents

Because a parent's tobacco product use impacts their child's health, it is appropriate for the child's health care provider to assess, counsel, and either recommend or prescribe tobacco dependence treatment for the parents. Most parents who are tobacco dependent would accept treatment or referral from their child's health care provider.[127] With appropriate assessment, counseling, and documentation, it is appropriate for pediatric health care providers to prescribe medication for parents to treat their tobacco dependence.[94]

Prenatal Effects of Maternal Active and Involuntary Nicotine and Tobacco Exposure

Tobacco and nicotine harms children from conception forward. Nicotine, carbon monoxide, and other tobacco-related toxins readily cross the placenta. Given the developmental processes in progress, fetuses as well as young children are at greater risk than adults. Maternal smoking as well as involuntary tobacco smoke exposure increases risk for premature birth and decreases birth weight, with dose-response effects demonstrated. Maternal smoking, oral tobacco use, and tobacco smoke exposure increase risk of stillbirth. Maternal smoking is associated with increased risk of placental complications, including placental abruption and placenta previa.[128–132]

Maternal smoking increases a child's risk of wheezing illnesses, including bronchiolitis and asthma. In utero exposure impacts lung development, with laboratory animal models demonstrating causation by impact of nicotine on alpha-7 nicotinic receptors on lung development.[133]

Maternal smoking is associated with increased risk of orofacial clefts and has possible associations with congenital heart defects, particularly septal and right-sided obstructive defects.[1] Association between in utero smoking and decreased fetal head circumference as well as later development of

attention deficit disorder and decreased academic performance have been demonstrated.[134–136]

Sudden Infant Death Syndrome

Risk of sudden infant death syndrome is increased by both active and second-hand maternal smoking during pregnancy, with reduced arousal responses and reduced recovery from hypoxic challenge as likely mechanisms to account for this risk.[137,138] Smoking during pregnancy causes an estimated 1,015 infant deaths per year in the United States.[12]

Respiratory Infections

Infants and children with parents who smoke have an increased risk of lower respiratory tract illness, including bronchiolitis, bronchitis, and pneumonia.[1]

Respiratory Symptoms

Respiratory symptoms, including cough, phlegm, and wheeze, are more common in the children of smokers. The greatest impact is at younger ages and if both parents smoke.[1]

Asthma and Other Lung Diseases

Tobacco smoke exposure is associated with increased asthma prevalence and severity, worse asthma control, increased bronchial hyperresponsiveness, increased risk of requiring emergency department care, and decreased corticosteroid responsiveness.[139,140] Tobacco smoke exposure accelerates decline in lung function in children with chronic pulmonary problems such as cystic fibrosis.[141]

Otitis Media

Tobacco smoke exposure increases risk of otitis media[1] and decreases resolution of chronic otitis media with effusion.[142]

Dental Caries

Parental smoking history and elevated cotinine levels (a biomarker of tobacco smoke exposure) are associated with increased rates of caries in deciduous teeth.[143,144]

Cancer Risk

Tobacco smoke exposure increases risk of childhood cancers. House dust samples in homes of smokers can contain carcinogens at levels high enough to increase the risk of cancer.[145] Toddlers commonly explore by placing objects in the mouth, increasing their level of exposure. Tobacco-specific carcinogens have been detected in the blood of children who have a tobacco smoker in the home.[146] Increased cancer risk in children whose parents

Box 61-3

Screening for Secondhand Smoke and Electronic Nicotine Delivery Systems Emission Exposure in Pediatric Practice

Questions to Ask

1. **Does anyone who lives with (name of child) smoke or vape? If yes: Does (person) smoke or vape inside of the home or car?**
2. **Does anyone who provides care for (name of child) smoke or vape?**
3. **Does (name of child) visit places where people smoke or vape?**
4. **Does anyone in the home use other tobacco products such as hookah, IQOS (heat not burn), or dip (chewing tobacco)?**

smoke has been demonstrated, with findings documenting increased risk for lymphoma, acute lymphocytic leukemia, and brain cancer.[147,148]

Cardiovascular Risk

Tobacco smoke exposure causes coronary heart disease and strokes in adults.[1,12] Tobacco smoke exposure has been shown to lead to preclinical findings of atherosclerosis in adolescents.[149]

Reducing Tobacco Smoke and ENDS Emission Exposure

Pediatric clinicians should routinely ask about a child's tobacco smoke and ENDS emission exposure (**Box 61-3**). Ask if a smoker or ENDS user lives in the child's home, cares for the child, or is visited on a regular basis.

The best way to eliminate a child's tobacco smoke and ENDS emission exposure is for those individuals close to the child to be nonsmokers and non–ENDS users. If the source of tobacco smoke or ENDS emission exposure cannot be eliminated, advise the parents to keep the home and car strictly smoke and ENDS free. Smoking should be kept well away from doors, windows, and any area where children are playing. Use of a high-efficiency particulate air (HEPA) filter in the home may provide some benefit if sources of smoke exposure cannot be eliminated.[150] Advise the family to stay away from places where people smoke or use ENDS, if possible. Advocate for smoke-free and ENDS-free communities.

key points

- Tobacco dependence is one of the most important preventable causes of premature death and disability.
- Tobacco dependence is a pediatric disease. The vast majority of tobacco and nicotine dependence starts in adolescence.
- Electronic nicotine delivery systems (electronic cigarettes, others) have substantial adverse health effects and are addicting a new generation to nicotine and tobacco.
- Pediatric health care providers should take an active role in addressing tobacco smoke exposure and smoking prevention through clinical practice and advocacy efforts.
- The incidence of tobacco and nicotine dependence among youth is increased by tobacco industry marketing efforts; availability of flavored products, including mint and menthol; parent and peer influences and role models; and the presence of psychiatric comorbidities.
- Ask about tobacco and nicotine product use and exposure. Anticipatory guidance to prevent tobacco and nicotine product use initiation should start as soon as a child is able to understand the concepts.
- Pediatric health care providers should assist both patients and parents in stopping tobacco product use, including prescribing or recommending pharmacotherapy for tobacco dependence.
- Pediatric health care providers need to be advocates for legislation and community action to reduce the incidence of tobacco dependence and reduce the risk for involuntary tobacco smoke exposure, both locally and worldwide.

Related American Academy of Pediatrics Policy

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Other Resources

American Academy of Pediatrics Julius B. Richmond Center of Excellence. https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Richmond-Center/Pages/default.aspx. The AAP Richmond Center is dedicated to the elimination of children's exposure to tobacco and secondhand smoke. The AAP Richmond Center provides the education, training, and tools needed to effectively intervene to protect children from the harmful effects of tobacco and secondhand smoke.

American College of Chest Physicians Tobacco Dependence Treatment Toolkit. https://foundation.chestnet.org/wp-content/uploads/2021/06/Tobacco_Dependence_Treatment_Toolkit_CHEST_Foundation.pdf. The toolkit provides practical strategies for helping patients stop tobacco product use, including use of pharmacotherapy, to suppress the withdrawal and overcome the reinforcing effects of nicotine, as well as strategies for coping with the nicotine withdrawal symptoms.

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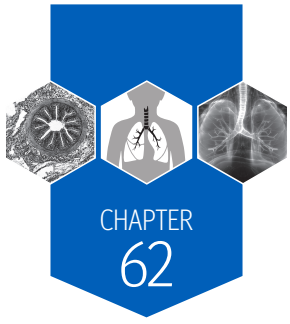
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Tracheostomy

Amy S. Whigham, MD, MS-HPEd

Introduction

As the incidence of long-term pediatric tracheostomy has risen, general pediatricians increasingly care for children with tracheostomies in the outpatient setting. Pediatric patients who require tracheostomy are a diverse group of patients with complex needs. Optimal care for the child with a long-term tracheostomy requires a collaborative medical home, with several interdisciplinary team members. In addition to the primary care physician, the team includes an otolaryngologist or surgeon to place the tracheostomy, coordinate equipment and supplies, and provide ongoing tracheostomy care; a pulmonologist to monitor the patient's respiratory status; a speech therapist to assist with speech and/or swallowing; home nursing care; often, a complex care physician; and family members well trained in tracheostomy care. The general pediatrician should understand indications for tracheostomy placement, changes in normal physiology following tracheostomy, the patient's respiratory equipment, home care procedures, common complications of tracheostomy, and indications for decannulation.

