Pediatric Pulmonology, Asthma, and Sleep Medicine

A QUICK REFERENCE GUIDE

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Monroe Carell Jr Children's Hospital at Vanderbilt
Nashville, TN

Allen J. Dozor, MD, FCCP, FAAP
Professor of Pediatrics and Clinical Public Health
New York Medical College
Director, Pediatric Pulmonology, Allergy, Immunology and Sleep Medicine
Boston Children's Health Physicians
Associate Physician-in-Chief
Maria Fareri Children's Hospital at Westchester Medical Center
Valhalla, NY

Associate Editors

Lee J. Brooks, MD, FAAP
Clinical Professor of Pediatrics
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Philadelphia, PA

Mary E. Cataletto, MD, MMM, FAAP, FCCP
Professor of Clinical Pediatrics
Stony Brook University School of Medicine
Stony Brook, NY
Associate Director, Pediatric Sleep Medicine
NYU Winthrop Hospital
Mineola, NY

Julie P. Katkin, MD, FAAP
Associate Professor of Pediatrics
Pediatric Pulmonology Section
Baylor College of Medicine
Attending Physician
Texas Children's Hospital
Houston, TX

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

James W. Stout, MD, MPH, FAAP
Professor of Pediatrics
Division of General Pediatrics
University of Washington
Seattle, WA

Kristin Van Hook, MD, MPH, FAAP
Attending Physician
Ochsner Children's Health Center
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Radiology Imaging Editor

Lisa H. Hutchison, MD, FAAP, FACR
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Contributing Authors

Matthew F. Abts, MD
Clinical Assistant Professor of Pediatrics
Pediatric Pulmonary and Sleep Medicine Division
University of Washington School of Medicine
Seattle Children's Hospital
Seattle, WA
Ch 21: Pulmonary Arteriovenous Malformations

Joshua Akers, PharmD, BCACP
Manager and Residency Program Director
Kelley-Ross Pharmacy Group
University of Washington
Seattle, WA
Ch 33: Pharmacological Management: Short-Acting β_2-Adrenergic Agonists

Nathan S. Alexander, MD
Director, Pediatric Otolaryngology
Greenville Health System
Greenville Children's Hospital
Clinical Assistant Professor
USC School of Medicine Greenville
Greenville, SC
Ch 10: Choanal Atresia

Julian Allen, MD, FAAP
Chief, Division of Pulmonary Medicine
Robert Gerard Morse Chair
The Children's Hospital of Philadelphia
Professor of Pediatrics
The Perelman School of Medicine at the University of Pennsylvania
Philadelphia, PA
Ch 24: Spinal Deformities: Idiopathic Scoliosis and Kyphoscoliosis

Matthew C. Altman, MD, MPhil
Assistant Professor of Medicine
Division of Allergy and Infectious Diseases
University of Washington
Seattle, WA
Ch 29: Allergic Rhinitis
Ch 40: Immunotherapy

Max M. April, MD, FACS
Professor of Otolaryngology and Pediatrics
NYU Langone Medical Center
New York, NY
Ch 12: Vocal Fold Paralysis

Casandra Arevalo-Marcano, MD
Pediatric Pulmonary Fellow
Division of Pulmonary Medicine
The Children's Hospital of Philadelphia
Philadelphia, PA
Ch 72: Pneumothorax
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Andrew G. Ayars, MD
Assistant Professor of Medicine
Division of Allergy and Infectious Diseases
University of Washington
Seattle, WA
Ch 29: Allergic Rhinitis
Ch 40: Immunotherapy

Molly K. Ball, MD, FAAP
Director of Neonatal Care, CTICU
Neonatal Assistant Director of Fetal Medicine
Division of Neonatology
Nationwide Children's Hospital
Ohio State University
Columbus, OH
Ch 71: Bronchopulmonary Dysplasia

Jean A. Ballweg, MD
Associate Professor, Pediatrics
University of Nebraska College of Medicine
Children's Hospital and Medical Center
Omaha, NE
Ch 88: Respiratory Considerations in Children With Congenital Heart Disease

Paula Barson, MA-CCC, SLP
Senior Speech-Language Pathologist
The Center for Childhood Communication
The Children's Hospital of Philadelphia
Philadelphia, PA
Ch 78: Vocal Cord Dysfunction

Ariel Berlinski, MD, FAAP
Professor of Pediatrics
Division of Pediatric Pulmonology
University of Arkansas for Medical Sciences
Arkansas Children's Hospital
Little Rock, AR
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Lee J. Brooks, MD, FAAP
Clinical Professor of Pediatrics
Perelman School of Medicine
University of Pennsylvania
Attending Physician
The Children's Hospital of Philadelphia
Philadelphia, PA
Ch 72: Pneumothorax
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Deborah M. Brooks, MD
Assistant Professor
Division of Child and Adolescent Psychiatry
Department of Psychiatry
University of Maryland
Baltimore, MD
Ch 104: Circadian Rhythm Sleep Disorders

Amy Brown, MD, MBe
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
Ch 33: Pharmacological Management: Short-Acting β_2-Adrenergic Agonists
Ch 34: Pharmacological Management: Long-Acting β_2-Adrenergic Agonists

Mary E. Cataletto, MD, MMM, FAAP, FCCP
Professor of Clinical Pediatrics
Stony Brook University School of Medicine
Stony Brook, NY
Associate Director, Pediatric Sleep Medicine
NYU Winthrop Hospital
Mineola, NY
Ch 11: Laryngomalacia

Christopher M. Cielo, DO, FAAP
Assistant Professor of Pediatrics
Perelman School of Medicine at the University of Pediatrics
Attending Physician, Division of Pulmonary Medicine
Children's Hospital of Philadelphia
Philadelphia, PA
Ch 82: Drowning

Jonathan D. Cogen, MD, MPH
Pediatric Pulmonologist
Division of Pulmonary and Sleep Medicine
Seattle Children's Hospital
University of Washington
Seattle, WA
Ch 25: Diagnosis of Asthma