Indications for Tracheostomy

The most common indications for tracheostomy have shifted substantially since the 1970s.[1] Widespread vaccination against *Haemophilus influenzae* and *Corynebacterium diphtheriae* as well as advances in endotracheal intubation have markedly decreased the need for tracheostomy for acute inflammatory airway compromise. In addition, medical improvements have led to increased survival of preterm neonates and those with complex congenital cardiopulmonary anomalies. Consequently, the general need for pediatric tracheostomy has shifted primarily to those patients with prolonged mechanical ventilation and anatomic airway abnormalities.[1-4] Of pediatric tracheostomies, 40% to 70% are now performed on children younger than 1 year,[5-7] and more than half of children may have their tracheostomy in place for more than 24 months.[2] Indications for tracheostomy may be organized into 2 main categories delineated in **Box 62-1.**

Box 62-1

Indications for Tracheostomy

Prolonged Ventilatory Support

- Chronic respiratory failure
- Bronchopulmonary dysplasia
- Congenital heart disease
- Pulmonary hypoplasia
- Neuromuscular diseases or impairment
- Central respiratory dysfunction

Upper Airway Obstruction

- Foreign body
- Craniofacial disorders, such as macroglossia/micrognathia
- Laryngeal or pharyngeal cysts/neoplasms
- Epiglottitis
- Bilateral true vocal cord paralysis
- Laryngeal, subglottic, or tracheal stenosis or agenesis
- Tracheobronchomalacia
- Facial or laryngotracheal trauma
- Laryngeal injury after smoke inhalation or caustic ingestion

In several recent series, the most common tracheostomy indication was prolonged mechanical ventilation due to an underlying chronic medical condition.[2] Tracheostomy is often indicated for more comfortable long-term ventilation or prolonged weaning from respiratory support. The recommended timing of tracheostomy for those children who require prolonged mechanical ventilation may be age and patient dependent. Preterm neonates may tolerate intubation with appropriately sized, uncuffed endotracheal tubes for several weeks with minimal inflammation and/or stenosis. However, because the laryngeal cartilage is firmer in older infants and children, intubation for only a few weeks in this patient population may result in more significant laryngeal inflammation and scarring. Thus, it is critical to ensure appropriate endotracheal tube sizing and cuff leaks in infants and children. Additionally, tracheostomy may be necessary for children with congenital or acquired anatomical abnormalities leading to critical upper airway obstruction that is not amenable to correction, such as micrognathia or subglottic stenosis. Finally, children with neuromuscular conditions leading to weak cough, aspiration, and difficulty clearing secretions may benefit from tracheostomy for improved control of secretions and pulmonary hygiene.

CASE REPORT 62-1

A 12-week-old former 26-week preterm infant has been intubated and hospitalized in the neonatal intensive care unit since birth. Extubation has failed 3 times, with early development of post-extubation stridor, retractions, and, ultimately, respiratory distress. The neonatal intensive care team consulted pediatric otolaryngology to evaluate her upper airway. She underwent microdirect laryngoscopy and bronchoscopy and was found to have anterior laryngeal stenosis extending into the subglottis due to granulation tissue and scarring (**Figures 62-1** and **62-2**). This was treated serially 3 times over several weeks with endoscopic laryngeal steroid injection, incision, and balloon dilation. After failure to provide an adequate laryngeal opening and an additional failed attempt at extubation, the infant ultimately underwent tracheostomy.



Figure 62-1. Normal pediatric larynx with patent glottis.

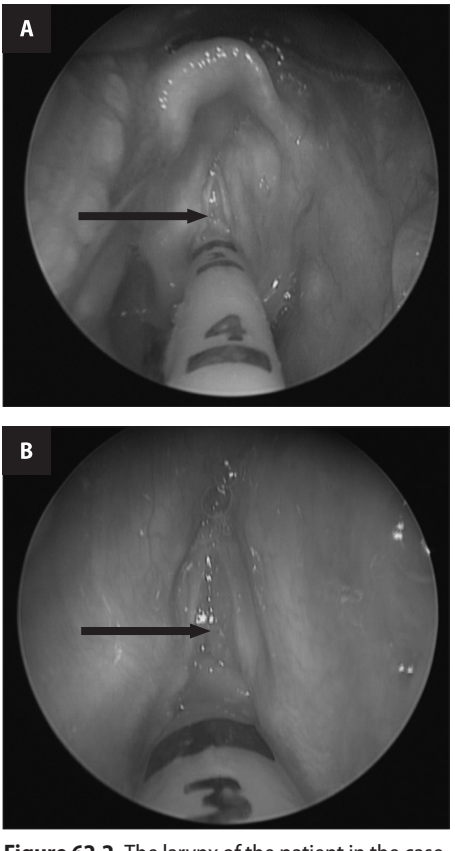


Figure 62-2. The larynx of the patient in the case report: Anterior glottic stenosis (arrow) after prolonged intubation.

Surgical Technique

Pediatric tracheostomy is usually performed under general anesthesia in the operating room. Preoperative airway evaluation, including direct microlaryngoscopy and bronchoscopy, may be beneficial to explore potentially treatable pathology. Prior to tracheal incision, non-absorbable retention sutures are placed through the tracheal cartilage rings on each side of midline. These sutures provide traction on the trachea in the event of accidental decannulation during the initial healing phase. For tracheal incision, the preferred technique is a midline vertical tracheal incision (**Figure 62-3**).[8,9] With any technique, there is a risk of bleeding, pneumothorax, pneumomediastinum, subcutaneous emphysema, acute loss of airway, false passage, granuloma, and tracheal stenosis. Early complication rates range from 7% to 11%.[10]

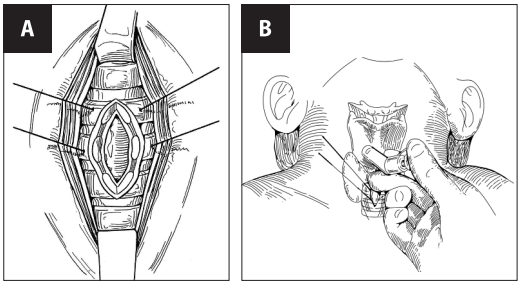


Figure 62-3. Standard pediatric tracheostomy with a vertical tracheal incision and retention sutures on either side of the tracheostomy opening.

From Rutter MJ, Hart CK. Trachea. In: Potsic WP, Cotton RT, Handler SD, Zur KB. *Surgical Pediatric Otolaryngology.* 2nd ed. Thieme;2016:360–370.

Tube Selection and Considerations

Tracheostomy tubes are available in neonatal, pediatric, and adult sizes, which vary by length and curvature. Cuffed and uncuffed pediatric tracheostomy tubes are shown in **Figure 62-4.** Tubes are made out of silicone, polyvinyl chloride, or, uncommonly, metal. Most plastic materials cause nominal local tissue reaction. Many recently manufactured nonmetal tracheostomy tubes are compatible with magnetic resonance imaging, but this should be confirmed for each specific tracheostomy tube. Ideally, tubes are made of a flexible material that conforms to the tissues of the trachea and neck, without causing discomfort, pressure, or injury. Choice of tube type and size depends on the initial indication for tracheostomy, keeping in mind the patient's pulmonary function, tracheal size and shape, upper airway resistance, and allowance for air leak to achieve vocalization. The diameter of the tracheostomy tube can often be estimated by determining the appropriate-sized endotracheal tube for the child. The tube size should be large enough to allow appropriate gas exchange without causing pressure injury on the tracheal mucosa. In general, uncuffed tubes are preferred for children to allow for vocalization and prevent tracheal injury. However, cuffed tubes are often necessary for patients who require mechanical ventilation with high pressures, or who are at risk for aspiration.

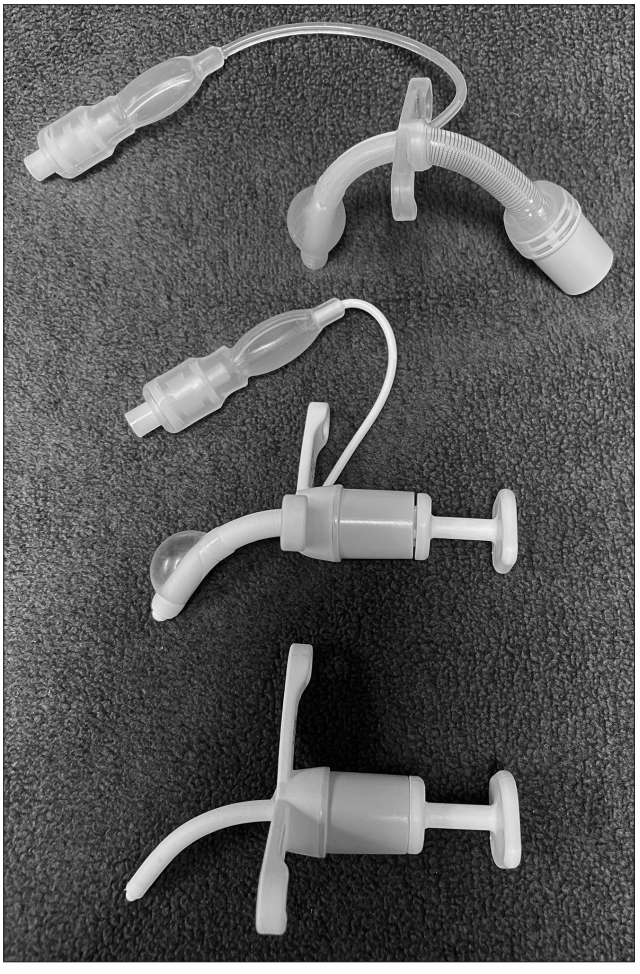


Figure 62-4. Cuffed tracheostomy tube (top), uncuffed tracheostomy tube (bottom).

Cuff pressures are kept below 20 cm H_2O to prevent necrosis and injury to airway epithelium. Customized tubes can be constructed if standard tubes do not correspond well to the child's anatomy, such as in cases of cervicofacial abnormalities, tracheal stenosis, or tracheomalacia.[2,11]

Altered Physiology After Tracheostomy

Once tracheostomy is performed, there are multiple consequences on normal tracheal function and physiology. Airway clearance may become impaired because scar tissue can develop in the anterior trachea at the tracheostomy site, and normal ciliary function will be disrupted in that location, leading to mucus stasis. In addition, cough clearance is less effective because the compressive phase of glottic closure before forced expiration is bypassed with the tracheostomy in place.[12] As a result, the patient is at increased risk for recurrent tracheitis and pneumonia. A normal sense of smell requires airflow

through the nose, and, if upper airway obstruction is significant, airflow will be directed through the tracheostomy tube, thereby decreasing subjective sense of smell. Similarly, speech requires adequate airflow past the vocal cords, which depends on the degree of upper airway obstruction and tolerance of a speaking valve or tracheostomy tube capping. To achieve speech without augmentative communication devices, the tracheostomy tube must not exceed two-thirds of the tracheal lumen.[11] Development of normal speech requires early speaking valve assessment and speech therapy. The humidification of inspired air is another important function of the nasopharynx that is bypassed with a tracheostomy. The lack of humidity can lead to desiccation of secretions, damage to mucus glands, mucus plugging, and impaired ciliary function unless external humidification is provided.[13] This, in turn, can cause increased infection risk and reduction of lung function. Finally, swallowing function can be affected by the presence of the tracheostomy tube because it limits superior excursion of the larynx with deglutition, may inhibit the normal laryngeal reflex that prevents aspiration, and may contribute to mass effect on the esophagus posteriorly.[2,14] Dysphagia and oral aversion are extremely common in neonates and infants with tracheostomy.[15]

Tracheostomy Care at Home

Caregiver education is an important step in successful transition from hospital to home care and ideally begins prior to tracheostomy placement. The benefits and risks of tracheostomy, as well as its associated care, should be discussed in detail with the caregivers before the surgery. As soon as the tracheostomy is placed, bedside hands-on teaching is initiated. Training initially begins with the relevant anatomic structures and the functions of the upper airway in warming, humidifying, and clearing secretions.[2] Education should take place in the hospital under the supervision of the nurses and physicians. Instruction should include decision-making as well as technical skills. It should encompass stoma care and evaluation, tracheostomy tube and tie changes, suctioning techniques, cardiopulmonary resuscitation (CPR) training, recognizing signs and symptoms of respiratory distress, and troubleshooting any problems. This teaching should be individualized to the child and family, taking into account the cultural and language needs. Audiovisual aids and mannequins may be used in addition to written materials. Many institutions require training of at least 2 adult caregivers who will provide consistent care to the child. They must demonstrate proficiency in both skills and decision-making prior to discharge. Some institutions require that caregivers provide all care for their child, using only home equipment, for 24 hours prior to discharge. All children with tracheostomy should receive skilled home nursing care during a transitional adjustment time after discharge. Unfortunately, a national shortage of

home nursing care availability may create significant challenges in receiving this care. The following resources may be helpful for caregivers.

- Aaron's Tracheostomy Page (independent nonprofit). www.tracheostomy.com
- Use of a Tracheostomy With a Child (American Thoracic Society). www.thoracic.org/patients/patient-resources/resources/tracheostomy-in-child.pdf
- Pediatric Tracheostomy App (Review) (iMedicalApps). www.imedicalapps.com/2013/02/pediatric-tracheostomy-app-kids-parents-trach

Tracheostomy Supplies for Home

Every child with a tracheostomy should have adequate supplies at home (**Box 62-2**). These include spare tracheostomy tubes (including one size smaller for emergencies), cleaning supplies, tracheostomy ties, suctioning equipment and catheters, humidification equipment, and monitoring equipment. To obtain the appropriate type and sufficient number of home supplies, advocacy to the insurance company by the provider is often required. Before a child is discharged, it is essential to make sure all the supplies are available from the durable medical equipment company. All home care equipment and supplies should be tested and used in the hospital prior to discharge.

Box 62-2

Tracheostomy Home Care Supplies

- Extra tracheostomy tube, same size
- Extra tracheostomy tube, ½ size smaller
- Suction machine and tubing
- Suction catheters
- Resuscitation bag with tracheostomy adapter and face mask
- Scissors
- External humidification (nebulizer, compressor or heat and moisture exchanger)
- Tracheostomy ties
- Sterile water
- Normal saline for suctioning
- Cotton swabs and gauze
- Oxygen with tubing (if ordered)
- Breathing monitor, such as pulse oximeter (if ordered)

Changing the Tube

Tracheostomy tubes should be changed on a regular basis to prevent infection, decrease granuloma formation, and reduce the risk of tube occlusion by thick or dried secretions.[2,11] The frequency of tube changes varies by the child's age, amount of secretions, and type of tube. Recommended tube-changing schedules may vary from daily to monthly; in many cases, weekly changes

are sufficient. Caregivers should comprehend that more frequent tube changes may be required when the child is sick or has increased secretions.

Cleaning the Tube

Most tracheostomy tubes may be cleaned and reused, as detailed in the manufacturer's instructions. Because tracheostomy tubes may develop cracks or become stiff over time, all tubes should be inspected for damage prior to insertion. Used tracheostomy tubes are generally cleaned using a mild liquid detergent and water. After rinsing thoroughly, the tube should be allowed to air-dry completely and then stored in a plastic bag.

Suction and Irrigation

Suctioning is a vital component in the management of a child with a chronic tracheostomy because occlusion of the tube by secretions or mucus plugs can be life-threatening. If possible, the child should be encouraged to cough and clear accumulated mucus. When suctioning is performed, the catheter should be inserted just past the end of the tracheostomy tube.[2] Attention to clean technique is important.[16] After each aspiration, the catheter should be flushed with saline solution until secretions are cleared from the lumen. The catheter should then be wiped with alcohol, allowed to air-dry, and stored in a clean, dry area.

Changing the Ties

Tracheostomy ties should be replaced during tracheostomy tube changes or when wet or soiled. Soft Velcro material helps to minimize irritation of the skin. The ties should be tight enough to minimize movement of the tube but still allow a finger to be inserted underneath the tie. If tracheostomy ties are too tight, skin breakdown can occur.

Skin Care

Usually, there is minimal skin care in pediatric patients with tracheostomy.[2] However, irritation of the stoma, area under the tube or flanges, and area under the ties may develop. These sites may be cleaned with cotton swabs and hydrogen peroxide. Occasionally, antibiotic ointment, antifungal powder, or specialized dressings may be necessary. If granulation tissue develops, it may be treated with topical steroid drops or silver nitrate.

Humidification

Ensuring adequate humidification is important as the tracheostomy bypasses the upper airway and the inspired air may have significantly lower humidity than normal. External humidification can be delivered with a humidifier, nebulizer, or heat and moisture exchanger (aka artificial nose). The latter is a passive humidification device that collects moisture from the patient's exhaled

gas and delivers it during inspiration; it may be particularly useful when the child is mobile.[2,11]

Speech

Special consideration and counseling regarding communication and language development should begin prior to tracheostomy placement. Some patients may be able to vocalize around their tracheostomy tube without an additional device in place. However, speech can be facilitated with the use of a speaking valve in suitable candidates. To use the speaking valve, the patient must be awake, interactive, and medically stable. The child should have a cuffless tube or be able to tolerate deflation of the tracheostomy tube cuff, and must not have excessive thick secretions or high tracheal pressures. Initial trials with a speaking device are performed in the hospital or clinic setting with close monitoring for discomfort or desaturations. If tolerated, the clinician may provide instruction on increasing speaking valve trials to be continued at home with monitoring. Other children may benefit from use of augmentative and alternative communication devices. A speech-language pathologist plays an integral role in speech development and should be consulted as soon as possible to assist with the care of every child with a tracheostomy.[11,17]

Monitoring

A well-trained, attentive, and properly equipped caregiver should be able to provide excellent monitoring. For young children or those unable to provide self-care of the tracheostomy, an awake caregiver should be available for monitoring for airway obstruction, which means many children require 8 to 12 hours of overnight nursing. Pulse oximeters are frequently used and are considered the best airway monitoring devices.[2] Home apnea monitors are of limited utility because they do not diagnose airway obstruction. For high-risk or medically complex patients with a tracheostomy (ie, those patients who are tracheostomy dependent secondary to a critically narrow airway), 24-hour nursing may be necessary. Provider advocacy is often necessary to obtain appropriate nursing coverage.