Robyn T. Cohen, MD, MPH
Director, Division of Pediatric Pulmonary and Allergy
Boston Medical Center
Boston University School of Medicine
Boston, MA
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John L. Colombo, MD, FAAP
Professor of Pediatrics
Division of Pediatric Pulmonology
University of Nebraska Medical Center
Omaha, NE
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Carol Conrad, MD
Associate Professor of Pediatrics
Director, Pediatric Lung Transplant Program
Lucile Packard Children's Hospital Stanford
Stanford University
Stanford, CA
Ch 58: Tuberculosis

Shailendra Das, DO, FAAP
Director of Flexible Bronchoscopy
Assistant Professor of Pediatrics
Division of Pulmonary Medicine
Baylor College of Medicine
Texas Children's Hospital
Houston, TX
Ch 8: Bronchoscopy

Elizabeth de la Riva-Velasco, 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
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Lourdes M. DelRosso, MD, FAASM
Assistant Professor of Pediatrics
University of California, San Francisco
San Francisco, CA
Ch 97: *Brief, Resolved, Unexplained Events and Sudden Infant Death Syndrome*

Robin R. Deterding, MD
Professor of Pediatrics
Chief, Pediatric Pulmonary Medicine
Medical Director, Breathing Institute
Children's Hospital Colorado
University of Colorado
Aurora, CO
Ch 89: Respiratory Disorders Associated With Collagen Vascular Disease
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Laura Beth Mann Dosier, MD
Pediatric Pulmonology Fellow
Duke University
Durham, NC
Ch 93: Respiratory Disorders Associated With Cerebral Palsy and Neurodegenerative Diseases
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Marisa A. Earley, MD
Assistant Professor of Otolaryngology
Division of Pediatric Otolaryngology
University of Texas Health San Antonio
San Antonio, TX
Ch 12: Vocal Fold Paralysis

Harold J. Farber, MD, MSPH, FAAP
Associate Professor of Pediatrics, Pulmonary Section
Texas Children's Hospital
Baylor College of Medicine
Houston, TX
Ch 3: Environmental History
Ch 26: Tobacco Smoke Exposure and Children
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Claudia Fernandez, MD
Assistant Professor of Pediatrics
Department of Pediatric Pulmonology
Herbert Wertheim College of Medicine
Florida International University
Miami, FL
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Edward W. Fong, MD
Assistant Clinical Professor of Pediatrics
Division of Pediatric Pulmonology, Asthma, and Sleep Medicine
Stanford University
Stanford, CA
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Nicholas L. Friedman, DO, FAAP
Fellow Physician
Division of Pulmonary Medicine
The Children's Hospital of Philadelphia
Philadelphia, PA
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Bindu Ann George, 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
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Emily S. Gillett, MD, PhD, FAAP
Assistant Professor of Clinical Pediatrics
University of Southern California
Division of Pediatric Pulmonology and Sleep Medicine
Children's Hospital Los Angeles
Los Angeles, CA
Ch 99: Congenital Central Hypoventilation Syndrome

Suzette T. Gjonaj, 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
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Samuel B. Goldfarb, MD
Division of Pulmonary Medicine
The Children's Hospital of Philadelphia
Associate Professor of Clinical Pediatrics
University of Pennsylvania
Philadelphia, PA
Ch 77: Pulmonary Hypertension

Karen A. Hardy, MD
Clinical Professor of Pediatrics
Division of Pediatric Pulmonology, Asthma and Sleep Medicine
Stanford University
Stanford, CA
Ch 113: Airway Clearance Devices and Techniques

Christopher Harris, MD, FAAP
Director, Pediatric Pulmonology
Cedars-Sinai Medical Center
Health Sciences Clinical Professor
University of California, Los Angeles
David Geffen School of Medicine
Los Angeles, CA
Ch 1: The Pediatric Pulmonology History
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Kenan Haver, MD, FAAP
Division of Respiratory Diseases
Boston Children's Hospital
Assistant Professor of Pediatrics
Harvard Medical School
Boston, MA
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Kelsey Hawkins, PharmD
University of Washington Medical Center
Seattle, WA
Ch 37: Pharmacological Management: Anticholinergic Agents

Calvin Huynh, PharmD
Clinical Pharmacist, Critical Care Services
Assistant Clinical Professor, UCSF School of Pharmacy
UCSF Medical Center
San Francisco, CA
Ch 38: Pharmacological Management: Systemic Corticosteroids

Thomas G. Keens, MD, FAAP
Professor of Pediatrics, Physiology and Biophysics
Keck School of Medicine of the University of Southern California
Division of Pediatric Pulmonology and Sleep Medicine
Children's Hospital Los Angeles
Los Angeles, CA
Ch 99: Congenital Central Hypoventilation Syndrome
Ch 117: Diaphragm Pacing by Phrenic Nerve Stimulation

Katharine Kevill, MD, MHCDS, FAAP
Assistant Professor of Pediatrics
Division of Pediatric Pulmonology
Stony Brook University Medical Center
Stony Brook, NY
Ch 75: Hypersensitivity Pneumonitis

Christy Kim, 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
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T. Bernard Kinane, MD
Unit Chief, Pediatric Pulmonary
Massachusetts General Hospital for Children
Boston, MA
Ch 17: Pulmonary Sequestration

BreAnna Kinghorn, MD
Fellow, Pediatric Pulmonology
Seattle Children's Hospital, University of Washington School of Medicine
Seattle, Washington
Ch 41: Exercise-Induced Bronchoconstriction

Jeffrey M. Kintner, PharmD
Kelley-Ross Pharmacy Group
Clinical Assistant Professor
University of Washington
Seattle, WA
Ch 35: Pharmacological Management: Inhaled Corticosteroids

Georgia Koltsida, MD
Pediatric Pulmonologist
Athens, Greece
Ch 23: Pectus Deformities: Pectus Excavatum and Pectus Carinatum
Ch 72: Pneumothorax

Richard M. Kravitz, MD, FAAP
Professor of Pediatrics
Division of Pediatric Pulmonary and Sleep Medicine
Duke University
Durham, CA
Ch 93: Respiratory Disorders Associated With Cerebral Palsy and Neurodegenerative Diseases
Ch 94: Respiratory Disorders Associated With Neuromuscular Disease