Routine Evaluation

Regular follow-up with a primary care physician, otolaryngologist, pulmonologist, and potentially complex care physician is indicated for children with tracheostomy. During the follow-up visit, the child should be assessed for related complications and the ongoing need for the tracheostomy. Routine evaluation with flexible tracheoscopy via the indwelling tracheostomy tube is usually performed every 6 to 12 months and can easily be done in clinic. Full upper airway evaluation, including direct laryngoscopy and bronchoscopy, is often performed every 12 to 18 months for surveillance and must be completed under general anesthesia. The purpose of this evaluation is to assess for

underlying airway pathology, detect and treat complications, assess tube size and position, and determine the readiness for decannulation. The tube length and width may need to be changed as the child grows or ventilatory requirements change. Decannulation should be considered if the original condition or need for the tracheostomy is no longer present and the patient is able to maintain a safe and adequate airway.

Complications

Between 10% and 51% of children will develop late complications following tracheostomy,[10] and each child should be regularly evaluated to minimize morbidity. Complications are more common in younger children and those with long-term tracheostomies.[11] Tracheal injury and lesions, such as granulomas, fistulas, and erosions, can develop as a result of rubbing of the tracheostomy tube or suction catheter against the tracheal wall. The suprastomal region is particularly vulnerable to collapse, malacia, and granuloma formation. Routine direct laryngoscopy and bronchoscopy can identify granulomas, which can then be excised.[2] Infection, particularly tracheitis, can develop as a result of direct communication with the external environment and inhibition of the normal defense mechanisms of mucociliary transport, cough, and upper airway filtration. Most patients with tracheostomies become colonized with bacteria such as *Pseudomonas aeruginosa*. Erythema and drainage at the stoma site are usually managed with more frequent tube changes, dressings, and topical antibiotics. Clinical signs of tracheitis or pneumonia, including increased cough and change in quality or color of secretions, accompanied by leukocytes and organisms identified by Gram stain, indicate acute infection. Cultures aspirated from the tracheostomy tube should guide antibiotic therapy.[18] Catastrophic bleeding as a result of erosion of the tracheostomy tube into a major vessel is rare, but any recurrent or significant bleeding should be promptly evaluated by the pulmonologist or otolaryngologist.[11] Lastly, obstruction or displacement of the tube can lead to life-threatening airway obstruction and even death; therefore, the family and caregivers should be comfortable with suctioning, replacing the tube, providing positive-pressure resuscitation through the tube or upper airway with a mask, and performing CPR should such an event take place.[19]

Decannulation

Decannulation should only be performed once the initial indication for tracheostomy placement has resolved and the patient has demonstrated the ability to maintain a patent airway and adequate respiratory physiology independent of the tracheostomy tube and mechanical ventilation for a minimum of several weeks. Decannulation is ultimately achieved in 35% to 75%

of patients.[4] The average time to decannulation ranges from 4 to 21 months and varies based on original indication.[6,20,21] Those patients undergoing tracheostomy for facial or laryngotracheal trauma have significantly shorter times to decannulation than patients with cardiopulmonary or neurologic indications.[2,4] The patient should first undergo direct laryngoscopy and bronchoscopy to evaluate the airway for feasibility of decannulation, including the presence or absence of laryngeal or subglottic stenosis, granulomas, suprastomal collapse, and/or tracheomalacia. The tube may be progressively downsized, although this approach is limited in small children due to the proportionately larger increase in airway resistance and mucus plugging of the smaller tube. Capping trials may be employed in the office of the otolaryngologist or pulmonologist. If tolerated, the specialist may provide instruction on short capping trials to be initiated at home with monitoring to determine how well the patient tolerates occlusion of the tube for extended periods. Finally, polysomnography can be performed to assess the adequacy of gas exchange with a capped tracheostomy tube prior to decannulation. Decannulation should be attempted in the inpatient setting, with initial high acuity monitoring. The patient should be monitored in the hospital for 24 to 48 hours following decannulation to observe for any obstructive symptoms.[2,11,22]

CASE REPORT 62-2

A 2-year-old boy sustained significant head trauma in a motor vehicle collision. Due to an inability to wean from ventilatory support, he underwent tracheostomy. He was transitioned to rehabilitation care and made significant improvements in his functional status, recovering the ability to speak, eat, and walk. He was successfully weaned to room air and underwent evaluation for decannulation by pediatric otolaryngology at the age of 4 years. Direct laryngoscopy revealed a normal larynx; however, there was suprastomal granulation tissue (**Figure 62-5**), which was excised. In addition, airway evaluation was notable for enlarged adenoids and tonsils. Capping trials were initiated, and he tolerated these well during the daytime. Overnight polysomnography demonstrated increased snoring, obstructive apnea/hypopnea, and desaturations when the tracheostomy tube was capped. He then underwent adenotonsillectomy, and his snoring resolved. Repeat capped polysomnography revealed resolution of obstructive apnea/hypopnea. He was able to tolerate overnight capping and was successfully decannulated.

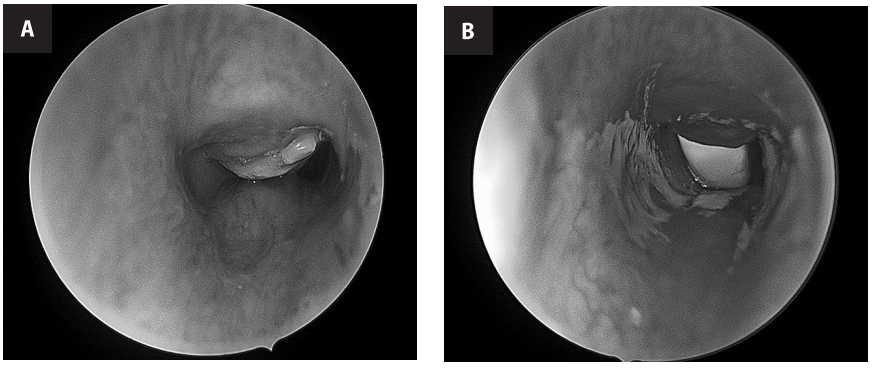


Figure 62-5. Suprastomal granulation tissue proximal to tracheostomy tube obstructing a portion of airway lumen. **A.** Suprastomal granulation tissue due to tracheostomy tube. **B.** Example of trachea without suprastomal granulation tissue

key points

- Caring for a child with a chronic tracheostomy requires a collaborative multidisciplinary team.
- Indications for tracheostomy placement include conditions requiring prolonged mechanical ventilation (ie, cardiopulmonary disease, neurologic impairment) and critical upper airway obstruction.
- Tracheostomy tubes are made in neonatal, pediatric, and adult sizes and are most commonly made of silicone or polyvinyl chloride.
- Uncuffed tubes are generally preferred to allow for vocalization and prevent tracheal injury, but cuffed tubes can be used for patients who are on ventilators or at risk for aspiration.
- Changes in airway clearance, sense of smell, speech, humidification, and swallowing function can be expected following tracheostomy.
- Parents and other caregivers should receive detailed counseling prior to tracheostomy placement, including the significant caregiver and home nursing responsibilities. Caregivers must be trained in suctioning, positive-pressure resuscitation, stoma and skin care, tracheostomy tube and tie changes, cleaning tubes, troubleshooting, and CPR prior to discharge from the hospital.
- Patients with tracheostomy should undergo routine airway evaluations to evaluate airway anatomy, evaluate for complications, assess size and fit, and determine readiness for decannulation.
- Long-term complications of tracheostomy include granulomas, fistulae, erosions, infection, bleeding, and life-threatening obstruction of the tube.
- Decannulation can be considered in patients once the initial indication for tracheostomy placement has resolved.
- Evaluation for decannulation includes direct laryngoscopy, bronchoscopy, capping trials, downsizing of the tube, and/or polysomnogram.

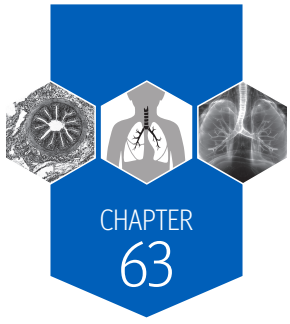
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Home Ventilation

Howard B. Panitch, MD
Thomas G. Keens, MD, FAAP

CASE REPORT 63-1

A neonate was born at 24 weeks' gestation weighing 20.36 oz (570 g). He developed respiratory distress and underwent endotracheal intubation and mechanical ventilation. Following stabilization, repeated efforts to wean ventilatory support resulted in episodes of respiratory distress and weight loss. At 5 months of age, he underwent elective tracheostomy placement to facilitate long-term mechanical ventilation. Following an interdisciplinary team meeting with the child's family where options for his ongoing care were discussed, the family expressed a desire to bring him home while he was still being supported by mechanical ventilation. Over the ensuing 8 weeks, his parents learned all aspects of their child's medical care, including how to suction and change his tracheostomy tube, how to assess his respiratory status, and how to ventilate him manually in the event of a ventilator failure. The necessary equipment and skilled nursing services were arranged, and the child was successfully discharged from the hospital at 8 months of age. With assisted ventilation and ongoing interdisciplinary and nutritional support, he demonstrated both somatic and developmental catch-up, and his respiratory status improved. He completely weaned off mechanical ventilation by age 17 months and had his trachea decannulated by age 20 months.