Sankaran Krishnan, MD, MPH
Associate Professor of Pediatrics and Clinical Public Health
Associate Program Director, Pediatric Pulmonology
New York Medical College
Maria Fareri Children's Hospital at Westchester Medical Center
Boston Children's Health Physicians
Valhalla, NY
Ch 9: Oximetry and Capnography
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Sheila S. Kun, RN, BSN, BA, MS, CPN, FCCP
Nurse Care Manager, Home Mechanical Ventilation and Diaphragm Pacing Program
Division of Pediatric Pulmonology and Sleep Medicine
Children's Hospital Los Angeles
Los Angeles, CA
Ch 117: Diaphragm Pacing by Phrenic Nerve Stimulation

Oren Kupfer, MD
Assistant Professor of Pediatrics
Section of Pediatric Pulmonary Medicine
University of Colorado School of Medicine
Children's Hospital Colorado
Aurora, CO
Ch 56: Mycoplasma Pneumonia
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Kevin N. Kuriakose, MD, FAAP
Medical Director
Children's Lung, Asthma, and Sleep Specialists
Winter Pack, FL
Ch 18: Overinflation and Congenital Lobar Emphysema

Deborah R. Liptzin, MD, MS, FAAP
Associate Director Colorado chILD
Assistant Professor of Pediatrics
Section of Pediatric Pulmonology
University of Colorado School of Medicine
Aurora, CO
Ch 65: Complications of Pneumonia: Postinfective Bronchiolitis Obliterans

Amy Ly, PharmD
Department of Pharmacy
University of Washington Medical Center
Seattle, WA
Ch 34: Pharmacological Management: Long-Acting β_2-Adrenergic Agonists

Jonathan Ma, MD
Pediatric Pulmonary Fellow
Department of Pediatrics
Division of Pulmonary Medicine
Children's Hospital of Richmond at Virginia Commonwealth University
Richmond, VA
Ch 67: Cystic Fibrosis

Evans Machogu, MD, FAAP
Assistant Professor of Pediatrics
Division of Pediatric Pulmonology
Indiana University
Riley Hospital for Children
Indianapolis, IN
Ch 68: Cystic Fibrosis Newborn Screening
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Erin Walker Mackintosh, MD, FAAP
Fellow Pediatric Pulmonary and Sleep Medicine
Seattle Children's Hospital
University of Washington
Seattle, WA
Ch 44: Allergic Bronchopulmonary Aspergillosis in Asthma

Hannah Y. Mak, PharmD
University of Washington Medical Center
Seattle, WA
Ch 34: Pharmacological Management: Long-Acting β_2-Adrenergic Agonists

Juan C. Martinez, MD, FAAP
Medical Director, Cystic Fibrosis, Pediatric Pulmonary & Sleep Center
Joe DiMaggio Children's Hospital
Affiliate Assistant Professor of Clinical Biomedical Science
Florida Atlantic University
Hollywood, FL
Ch 80: Smoke Inhalation
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Stacey L. Martiniano, MD, MSCS
Assistant Professor of Pediatrics
Division of Pediatric Pulmonology
University of Colorado School of Medicine
Aurora, CO
Ch 59: Nontuberculous Mycobacterial Pulmonary Disease

Oscar Henry Mayer, MD
Division of Pulmonary Medicine
Medical Director, Pulmonary Function Testing Laboratory
The Children's Hospital of Philadelphia
Associate Professor of Clinical Pediatrics
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, PA
Ch 22: Chest Wall Deformities: Thoracic Insufficiency Syndrome
Ch 23: Pectus Deformities: Pectus Excavatum and Pectus Carinatum

Susanna A. McColley, MD, FAAP, FCCP
Associate Chief Research Officer
Stanley Manne Children's Research Institute
Attending Physician, Division of Pulmonary Medicine
Ann & Robert H. Lurie Children's Hospital of Chicago
Professor of Pediatrics
Northwestern University of Feinberg School of Medicine
Chicago, IL
Ch 21: Pulmonary Arteriovenous Malformations

David R. Naimi, DO, FAAAAI
Northwest Asthma and Allergy Center
Clinical Associate Professor of Pediatrics
University of Washington
Seattle, WA
Ch 39: Pharmacological Management: Anti–Immunoglobulin E Therapy

Manisha Newaskar, MBBS
Clinical Assistant Professor of Pediatrics
Department of Asthma, Allergy & Sleep Medicine
Stanford University
Palo Alto, CA
Ch 112: Tracheostomy Care and Complications

Brian P. O'Sullivan, MD
Professor of Pediatrics
Geisel School of Medicine at Dartmouth
Manchester, NH
Ch 16: Pulmonary Hypoplasia

Howard B. Panitch, MD
Director, Technology Dependence Center
Division of Pulmonary Medicine
The Children's Hospital of Philadelphia
Philadelphia, PA
Ch 116: Home Mechanical Ventilation

Derek Pepiak, MD, FCCP, FAAP
Senior Lecturer
Division of Pediatric Pulmonology
Ochsner for Children
New Orleans, LA
Ch 49: Papillomatosis

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
Ch 99: Congenital Central Hypoventilation Syndrome
Ch 117: Diaphragm Pacing by Phrenic Nerve Stimulation

Emma L. Peterson, PhD
Postdoctoral Fellow
Yale University
School of Public Health
New Haven, CT
Ch 96: Sleep Disorders: Evaluation and Prevention

Joseph Piccione, DO, MS, FAAP
Division of Pulmonary Medicine & Center for Pediatric Airway Disorders
The Children's Hospital of Philadelphia
Assistant Professor of Clinical Pediatrics
University of Pennsylvania School of Medicine
Philadelphia, PA
Ch 78: Vocal Cord Dysfunction

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
Ch 28: Nonpharmacological Management and Use of Complementary and Alternative Medicine Therapies for Asthma

Priya Prashad, MD
Pediatric and Adult Sleep Medicine
Division of Pediatric Pulmonology, Allergy, Immunology, and Sleep Medicine
Boston Children's Health Physicians
Maria Fareri Children's Hospital at Westchester Medical Center
New York Medical College
Valhalla, NY
Ch 100: Insomnia
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Clement L. Ren, MD, MS
Professor of Clinical Pediatrics
Associate Section Chief
Cystic Fibrosis Center Director
Section of Pediatric Pulmonology, Allergy, and Sleep Medicine
Indiana University School of Medicine
Riley Hospital for Children
Indianapolis, IN
Ch 5: Complete Pulmonary Function Tests
Ch 68: Cystic Fibrosis Newborn Screening
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Margaret Rosenfeld, MD, MPH
Professor of Pediatrics/Pulmonary
University of Washington School of Medicine
Seattle Children's Hospital
Seattle, WA
Ch 44: Allergic Bronchopulmonary Aspergillosis in Asthma

Bruce K. Rubin, MEngr, MD, MBA, FRCPC, FAAP
Jessie Ball duPont Distinguished Professor and Chair, Department of Pediatrics
Professor of Biomedical Engineering
Virginia Commonwealth University School of Medicine
Physician in Chief
Children's Hospital of Richmond at VCU
Richmond, VA
Ch 70: Primary Ciliary Dyskinesia

Paul H. Sammut, MB, BCh, FAAP, FCCP
Professor, Pediatric Pulmonology
University of Nebraska Medical Center
Children's Hospital and Medical Center
Omaha, NE
Ch 73: Pulmonary Aspiration: Foreign Bodies and Massive
Ch 74: Gastroesophageal Reflux and Recurrent Small-Volume Aspiration

Maria Teresa Santiago, MD
Chief, Division of Pediatric Pulmonary and Cystic Fibrosis Center
Cohen Children's Medical Center
Hofstra Northwell School of Medicine
New Hyde Park, NY
Ch 14: Tracheomalacia, Vascular Rings and Slings, and Bronchomalacia

Michael S. Schechter, MD, MPH, FAAP
Professor of Pediatrics
Chief, Division of Pediatric Pulmonary Medicine
Children's Hospital of Richmond at Virginia Commonwealth University
Richmond, VA
Ch 67: Cystic Fibrosis

Matthew Schefft, DO, MSHA, FAAP
Assistant Professor of Pediatrics
Division of Hematology, Oncology, and Stem Cell Transplantation
Children's Hospital of Richmond at VCU
Richmond, VA
Ch 95: Respiratory Disorders in Cancer Survivors

H. Joel Schmidt, MD, FAAP, FCCP
Professor of Pediatrics
Division of Pediatric Pulmonology
Virginia Commonwealth University
Richmond, VA
Ch 95: Respiratory Disorders in Cancer Survivors

James W. Schroeder, Jr, MD, FACS, FAAP
Pediatric Otolaryngology
Ann & Robert H. Lurie Children's Hospital of Chicago
Program Director – Pediatric Otolaryngology Head & Neck Surgery Fellowship
Associate Professor, Departments of Otolaryngology Head and Neck Surgery and Medical Education
Northwestern University Feinberg School of Medicine
Chicago, IL
Ch 10: Choanal Atresia
Ch 15: Tracheoesophageal Fistulas

John Norman Schuen, MD, FAAP
Pediatric Pulmonary and Sleep Medicine Physician
Chief, Pediatric Medical Specialties; Pediatric Pulmonary and Sleep Medicine
Helen DeVos Children's Hospital/ Spectrum Health Medical Group
Associate Professor of Pediatrics
Michigan State University – College of Human Medicine
Grand Rapids, MI
Ch 98: Obstructive Sleep Apnea

Sabah Servaes, MD, FAAP
Associate Professor of Radiology
University of Pennsylvania
The Children's Hospital of Philadelphia
Philadelphia, PA
Ch 6: Imaging

Girish D. Sharma, MD, FCCP
Professor of Pediatrics
Director Section of Pediatric Pulmonology and Rush Cystic Fibrosis Center
Rush University
Chicago, IL
Ch 46: Laryngitis
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Eugene R. Soares, MD, PhD, FAAP
Medical Director, The Center for Medical Genetics
An affiliate of Wentworth-Douglass Hospital
Dover, NH
Ch 66: Surfactant Metabolism Disorders, Including Surfactant Protein Deficiencies

Jennifer J. Soares, MD, FAAP
Assistant Professor of Pediatrics
Director Flexible Bronchoscopy Program
Medical Director, Aerodigestive Program
Pediatric Pulmonary and Sleep Medicine Division
Seattle Children's Hospital
University of Washington School of Medicine
Ch 66: Surfactant Metabolism Disorders, Including Surfactant Protein Deficiencies

Marianna M. Sockrider, MD, DrPH, FAAP
Associate Professor, Pediatric Pulmonology
Baylor College of Medicine
Chief of Pulmonary Clinics
Texas Children's Hospital
Houston, TX
Ch 19: Congenital Pulmonary Airway Malformation
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Saumini Srinivasan, MD, MS
Associate Professor of Pediatrics
University of Tennessee College of Medicine
Division of Pulmonary and Sleep Medicine
Le Bonheur Children's Hospital
Memphis, TN
Ch 83: Thoracic Tumors
Ch 88: Respiratory Considerations in Children With Congenital Heart Disease

Paul C. Stillwell, MD, FAAP
Senior Instructor, Department of Pediatrics
University of Colorado Anschutz Medical Campus
Pediatric Pulmonologist
Children's Hospital Colorado
Aurora, CO
Ch 54: Bacterial Pneumonia
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James W. Stout, MD, MPH, FAAP
Professor of Pediatrics
Division of General Pediatrics
University of Washington
Seattle, WA
Ch 4: Office Pulmonary Function Testing
Ch 32: Asthma Guidelines: Management of Chronic Asthma

Renee Benson Stromsness, MD, FAAP
Division of Pediatric Pulmonology
The Permanente Medical Group
Kaiser Permanente
Oakland, CA
Ch 112: Tracheostomy Care and Complications