History and Epidemiology of Pediatric Home Mechanical Ventilation

Chronic respiratory failure (CRF) can be defined as the need for mechanical ventilatory support for at least 4 hours per day for a month or longer.[1] The concept of supporting patients with CRF at home arose during the polio epidemics of the late 1940s and early 1950s, both because of the numbers of patients versus the number of available acute care beds and the desire of families to have their loved ones home.

The medical indications for chronic ventilatory support have shifted over time. In the 1970s and 1980s, the group of children with CRF comprised infants with chronic respiratory disease, children with anoxic encephalopathy, and infants surviving formerly fatal congenital anomalies.[2] Infants chronically dependent on ventilatory support were identified as having a new form of disability, and were considered "a creature of our new technology."[3] Over the last 3 decades, the population most likely to require chronic ventilatory support at home has shifted again, from survivors of neonatal disease to children with underlying neuromuscular or central nervous system diseases.[4,5]

As the types of patients receiving mechanical ventilation at home have changed over the years, the number of children receiving such care has continued to increase. In 1987 there were an estimated 600 to 2,000 children dependent on ventilatory support in the United States.[6] In Massachusetts, a 2005 survey of children supported by mechanical ventilation outside of an acute care hospital showed an almost threefold increase in number when compared with numbers derived from a similar survey conducted 15 years earlier. A similar shift was seen in the reasons for mechanical ventilation from children born prematurely with chronic lung disease to those with neuromuscular and central nervous system conditions.[4] Data extrapolated from the Pennsylvania Ventilator Assisted Children's Home Program provided estimates of approximately 8,000 children receiving some type of home mechanical ventilation in the United States in 2012.[7]

Goals of Home Mechanical Ventilation

No matter what the diagnosis is, growing up in an acute care hospital is considered detrimental to a child's overall health and development. Children who receive their respiratory support in hospitals for prolonged periods are at risk for nosocomial infection, in part because resistant bacteria are selected for in hospital environments and also because other children with communicable diseases from the community are admitted into the hospital and increase the risk of exposure. Growth and development are enhanced when hospitalization can be shortened, in part because therapies and play activities can occur according to the child's schedule at home rather than fit into regimented days with caregivers who are responsible for the care of several other children as well. In addition to the drawbacks for the child, caring for children in acute care hospitals is expensive, and excellent quality care can typically be accomplished for less in the home environment.[1,8]

The goals of home mechanical ventilation are listed in **Box 63-1.** In the hospital, assisted ventilation represents an impediment to advancing to the next step of rehabilitation and eventual discharge; thus, the focus is on withdrawing support even at the expense of increasing the patient's own breathing effort.

Since the patient requiring home ventilation is no longer taking up the limited resources of a hospital, weaning can proceed as the natural outcome of growth, development, and rehabilitation. For some children, as the underlying disease improves and growth and developmental milestones are achieved, mechanical ventilatory support becomes less needed and finally unnecessary. This philosophy is the key to understanding many of the factors that are considered in the weaning process of children with CRF, as discussed in the following sections.

Box 63-1

Goals of Home Mechanical Ventilation

- Extend life and enhance its quality
- Reduce morbidity and risk of nosocomial infection
- Improve physiological function
- Achieve normal growth and development whenever possible
- Optimize habilitative potential
- Reintegrate with home and community
- Reduce health care costs

Derived from O'Donohue WJ Jr, Giovannoni RM, Goldberg AI, et al. Long-term mechanical ventilation. Guidelines for management in the home and at alternate community sites. Report of the Ad Hoc Committee, Respiratory Care Section, American College of Chest Physicians. *Chest.* 1986;90:1S–37S.

Causes of Chronic Respiratory Failure

Ventilatory muscle power and central respiratory drive need to be adequate to overcome the respiratory load to achieve adequate ventilation (**Figure 63-1**).

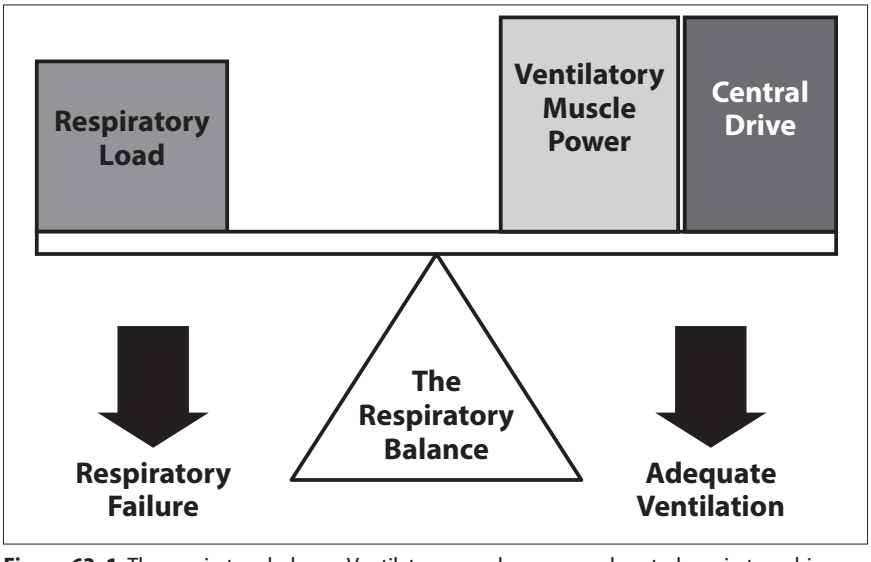


Figure 63–1. The respiratory balance: Ventilatory muscle power and central respiratory drive must be sufficient to overcome the respiratory load to achieve adequate ventilation. Respiratory failure results when ventilatory muscle power and/or central drive are decreased, and/or the respiratory load is increased.

Respiratory failure occurs when ventilatory muscle power and/or central respiratory drive are sufficiently decreased, and/or the respiratory load is sufficiently increased, to the point that a child cannot achieve adequate ventilation. Conditions that cause respiratory failure in children can be broadly considered within the context of disorders of the respiratory pump (the chest wall, ventral abdominal wall, and muscles of respiration), respiratory control center abnormalities, lung parenchymal abnormalities, and airway anomalies. One way to categorize these conditions is shown in **Box 63-2.** In general, a patient's suitability for home mechanical ventilation has less to do with the underlying diagnosis than with the degree of medical stability and the extent of support available for home care.

Box 63-2

Conditions for Which Home Mechanical Ventilation Might Be Considered

Thoracic/Intrathoracic
- Obstructive lung disease
  - Chronic lung disease of infancy (bronchopulmonary dysplasia)
  - Tracheomalacia
  - Cystic fibrosis
- Restrictive lung disease
  - Neuromuscular diseases
  - Chest wall disorders
  - Spinal cord injury
  - Lung hypoplasia
  - Recurrent aspiration syndromes

Extrathoracic
- Craniofacial malformations
- Obstructive sleep apnea

Central Control
- Congenital central hypoventilation syndrome
- Brain/brain stem injury
- Central nervous system tumors

Clinical Features of Chronic Respiratory Failure

Often, CRF follows an acute illness from which the child does not recover completely. In such situations, it is not possible to reduce ventilatory support because respiratory distress or signs of respiratory insufficiency quickly ensue. In other situations, the effects of respiratory failure are more insidious. Because nobody breathes as well during sleep as they do when awake, children with progressive neuromuscular diseases, for example, develop sleep-disordered breathing before inadequate ventilation while awake. They may report frequent awakenings and morning headaches when nocturnal hypoventilation is present.[9] As respiratory muscle weakness progresses, daytime fatigue, poor school functioning, and weight loss will ensue. Older children and adolescents with respiratory muscle weakness who chronically breathe at low tidal volumes eventually develop reduced chest wall compliance as ligaments and tendons stiffen and ankylosis of the costovertebral joints develops,[10] adding to the load against which respiratory muscles have to work.

Respiratory load can also increase because of airway obstruction from uncontrolled bronchospasm or during acute viral illnesses, with atelectasis or pneumonia, or when mechanical ventilator support is weaned too aggressively. When the respiratory load increases, the work of the respiratory pump must also increase to avoid failure. This work of increasing respiratory pump expenditure to attain near-normal gas exchange often comes at the expense of growth,[11] energy for play, or acquisition of developmental milestones. Inadequate ventilatory support can also be associated with hypoxemia, and even intermittent hypoxemia can lead to pulmonary hypertension, cor pulmonale, right heart failure, and neurodevelopmental damage.

Mechanical ventilation can be used to provide occasional breaths that are larger than tidal volume (sigh breaths) to maintain chest wall flexibility and reverse areas of microatelectasis that occur after prolonged low tidal volume breathing. By shifting inspiratory work from the muscles of ventilation to the mechanical ventilator, calories can be conserved and redistributed for somatic growth and other physical (developmental) activities. Ventilatory support improves sleep quality in patients who have sleep-related hypoventilation,[9] and restoration of normal gas exchange can often help reverse pulmonary hypertension and cor pulmonale.

Patient Selection for Home Ventilation

There are several criteria that must be fulfilled to consider a child eligible for home ventilation, independent of the cause of CRF. These include medical, social, and economic factors. If a child with a life-threatening condition or irreversible, progressive respiratory failure does not meet the usual criteria but would be better managed in the home environment, a shared decision-making approach with the family should be used and assessment must be individualized.

Medical Stability

The child must fulfill both physiological and clinical requirements for safe care outside of the intensive care unit (ICU) (**Box 63-3**). Physiological criteria refer to the child's airway and gas exchange capabilities. The child's airway must be stable, whether it is the natural airway or an artificial one. A stable airway means that, under usual circumstances, (1) there is a patent passage from atmosphere to alveoli, (2) any artificial airway will remain in place despite movement of the child, and (3) tube repositioning, if it occurs, does not require routine radiographic confirmation. Children with parenchymal lung disease should be able to maintain a Pa_{O_2} above 60 mm Hg in a fraction of inspired oxygen (F_{IO_2}) less than 0.40 while on ventilatory support. This is not only a practical consideration (it is technically difficult to maintain a supply of home oxygen when demands are greater than 0.50) but also

Box 63-3

Determinants of Medical Stability for Ventilator-Dependent Children Outside of the Intensive Care Unit

Physiological Criteria

- **Stable airway**
- **Parenchymal lung disease**
  - **Pa_{O_2} > 60 mm Hg in F_{IO_2} < 0.40 on ventilatory support**
  - **Pa_{CO_2} < 50 mm Hg on ventilatory support**
- **Chest wall/neuromuscular disease**
  - **Pa_{O_2} > 60 mm Hg in room air on ventilatory support**
  - **Pa_{CO_2} < 45 mm Hg on ventilatory support**
- **No need for frequent ventilator changes to maintain adequate gas exchange**

Clinical Criteria

- **Positive trend on growth curve**
- **Stamina for periods of play or therapies**
- **No frequent fevers or infections**
- **Resolution of any outstanding medical issues requiring evaluation**

Abbreviations: F_{IO_2}, fraction of inspired oxygen; Pa_{CO_2}, partial pressure of arterial carbon dioxide; Pa_{O_2}, partial pressure of arterial oxygen.

somewhat of a pragmatic one: it suggests that the child has some degree of reserve so that in the event of a mild illness, the child's condition is unlikely to deteriorate precipitously and the child might be able to be cared for through the acute illness at home. The child's Pa_{CO_2} should be less than 50 mm Hg on the current level of ventilatory support. In the case of children with respiratory failure from causes other than parenchymal lung disease, the Pa_{O_2} and Pa_{CO_2} should both be normal on ventilatory support without the need for supplemental oxygen. Frequent changes in ventilator settings should not be required to maintain adequate gas exchange.

Clinical criteria that must be satisfied include a positive trend on the growth curve for infants and young children or weight maintenance for older children, stamina for periods of play or participation in therapy sessions, freedom from infection or frequent fevers, and resolution of any outstanding diagnostic considerations. Other medical conditions should be controlled similarly, such that frequent alterations to the medical plan are not required to maintain the child's stability. Once a decision has been made to send a child home on mechanical ventilatory support, there must be a predefined period, which can range from 1 to 4 weeks before the planned discharge, where no changes are made to any aspect of the medical regimen.[12] In this way, the treating team gains understanding of how the patient is tolerating the current level of

support. Furthermore, the care team is better able to smooth the transition to home, which often is a tumultuous time, and unexpected medical issues resulting from a change in support are avoided.

CASE REPORT 63-2

A neonate with a congenital diaphragmatic hernia and severe pulmonary hypoplasia received support with extracorporeal membrane oxygenation therapy for 19 days and underwent patch repair of her defect at 9 days of age. She developed persistent pulmonary hypertension that was managed with chlorothiazide and sildenafil. A tracheostomy was placed to facilitate chronic mechanical ventilation at 3 months of age. Her parents discussed home care issues with the care team and learned all aspects of their daughter's medical care. At the same time, a home equipment company and nursing agency were identified. The home was assessed for adequacy of supporting the child, and the care team and insurance case managers agreed on the amount of nursing care and types of durable and disposable equipment that would be covered by the insurance company. Episodically, however, the infant experienced severe spells of respiratory distress, with oxyhemoglobin desaturation, diaphoresis, and poor air entry on chest auscultation. Treatment of the spells typically required sedation rescues, a temporary increase in positive end-expiratory pressure, and increased FIO_2. The planned discharge was suspended. Evaluation disclosed severe gastroesophageal reflux despite the use of acid blockers and motility agents. The infant underwent fundoplication and placement of a gastrostomy tube at 4 months of age. Following recovery from her surgery, she experienced a 2-week period without spells. Over the same time, no changes were made to any of her medications or ventilator settings. At 5 months of age, she was considered to be safe for home care and was successfully discharged home using continuous mechanical ventilation and medications for the treatment of her pulmonary hypertension.

Caregiver Training

Early in the process of identifying a child as a candidate for home ventilation, the family must agree to the concept and be willing and able to learn all aspects of the child's medical care. A brief checklist of the issues that need to be addressed before a child can be safely discharged using assisted ventilation is presented in **Box 63-4.** There should be at least 2 adults available to learn the care, although additional family members should be encouraged to learn as well, to provide support to the primary caregivers. This will require family caregivers to understand the ventilator or bilevel pressure generator and its circuit, issues related to the patient/machine interface (eg, tracheostomy care or skin care for noninvasive ventilation), a general respiratory assessment and what to do in emergency situations, and all aspects of the child's medical regimen. Special attention should be paid to educating families on how to

Box 63-4

Checklist of Items Required for Safe Home Ventilation Discharge

Caregiver training (2 people)
- Ventilator and monitors
- Tracheostomy or noninvasive interface
- Airway clearance equipment
- General respiratory assessment
- Medications
- Cardiopulmonary resuscitation
- Responses to potential emergency situations in the home

Identification of home care providers
- Primary care provider
- Skilled nursing agency
- Durable medical equipment company with 24-hour emergency availability
- Local ambulance service/emergency care facility

Written agreement with insurance company of what and how much will be covered
- Durable and disposable equipment
- Hours of skilled nursing
- Therapies

Home assessment and any necessary modifications
- Adequate space for equipment and personnel
- Electrical, water, heat
- Generator if frequent power outages are expected
- Telephone
- Ramps or elevators

Notification to community services
- Electrical company to provide priority services in the event of interruption of service and medical discount utility rate
- Local ambulance service/emergency department
- Telephone company to provide priority services in the event of interruption of service
- School

Prescriptions filled

All necessary equipment and supplies delivered to home before discharge

Child adequately supported on home equipment in the hospital 1 to 7 days

handle emergency situations in the home. Family members and in-home nurses often lack knowledge in this area.[13] A curriculum focused on response to in-home emergencies should be given to all caregivers.[14] The family also should have some understanding of the child's underlying condition that has caused the CRF. The primary caregivers do not necessarily need to be the

child's biological parents; in single-parent homes, a grandparent, close friend, or neighbor can be the backup caregiver. Given the plethora of information and skills that family members must acquire, the family can expect the process to take 6 to 8 weeks between the time that they commit to taking the child home and being prepared to do so.

Preparing the Home

The home environment must be adequate to support a child who requires ventilatory support. There must be sufficient space for the equipment and additional personnel who will be caring for the child, as well as adequate heat, electricity, and water supply. A working telephone is critical, as the telephone becomes the lifeline between the family and the child's medical caregivers. A child who is confined to a wheelchair will require alterations to the home for access and egress. If the child lives in a remote area, or in an area where power outages are frequent, it is prudent for the family to have a backup generator. When the child lives a distance from the discharging tertiary care center, community resources such as the local hospital's emergency department and local ambulance service must be identified, so that the child can be stabilized and transported in the event of an acute illness.

Skilled Nursing Care

Care of a child with CRF at home is stressful for parents, and parental stress has been shown to increase with duration of time at home.[15] Skilled nursing care is often prescribed to help parents cope with the extraordinary demands of caring for the child. Any child who would experience life-threatening respiratory embarrassment if the ventilator interface were to become inadvertently disconnected or obstructed, and who would be unable to physically correct the problem, should receive a minimum of 8 hours of skilled nursing care. In this way, parents can be assured that a trained adult is available to assess and intervene on their child's behalf while they sleep. The nurse provides care as directed by a written medical plan and provides ongoing assessments and documentation of the child's medical status as well as the family's level of functioning. The nurse can also teach and reinforce procedures and assessment skills that were introduced to the family during the initial hospitalization of the child. The home care nurse must be knowledgeable and proficient in all aspects of high-technology home care, including function of home ventilators, assessment of respiratory and cardiac status, care of long-term tracheostomies or nasal interfaces, use of airway clearance techniques and devices, and appropriate responses to emergency situations.