David Stukus, MD
Associate Professor of Pediatrics
Division of Allergy and Immunology
Nationwide Children's Hospital and The Ohio State College of Medicine
Columbus, OH
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Jocelyn H. Thomas, PhD
Licensed Psychologist
Sleep Center
Division of Pulmonary Medicine
The Children's Hospital of Philadelphia
Philadelphia, PA
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Karen Kay Thompson, MD
Assistant Professor Pediatrics
Michigan State University
Division of Pediatric Pulmonology and Sleep Medicine
Helen DeVos Children's Hospital
Grand Rapids, MI
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Nadav Traeger, MD, FAAP, FCCP, DABSM
Associate Professor of Clinical Pediatrics
Director, Pediatric Sleep Medicine
Division of Pediatric Pulmonology, Allergy, Immunology, and Sleep Medicine
New York Medical College
Boston Children's Health Physicians
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Valhalla, NY
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Fernando Urrego, MD
Section Head, Pediatric Pulmonology
Ochsner for Children
New Orleans, LA
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Amarachi Uzosike, PharmD
Clinical Pharmacist
Surgical ICU/General Surgery Services
University of Washington Medical Center
Seattle, WA
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Jessica Van Beek-King, MD
Division of Pediatric Otolaryngology, Head and Neck Surgery
Anne and Robert M. Lurie Children's Hospital
Chicago, IL
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Timothy J. Vece, MD
Assistant Professor of Pediatrics
Division of Pediatric Pulmonology
University of North Carolina
Chapel Hill, NC
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Girish Vitalpur, MD, FAAP
Director, Allergy/Immunology Fellowship Program
Assistant Professor of Clinical Pediatrics
Section of Pediatric Pulmonology, Allergy, and Sleep Medicine
Riley Hospital for Children at Indiana University Health
Indiana University School of Medicine
Indianapolis, IN
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Karen Z. Voter, MD, FAAP
Associate Professor of Pediatrics
Interim Division Chief, Pediatric Pulmonology
University of Rochester School of Medicine
Rochester, NY
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Miles Weinberger, MD, FAAP
Professor Emeritus
University of Iowa
Visiting Clinical Professor of Pediatrics
University of California San Diego
San Diego, CA
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John Welter, MD
Assistant Professor of Pediatrics
Division of Pediatric Pulmonology, Allergy and Sleep Medicine
Boston Children's Health Physicians
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New York Medical College
Valhalla, NY
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Hiromi Yoshida, MD, MBA, FAAP
Pediatric Emergency Fellow
University of Washington
Seattle Children's Hospital
Seattle, WA
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Introduction

Respiratory symptoms, including sleep-related issues, are some of the most common reasons for children to seek medical attention, and most respiratory diseases are diagnosed and managed by primary care pediatricians. So, in a sense, every primary care pediatrician is a pediatric pulmonologist. With this book, our goal was to design a practical guide for the busy practitioner, building upon the first publication of the American Academy of Pediatrics (AAP) Section on Pediatric Pulmonology and Sleep Medicine (SOPPSM), *Pediatric Pulmonology*. Rather than another exhaustive pediatric pulmonology textbook, we chose to create a rapid reference guide, including useful and practical information about the many common respiratory disorders encountered in day-to-day pediatric practice, as well as a wide array of rarer pulmonary and sleep disorders your patients may be struggling with, even if their conditions are primarily managed by subspecialists.

It is our hope that this guide will prove useful to a wide range of health care providers, including physicians, nurses, nurse practitioners, physician assistants, respiratory therapists, physical and occupational therapists, dietitians, and pharmacists who contribute to the care of children with complex respiratory and sleep disorders. There are also many medical and surgical subspecialists who may be looking for a brief yet authoritative description of respiratory and sleep disorders in children.

We were fortunate that most of the original authors from *Pediatric Pulmonology* agreed to revise and update their topics in a new, streamlined format, and we were able to recruit outstanding authors for new topics not previously included. We have used a standard format for each chapter that captures the essential information, including clinical features, diagnostic considerations, management, expected outcomes, and when to refer or admit. Whenever possible, we have included practical resources for patients and families. The bulk of the work in putting this complex project together was done by an outstanding team of section editors chosen by the SOPPSM, and we greatly benefited from the experience and expertise of our AAP developmental editor, Chris Wiberg. The work has also benefited from models of prior AAP publications prepared by subspecialists for a primary care audience and from critical reviews of relevant sections by other AAP sections, committees, and councils.

Although we have spent most of our careers as subspecialists, it was the love of pediatrics that first led us to practice pediatric pulmonology, and one of the great joys we have had in practice has been collaborating with so many primary care practitioners and working together to care for infants, children, and adolescents with respiratory diseases. It is our hope that this volume will enhance your care of these patients and families, whom we serve together.

Dennis C. Stokes, MD, MPH, FAAP
Allen J. Dozor, MD, FCCP, FAAP

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Part I. Evaluation of Children With Respiratory Disease

Associate Editor: Julie P. Katkin, MD, FAAP

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Chapter 1

The Pediatric Pulmonary History

Christopher Harris, MD, FAAP

History of Present Illness

The medical history for pulmonary concerns may differ from a routine history because there is often a waxing and waning or a recurrent aspect to respiratory diseases in children. Elements of particular importance include

- Attention to the timeline of events
- Occurrence, timing, and relative severity of symptoms
- Past therapies and previous responses to them

Primary Concern

- Ask parents and care providers about the reason for the visit.
- If the patient is an older child or adolescent, make sure to ask him or her about the primary concern.
- The history may include the duration of the symptom or problem.

Presenting Problem or Symptom

- Onset (gradual vs sudden)
- Duration (acute vs chronic)
- Recurrence or persistence (Are there symptom-free intervals?)
  - Is there a specific time of day when symptoms appear or worsen?
  - Is there a seasonal appearance or recurrence of symptoms?
- Are there obvious physical findings when the symptom is present?
  - Retractions or accessory muscle use
  - Nasal flaring
  - Shortness of breath or impaired ability to speak, eat, or cry
- Factors that worsen or improve the symptom
- Inquire specifically about environmental tobacco smoke exposure and, among teenagers, personal tobacco use or vaping

Associated Symptoms

- Constitutional symptoms
  - Fever
  - Weight loss

- Ear, nose, and throat (ENT)
  - Snoring or observed apnea
  - Chronic rhinitis
  - Recurrent infections of the throat or sinuses
- Gastrointestinal system
  - Frequent vomiting or reflux
  - Dysphagia or poor control of oral secretions
- Dermatologic concerns
  - Eczema
  - Contact- or food-related dermatitis

Other Factors

- *Environmental:* It is well known that outdoor air pollutants can compromise lung health, especially in the young. Living in proximity to vehicle exhaust or areas of agricultural or waste burning may cause particularly severe symptoms for certain children.
- *Exercise*: Can the child keep up with peers when exercising? Does the child cough or wheeze during exercise?
- *Feeding*: Breast- or bottle-feeding can be a stress on the cardiopulmonary system in infants.

Past Medical History

- *Perinatal/neonatal history*: It is important to note pregnancy and delivery complications, as well as clinical course, in the delivery room and afterward.
  - Was the newborn stabilized and allowed to stay in the mother's room or admitted to the intensive care nursery?
  - Was the newborn intubated?
  - How long was mechanical ventilation required?
  - How long was oxygen needed by the baby?
- *Other medical conditions:* Inquire especially about cardiac diagnoses; neurological conditions; ENT conditions; and genetic abnormalities.
- *Surgical history:* Ask about a history of cardiac, ENT, and orthopedic procedures.
- *Other hospitalizations, emergency department visits, and urgent care visits:* Information gathered about previous care will provide some idea of the severity of acute or chronic illness.
- *Immunization history:* Given wariness among some parents to administer vaccines on schedule, make sure to ask about vaccination status.
- *Family history:* Are there family members with cystic fibrosis, primary ciliary dyskinesia, α_1-proteinase inhibitor deficiency, or other immunodeficiencies? Asthma and allergies have a genetic component, as well.

- *Social history:* Exposure to other young children in care and educational settings may be a source of frequent infections that cause respiratory symptoms. Pets in the home may be a source of allergic exposures for some children.
- *Travel history:* This may be important because certain fungal infections, such as histoplasmosis, coccidioidomycosis, or *Mycobacterium tuberculosis* infection, might be considered for some presentations.
- *Review of systems:* While inquiry into all organ systems is important, particular attention must be paid to cardiovascular, gastrointestinal, and neurological conditions.
- *Medication history:* Trials of various therapies must be reviewed. Knowing which classes of medications have been effective may provide clues to a diagnosis.
- *Allergies and reactions to medications:* Adverse effects of therapies should be considered as an important step in understanding a patient's complete history.

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Chapter 2

The Pediatric Pulmonary Physical Examination

Christopher Harris, MD, FAAP

Anthropometrics

- Important features of the physical examination pertinent to the respiratory tract begin with a careful assessment of the patient's anthropometrics. Children with chronic respiratory distress do not grow well, whether because of calories being expended with increased respiratory effort or because of chronic hypoxia.
- Weight and height must be measured accurately, particularly in children with concerns about failure to thrive.
- Accurate height measurement is also required for correct interpretation of spirometry data.

Vital Signs

- Respiratory rate varies widely, especially in the first several years of life. It is helpful to have charts of normal ranges available to determine if values are outside of the expected range.
- Pulse oximetry (see Chapter 9, Oximetry and Capnography) has become readily available in many practices and is now practically a fifth vital sign.
  - Pulse oximetry is most useful in ensuring that levels of oxygenation are adequate, especially during times of stress to the pulmonary system.
  - Staff must be well trained in the intricacies of probe application and interpretation of pulse waveforms.

Upper Airway

Ear, Nose, and Throat

- Chronic otitis may be a sign of immunodeficiency or primary ciliary dyskinesia.
- Nasal examination is key for determining whether the patient has allergic rhinitis.
  - Pale, edematous mucosa is the usual finding in allergic disease.
  - Nasal polyps should be noted because they are a key finding in the "aspirin allergy, nasal polyps, and asthma" triad, as well as in children with cystic fibrosis.

- Sinusitis may be tricky to diagnose, but experiencing purulent drainage for an extended period in conjunction with pain on palpation is highly suggestive of this diagnosis. Chronic sinus disease is found nearly universally in cystic fibrosis and primary ciliary dyskinesia.
- Oral examination is vital for evaluating causes of respiratory difficulty, particularly in infants. Inspection and palpation for cleft palate (including submucous clefts) must be performed because the risk for aspiration in these infants is high.
  - Macroglossia and tonsillar hypertrophy place patients at risk for the development of obstructive sleep apnea.
  - Assess the patient's voice, cry, and cough. The character of the voice and the cough provide clues regarding normal vocal fold function. Having normal vocal fold movement is key to ensuring that the airway is protected from aspiration.

Thorax

- Young infants have ribs that are not fully ossified. Therefore, with airway obstruction and increased airway pressure, the pliable portions of the thorax may be seen to retract. This may include the intercostal spaces and the areas above the sternum and clavicles. One should also inspect the subcostal region for retractions.
- Use of accessory muscles of respiration (sternocleidomastoid and scalene muscles) also indicates respiratory distress.
- Further inspection of the chest wall may demonstrate abnormalities of the bony structures of the thorax.
  - Congenital abnormalities of the thoracic cage (ribs, spine, and associated cartilages)
    - These are rare conditions.
    - Various dwarfisms and thoracic growth abnormalities (such as Jeune syndrome) are associated with smaller or altered thoracic configurations.
    - Restrictive lung disease should always be suspected in these children.
  - Pectus deformities
    - Pectus excavatum is caused by a depressed sternum, which results from the costochondral cartilages attaching to the sternum in an altered plane. This may be seen in Marfan or Poland syndrome.
    - Pectus carinatum is seen with a protruding sternum. This may occur directly over the sternum or over the costochondral junctions.
    - Controversy exists about functional difficulties in patients with either pectus excavatum or pectus carinatum defects.
      - ~ Referral for evaluation of lung function may be useful.
      - ~ Older children with severe pectus deformities may have problems with exercise. Referral for exercise testing may help rule out underlying exercise-induced bronchospasm as a contributor to this symptom.