Depending on the medical needs of the child, up to 24 hours per day of nursing care may be necessary for the safety and well-being of the child.[16] Nursing care represents the most expensive aspect of home mechanical ventilation.[1] Nevertheless, there are no uniform criteria to determine the quantity or duration of nursing care that children who require ventilatory support should receive.

The period following the initial discharge of the child is perhaps the most tenuous with regard to achieving a successful transition from hospital to home care. For this reason, many advocate that families receive around-the-clock nursing care for 1 to 2 weeks until the child's home regimen is well-established, after which the number of nursing hours provided can be reduced based on the child's status and level of the family's functioning.[16] The number of nursing hours funded by third-party payers may require temporary increases during periods of acute illness of the child or family caregivers. In addition, the well-being of caregivers demands a rational approach to providing funded periods of respite care for families.[17] The need for respite care services, to allow families some time off from the highly stressful duties of caring for a child supported by mechanical ventilation, has been repeatedly identified both by parents and experts in the field as essential and a mechanism to help avoid a care crisis or family breakdown.[16,18,19] Presently, however, respite care is not routinely funded by insurers; therefore, families or home ventilation programs have to find alternate sources of funding for these services.

Sometimes, nursing agencies cannot provide in-home nursing due to illness of the nurse, nursing shortages, etc. Therefore, the family must be fully trained to provide all aspects of the child's care when in-home nursing is not available.[20]

Economic and Payment Issues

Home mechanical ventilation is purported to be cost saving when compared with caring for children in ICUs.[1] Nevertheless, it is still expensive and beyond the financial capabilities of most families. Thus, funding for durable medical equipment (DME), nursing services, disposable supplies, medications, and specialized formulas all must be established and guaranteed. This is typically accomplished through third-party payers, state Medicaid programs, or model waiver programs. Since the establishment of the Katie Beckett Waiver in 1982, children who require ventilatory assistance are eligible for Supplemental Security Income (SSI) independent of their parents' income to help offset costs related to their care. The items and services that these programs will cover must be established before the child is discharged from the hospital to avoid unexpected catastrophic financial burdens for the family. Some expenses that are bundled into a hospital stay will become out-of-pocket costs for families, such as medications or formula. The home electric, water, and telephone bills are also likely to increase. However, medical discount utility rates are often available for electricity and telephone. Each family must consider this in their decision to bring the child home. Families must also try to anticipate the effect of lost income related to the child's unexpected illnesses and if there is no nurse available. By discussing these issues early in the discharge process, the family can often make contingency plans, seek additional funding from other community resources, or devise alternate strategies to make up any shortfalls.[21]

Organizational Issues

Successful discharge from the hospital of a child who receives ventilatory support requires the efforts and input of a multidisciplinary team that includes appropriate medical subspecialists; case managers; nurse coordinators; social workers; nutritionists; respiratory, speech, physical, and occupational therapists from the discharging institution; a case manager from the insurance company; and the primary care physician and home nursing and DME company personnel in the community.[19,20] While no single care model is used universally to support patients following hospital discharge, home ventilation programs should provide family- and patient-centered care in a medical home model.[20] Local customs and practices often dictate roles of various providers, but comanagement between professional caregivers in the community, the primary care provider, appropriate subspecialists determined by the child's medical needs, and members of the hospital-based home ventilation program is the approach most likely to provide such care successfully.[20]

The complexity of care of children supported by mechanical ventilation will be exacerbated by social inequities. Financial stresses and lack of family resources can make such care disruptive or even untenable. Limitations in transportation can result in missed visits and compromised care. While tertiary care centers usually have translation services, language barriers can still exist between families and community caregivers, including home nurses. Caregivers, in accordance with ideals of the medical home, must ensure equal access to care that is culturally competent and that addresses social determinants of health.

Any child who receives skilled nursing care at home must also have a set of written medical orders. These encompass everything from the recommended ventilator settings and routine medication regimen to frequency of vital signs, the types of monitoring to be used, the amount of skilled nursing the child should receive, the type and frequency of airway clearance to provide, and the nutritional plan. Actions to take in case of a change in the child's medical status, such as the range of supplemental oxygen permissible, frequency of extra bronchodilator aerosol treatments to be given, or other changes in support, are documented as well. The initial plan is written by the discharging team before the child first leaves the hospital, but it must be reviewed periodically. This review can be the responsibility of the primary care physician or the subspecialist (usually a pulmonologist or critical care medicine physician) who monitors the child's ventilator care.

The role and responsibilities of the primary care physician will vary depending on the level of comfort of the physician regarding the care of a child who requires mechanical ventilation, prior training, proximity of the patient to the tertiary care center, regional customs of care delivery, and established

relationships with the family.[22] In general, the primary care physician is the person responsible for general pediatric care, but, as noted previously, this professional may also want to be responsible for care plan review and even ventilator management. In some programs, a multidisciplinary team of pulmonologists, advanced practice nurses, social worker, nutritionist, and therapists provide ongoing care through telephone contact and scheduled outpatient visits, and work in concert with the primary care physician to ensure continued success of the child and family at home. Patients are seen for routine visits at intervals from 1 to 6 months, depending on their underlying disease, expected trajectory regarding weaning, and degree of illness. In many programs in the United States, when children require rehospitalization, they return to the discharging institution. In contrast, in other systems like that of the United Kingdom, when a child is discharged home with ventilatory support, the care of the child is also transferred from the tertiary care center to a community health care team.[23]

Modes of Mechanical Ventilation

Most types of mechanical ventilation provided at home involve the application of positive pressure to the airway, although negative pressure and positive-pressure body ventilators are occasionally used. Whether a child receives positive pressure noninvasively or invasively depends on several factors, as listed in **Box 63-5.** In general, if a child cannot control secretions, requires support for more than 16 hours per day, has facial features that make a standard nasal interface difficult to use, or is not (or the child's caregivers are not) committed to a noninvasive approach, then tracheostomy placement should be considered to facilitate assisted ventilation. At times, supporting a young child with noninvasive ventilation can increase the complexity of care for families who must also manage airway clearance and provide physical and other therapies. In these situations, placement of a tracheostomy can actually simplify care, even though the caregivers must learn additional skills related to tracheostomy management. Thus, the decision to manage a child with invasive or noninvasive ventilation is a highly individualized one.

The mode of ventilation, whether pressure or volume controlled, is also a choice that is individualized. There are no data that generally support one style over the other, and newer portable mechanical ventilators designed for home

Box 63-5

Factors to Consider for Noninvasive Versus Tracheostomy Positive-Pressure Ventilation

- Level of consciousness
- Ability to control oral secretions
- Duration of daily support
- Adequacy of available interfaces
- Willingness of patient and family
- Caregiver skills and aptitude

use can provide either method of support. Occasionally, one style is preferred over the other. For example, volume control ventilation in patients with neuromuscular weakness provides an option for breath stacking and lung volume recruitment that cannot be accomplished in a pressure control mode. In contrast, when leak around a tracheostomy is large, ventilation in a volume control mode will be unreliable and can lead to significant episodes of hypoventilation.[24] In this situation, pressure-controlled ventilation can help overcome the leak and avoid the need for a cuffed tracheostomy tube. An uncuffed tracheostomy tube that is small relative to the diameter of the airway is preferred when possible, because the leak around the tube permits speech. Use of a small tracheostomy tube also decreases the risk of tracheomalacia; use of a large tube, which can compress the tracheal mucosa and compromise blood flow, can result in tracheomalacia or tracheal stenosis.

Equipment and Monitoring

There is no single home mechanical ventilator that is the most appropriate for all situations. Current models provide continuous flow and are capable of giving pressure support during spontaneous efforts. They differ from each other in size and weight, circuit configurations they support, trigger and cycle sensitivities, and special algorithms used for monitoring patient-ventilator interactions. The model of ventilator or bilevel pressure generator should be chosen based on its ability to deliver the mode of support prescribed, adequate trigger and cycle sensitivity, and portability (for those who require support for most of the day).[25] Accompanying equipment for the ventilator will vary, depending on whether the child receives support via tracheostomy or noninvasively.[2] Children who cannot be independent of mechanical ventilation for at least 4 hours of the day, or who live more than 1 to 2 hours from their DME company or health care facility, should have a second complete ventilator and circuit in the event that the primary unit fails,[26] although this is uncommon.[27]

While all portable ventilators have alarms to detect obstruction, accidental disconnection, or decannulation, these are not adequate to be used as the sole means of monitoring patients. This is especially true for children with tracheostomy tubes that have inside diameters smaller than 4.5 mm, where high tube resistance can mask an inadvertent tracheal decannulation.[28] A monitor on the patient, which alarms separately from ventilator alarms, is required. Such monitoring is typically needed at minimum when the child is asleep or not in direct line of sight of an awake and vigilant caregiver. There is, however, no consensus regarding the type and extent of monitoring to be used beyond that supplied by the ventilator. Pulse oximetry can be used both as a routine monitoring device and as an aid in adjusting ventilator settings during acute illnesses, or as a monitoring device during weaning of the patient if appropriate. Cardiorespiratory monitors are advocated by some[2] but considered

redundant by others.[29] Continuous capnometry is not indicated for patients at home, but intermittent determinations of end-tidal carbon dioxide can be useful to assess adequacy of ventilation, especially during weaning trials or during acute illnesses. At present, transcutaneous carbon dioxide determinations are not routinely performed in the home, but advances in monitor technology may make such measurements more commonplace, especially in individuals supported by noninvasive ventilation.