    - Harrison grooves may develop in children with severe obstructive sleep apnea. These are horizontal indentations beneath the ribs at the site of diaphragmatic insertion.
- Percussion of the chest
  - Listen for a hyper-resonant, high-pitched note during pulmonary hyperinflation or a pneumothorax.
  - A short, low-pitched, and dull percussion note indicates that the lung is consolidated, as in lobar pneumonia or when the pleural space is filled with fluid.
- Auscultation of the chest may provide clues to multiple conditions involving the respiratory system. Some patients may have multiple sounds at examination. For example, a toddler with bronchiolitis may present with wheezes, crackles, and rhonchi.
  - Normal breath sounds may vary, depending on which area of the lung is being assessed. Vesicular breath sounds are heard over the lung periphery; they are low pitched, heard throughout inspiration, and continue one-third of the way into exhalation.
  - Bronchial breath sounds are not normally heard; they occur when a portion of the lung is no longer air filled. They are louder than vesicular breath sounds and last longer into exhalation.
    - Adventitial breath sounds
      - ~ Crackles are discontinuous, short sounds akin to the sound of Velcro opening. Crackles may be described as fine or coarse. Fine crackles are higher pitched and very short in duration; they are usually associated with interstitial lung disease or pulmonary edema. Coarse crackles are louder and usually found in pneumonia, cystic fibrosis, or other cases of bronchiectasis.
      - ~ Wheezes are high-pitched, continuous musical sounds often found in asthma or bronchiolitis. They are usually heard during expiration but, depending on the severity of airway obstruction, wheezes may also extend into inspiration.
      - ~ Rhonchi are low-pitched, continuous noises that are observed with secretions that have collected in the large airways. Rhonchi clear with coughing or suctioning of the airway.
      - ~ Pleural rubs are found when inflammation affects the linings of the lung. They sound similar to leather creaking when the patient inhales.

Cardiovascular System

- Diagnosing pulmonary hypertension on the basis of physical examination findings may be tricky because of nonspecific symptoms, such as exercise intolerance and shortness of breath. A useful sign of increased pulmonary arterial pressure is a loud second heart sound. One may also hear wide splitting of the second heart sound.

- As the right ventricle undergoes hypertrophy in association with increased resistance within the lung, it may strike the chest wall more forcefully, leading to right ventricular heave. When the heel of the hand is placed just to the left of the sternum, it may be lifted off of the chest by the increased force generated by the right ventricle.

Other Sounds

- Stertor is an upper-airway noise heard when obstruction of the naso-pharynx is found. It is usually caused by hypertrophy of the adenoids and/or tonsils.
- Snoring is upper-airway obstruction while asleep. It is caused by some combination of loss of upper-airway muscle tone, tonsillar and/or adenoidal hypertrophy, and anatomic crowding of the upper airway.

Back

- Severe scoliosis often is found in association with genetic syndromes.
- This often leads to a smaller than usual thoracic cage, which subsequently impairs lung growth (in the developing child) and lung expansion once full stature has been achieved.

Chapter 3

Environmental History

Harold J. Farber, MD, MSPH, FAAP

Introduction

- Respiratory irritants, toxins, and allergens may all contribute to a child's breathing problems.
- Problems can arise from indoor and outdoor sources; however, indoor exposures contribute most to respiratory symptoms in children.
- Exposures can occur in the home, at school, at day care, at play, or at work.

Types of Environmental Exposures

- *Irritants* stimulate airway inflammation by a mechanism of action not dependent on prior sensitization.
- *Toxins* directly cause damage to airway or lung tissues.
- *Allergens*
  - Airway inflammation is stimulated by an allergic reaction.
  - Mast cells, eosinophils, and immunoglobulin E (IgE) play important roles in allergic reactions.
  - The individual needs to have been previously sensitized (ie, allergic) for exposure to the allergen to be a problem. Seasonal allergies are uncommon prior to the second year after birth.
  - Relevant allergens are usually inhaled. It is unusual for a food allergy to cause only respiratory symptoms.
- *Hypersensitivity pneumonitis*
  - Organic and inorganic antigens can trigger a T cell–mediated reaction in sensitized persons.
  - Acute and subacute hypersensitivity pneumonitis can mimic pneumonia.
  - Chronic hypersensitivity pneumonitis can lead to pulmonary fibrosis and severe lung disease.
  - Implicated antigens include avian (bird) antigens, fungi and fungal spores, bacterial antigens, and low–molecular-weight chemicals.
  - This type of reaction is uncommon; however, it is important to recognize.

Identifying a Child's Relevant Environmental Exposures

- The most important part of identifying an environmental contribution to a child's respiratory illness is the history of relevant exposures.
- The patient or parent may not connect the relevant exposure to the respiratory symptom.
- Often it is not 1 exposure exclusively that contributes to the respiratory symptoms but a combination of several.

Respiratory Irritants and Toxins

Respiratory irritants and toxins can be a problem for anyone with respiratory symptoms. Previous sensitization is not needed.

Common Indoor Respiratory Irritants and Toxins

- Smoke from any source
  - Common sources of smoke include tobacco, other substances of abuse, incense, fireplaces, wood-burning stoves, barbecue grills, gas stoves, gas heaters, and kerosene heaters.
  - Sometimes the source of smoke may be from a friend or neighbor. Smoking in multi-unit housing involuntarily introduces smoke exposure to those who live in proximity to smokers.
  - Although not technically smoke from combustion, the emissions from electronic nicotine delivery systems (ENDS) contain chemicals that are known respiratory irritants and toxins.
- Strong chemicals
  - These include air fresheners, cleaning agents, and insecticides.
  - Chemicals used in hobbies or home remodeling can be irritants or a source of toxic exposures.
  - Ask about exposure to formaldehyde due to off-gassing from building materials, household products (glues, paints, finishes, etc), and products of combustion (from gas stoves, kerosene space heaters, tobacco smoke, etc).

Common Outdoor Respiratory Irritants and Toxins

- Air pollution worsens asthma problems. Important effects on lung function have been demonstrated for ozone, fine particulate matter, oxides of nitrogen, volatile organic compounds, and diesel smoke.