Long-term Outcomes of Home Mechanical Ventilation

Outcomes of children who depend on ventilatory support can be gauged in terms of survival, ability to wean from support, quality of life of the child, and quality of life of the caregivers. In general, survival is considered quite good. Factors to consider regarding survival include the natural history of the underlying disease (ie, is the child's underlying condition expected to improve over time, remain static, or worsen) and whether the child is supported noninvasively or via tracheostomy.

Recent reports of outcomes of children supported at home by mechanical ventilation represent single-center experiences. In general, all reflect that home mechanical ventilation extends life. The cumulative survival at 5 and 10 years among 228 children who receive chronic mechanical ventilation via tracheostomy was 80% (95% CI, 75%–85%) and 63% (95% CI, 51%–73%), respectively.[30] In a center that followed 379 children ventilated both invasively (17%) and noninvasively (83%), 324 children (86.5%) survived over 20 years of follow-up, while 106 (28%) transitioned to adult care. Similarly, another center that used only noninvasive ventilation in 449 children younger than 18 years of age over an 18-year period reported survival in 340 (76%), with 181 (40%) transitioning to adult care.[31] Chronic mechanical ventilation does not reverse the respiratory failure associated with a progressive parenchymal disease like cystic fibrosis,[32] but it does contribute to a longer survival of patients with neuromuscular disease after the onset of respiratory failure.[33]

The presence of a tracheostomy adds a small but significant survival risk because of the possibility of inadvertent decannulation, tube obstruction, and, less commonly, serious bleeding from erosion of the tube into a major vessel. Furthermore, life-threatening tracheostomy-related accidents are more likely to occur in the home than in the hospital. In one review, life-threatening airway accidents in children who receive chronic mechanical ventilation by tracheostomy occurred among hospitalized children at a rate of 0.9/10,000 patient days, whereas the rate at home was almost 3 times greater, or 2.3/10,000 patient days.[34] Among the 47 deaths reported in a group of children invasively mechanically ventilated at home, 19% were related to a tracheostomy complication.[30]

Other outcomes frequently measured in children who receive mechanical ventilatory support outside of the ICU are reduction of mechanical ventilator support to fewer than 12 hours per day and complete liberation from mechanical ventilation.[35] The likelihood that a child with CRF will wean from mechanical ventilation is greatly influenced by the underlying cause of respiratory failure. Children with chronic lung disease after prematurity or a central airway problem like tracheomalacia are less likely to require long-term mechanical ventilation compared with children who have underlying neurologic or neuromuscular conditions.[30,35] In the home setting, 18% to 59% of children with CRF can be liberated from mechanical ventilation, most of whom are infants with a history of chronic lung disease or a central airway disorder.[30,36]

In general, patients supported by home mechanical ventilation view it positively. Its use is associated with improved physiological function and sleep quality, and fewer rehospitalizations.[9,33,37] Home ventilation of 23 males with Duchenne muscular dystrophy not only resulted in 1- and 5-year survival rates of 85% and 73%, respectively, but nocturnal ventilatory support also normalized daytime unassisted oxygen and carbon dioxide values.[33] Among 15 children with neuromuscular diseases who received noninvasive mechanical ventilation at home, there was an 85% reduction in the number of hospital days after initiation of mechanical ventilation compared with the pre-ventilation period.[9] In another retrospective series, patients experienced an average of only 0.7 rehospitalizations per year over the 20-year observation period.[38]

Adjustment to Mechanical Ventilation at Home

Home ventilation is psychologically acceptable to the children who use it.[39] Interviews with 38 children requiring ventilatory support showed that 79% were satisfied with their quality of life.[40] Most (77%) were also considered to be well-adjusted. Adolescents were, in general, less content with their daily activities than were younger children, but greater satisfaction trended with greater activity levels. Notably, quality of life did not correlate with whether the child had required ventilatory support from birth or acquired respiratory failure later in life, with duration of ventilation at home, or with the child's disease being static or progressive.

Although children who require ventilatory support have expressed concern about their health and being a burden to their families,[18] their outlook toward mechanical ventilation in general is a positive one, and mechanical ventilation is considered a minor aspect of their lives.[39,41] Furthermore, access to information and communication technologies enhance their lives.[39] One group noted that 83% of their subjects left home each day to attend school, and many reported traveling for vacations.[38] Others note, however, that some children who require mechanical ventilation feel isolated and stigmatized.[41] Some

children also express a concern that they are burdens to their families.[18] Perhaps paramount in the discussion is that health care providers routinely underestimate the quality of life of patients who require ventilatory support and so might not consider chronic mechanical ventilation as a reasonable choice for some patients.[42]

While children who use ventilatory support generally express satisfaction with their general condition, the feelings of their family caregivers are more complicated. Parents (or other family caregivers) commonly express that having their child at home is both good and desirable, but they also speak about the stresses of caring for their child. Parents frequently voice a fear of having the child die at home.[18] Several studies cite a lack of privacy associated with home nursing care, as well as a concern for the quality of professional care provided as sources of family stress.[43,44] Financial concerns result not only from increased expenses (utility bills, special formulas, medications), but also from the loss of income that occurs when one spouse must remain home to care for the child.[21] Parents often feel isolated, since it is difficult or impossible to find a babysitter who is trained to care for a child who requires ventilatory support, and some public facilities restrict access to people with tracheostomies or mechanical ventilators.[18,43] Parents also experience frequent sleep disruption to answer alarms or to provide care when nighttime nursing is not available.[45] The degree of sleep disruption as well as ventilation via tracheostomy as compared with noninvasive ventilation both contribute to worse parental quality of life and family functioning.[15] The stresses related to caring for a child who is supported by mechanical ventilation increase over time.[8] Despite these hardships, parents would choose to do so again if given the choice.[46] In general, both medical professionals and family members have a sense that having the child at home improves both growth and developmental outcomes.

When to Admit

The general goal of chronic mechanical ventilation is to support the child's growth and development. These, therefore, must be monitored routinely by either the primary care provider or the team that manages the child's ventilator care. Adjustments to routine care, including a change in ventilator settings, can be achieved without the need for hospitalization. If ventilator support is being gradually weaned, weekly status updates with the caregivers should be arranged by phone. Acute illnesses often can be cared for without the need for emergency department or hospital visits. Tracheal samples and even appropriate blood work can be obtained at home and sent for analysis with advanced planning. Antibiotic therapy can be instituted, and bronchodilator administration can be started or increased based on reports and observations of home nurses or family caregivers. Ventilatory support can also be adjusted based on reports of physical examination, pulse oximetry, and capnography evaluations. It is imperative that families always have ready

access to a medical provider who can help them navigate where, how, and which interventions should occur. Since the late 2010s, telemedicine has also been used to assist in the assessment of patients, and the visual evaluation can add to the information that parents or skilled caregivers transmit to the provider. Use of remote ventilator downloads can also provide insight into patient-ventilator interactions and assist with acute interventions.

Hospitalization for acute illnesses or deterioration in the patient's status is warranted any time anyone on the family/health care team feels uncomfortable with the child's situation. That means if the parent or home nurse is uneasy about keeping the child home under current conditions, or if members of the health care team do not feel that they have an adequate understanding of the child's status, hospitalization or a visit to the emergency department should be recommended. Practical limitations of care delivery also will dictate hospitalization. This could include a need for supplemental oxygen beyond what is deliverable in the home environment (eg, $F_{IO_2} > 0.50$), or exhaustion of caregivers, especially if skilled nursing care is not available. Return to the hospital must never be seen as a hurdle for families, because this undermines the relationship with the health care team. Rarely, children will be hospitalized electively for a comprehensive evaluation. Hospitalization, however, is disruptive for the patient and the family and increases the child's risk of nosocomial infection; thus, this should occur only when the necessary tests cannot be performed on an outpatient basis.

key points

- The indications for chronic home mechanical ventilation, and the number of children so supported, continue to grow.
- Successful discharge of a child who needs ventilatory support requires careful planning and intense training of family caregivers.
- Maintaining a child who is on home mechanical ventilator support requires a patient- and family-focused care team that includes hospital-based multidisciplinary team of health care professionals, the primary care provider, community health care professionals, and family working together with defined roles and a written, shared care plan.
- Outcomes of children requiring ventilatory support generally are good and are determined primarily by the prognosis of the underlying disease.
- While the practice of caring for a child with CRF at home on mechanical ventilatory support has become more commonplace, such care must be considered an extraordinary commitment on the part of the health care team, and especially on the part of the family who agrees to undertake this care.
- The remarkable efforts and needs of families and patients must be recognized and supported by health care and societal systems so that they may achieve optimal growth, development, and wellness.

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