Allergens

- Allergens are only a problem for an individual who has been sensitized to them.
- Symptoms may be difficult to associate with the exposure if the exposure is continuous, such as in the home.
- Late-phase allergic reactions can occur 8–12 hours after exposure, creating further challenges in identifying the relevant exposure.

- Sensitization to common inhaled allergens can be determined by means of blood testing for allergen-specific IgE or allergy skin testing by a qualified allergist. Testing should focus on relevant respiratory (inhaled) allergens.

Common Indoor Respiratory Allergens

- House dust mites
  - — House dust mites thrive on humidity and shed skin, both of which are in ample supply in the bed and bedding.
  - — Dust mites also thrive in the fabric of carpets and upholstered furniture.
  - — Dust mites do not grow well in areas of low humidity (<40%).
  - — Dust mite allergy is common.
- Allergens including the dander (shed skin), saliva, and urine of furry or feathered pets may stay airborne for long periods. Rodent infestation can be an important asthma and allergy trigger.
- Cockroach secretions and droppings can be highly allergenic. In the inner cities, cockroach infestation combined with cockroach allergy contributes to poor asthma control.
- Indoor molds
  - — Molds grow in water-damaged or moist areas of the home.
  - — Mold contamination of basements, windowsills, shower stalls, bathroom carpets, and humidifiers is common.
  - — The most common indoor molds are *Aspergillus* and *Penicillium*.
  - — *Alternaria* can be found in both indoor and outdoor environments. Sensitization to *Alternaria* can be important because of its association with increased risk for near-fatal asthma.

Common Outdoor Respiratory Allergens

- Pollens of trees, grasses, and weeds can contribute to allergic respiratory symptoms.
- Outdoor molds grow on decomposing plant matter and leaf litter. Outdoor mold spore levels are generally highest in the autumn.

Guidance for Patients and Families

Respiratory Irritants

Smoke From Any Source

- Tobacco smoke
  - — The most effective solution is to help tobacco and ENDS users to stop using these products.
    - ▪ Tobacco dependence is a severe, treatable addiction. Pediatricians can recommend treatments for parents and/or caregivers to protect the health of the child. State-of-the-art approaches base intensity of treatment on severity of tobacco dependence and base medication adjustment on control of nicotine withdrawal. (See Chapter 27, Preventing and Treating Tobacco Dependence, for details.)

    - Refer parents for free telephonic tobacco cessation support at 1-800/QUIT-NOW (1-800/784-8669).
  - The next best approach is to keep the home and car free of smoke and ENDS emissions.
    - Restrict smoking to outdoors only and away from doors, windows, and children.
    - These measures can reduce a child's exposure to tobacco smoke; however, they are unlikely to eliminate it.
  - If a smoke-free home is not an option, use of high-efficiency particulate air (HEPA) filters in the home can reduce a child's exposure to smoke particulates.
- Cooking smoke
  - Ensure ventilation when cooking (use an exhaust fan and/or open a window).
- Other smoke
  - Identify and advise against the use of incense, fireplaces, and other burned substances in the home.
  - Be sure that exhaust from gas heaters is released outside the home.

Strong Chemicals in the Home

- Inquire about and advise against the use of air fresheners, strong-smelling cleaning agents, hair sprays, perfumes, and strong chemicals and paints used for hobbies.
- Provide information on less toxic products that can be used.
- Formaldehyde off-gassing from building materials and household products (glues, paints, finishes, etc) may be minimized as follows:
  - Open windows to bring fresh air indoors.
  - Try to avoid bringing formaldehyde-emitting products into the home.

Air Pollution

- Avoid outdoor activities on days when air pollution levels are high.
- Avoid living near a high-traffic road, if possible.
- Avoid leaf burning, wood fires, bonfires, charcoal fires, and so on.
- Advocate for implementation and enforcement of public policies to reduce air pollution.
- Advocate for school policies to prohibit the idling of diesel buses near schools.

Allergens

See Chapter 29, Allergic Rhinitis, for details.

Indoor Respiratory Allergens

- House dust mites
  - Encase your child's mattress, box spring, and pillow in allergen-proof covers.
  - Wash bedding in hot water weekly.

  - Minimize the number of stuffed animals on your child's bed, and wash them weekly in hot water. Alternatively, after an initial washing, they can be run through a dryer on high heat once a week.
  - Use a dehumidifier to reduce indoor humidity to <40% (may not be possible in very humid areas).
  - Air filters are not helpful for dust mite allergens, as they fall out of the air quickly.
  - Acaricides are not helpful for dust mites.
- Furry or feathered pets
  - The best approach is to remove the pet from the home or keep the pet outside only. It may take months for allergen levels to decrease after a pet is removed.
  - If removal of the pet is not an option, keep the pet out of the child's bedroom, bathe the pet weekly, and use HEPA filters, especially in the child's bedroom.
  - Balance the importance of the pet to the family against the severity of allergic symptoms. It is not necessary to advise removing pets from the home unless specific allergic sensitization is documented.
- Rodent infestation
  - Find and close holes in walls and around plumbing.
  - Do not leave food or water out.
  - If using rodent poisons, keep them well out of reach of children.
  - Consider calling an integrated pest management professional.
- Cockroach infestation
  - Attempt to locate and close off holes that insects are getting in through.
  - Do not leave food or water out.
  - If insecticide is needed, use bait stations, traps, powders, or gels rather than sprays.
  - Consider calling an integrated pest management professional.
- Indoor mold contamination
  - Find and fix water leaks.
  - Improve ventilation in bathrooms. Open a window or use an exhaust fan.
  - Clean moldy surfaces with bleach.
  - Severe water damage may require more extensive remediation.

Outdoor Respiratory Allergens

- Pollens
  - Know the pollen seasons in your area. In most areas, tree pollen levels are highest in the late winter to early spring, grass pollen levels are highest in the spring to summer, and weed pollen levels are highest in the late summer to fall.
  - Stay inside and keep windows closed when pollen levels are high—usually in the morning to midafternoon.

  - For individuals with specific sensitivities, immunotherapy may provide substantial relief from allergic symptoms.
- Outdoor molds
  - Stay inside and keep windows closed when mold spore levels are high. Outdoor mold spore levels are highest in the autumn.
  - Avoid playing in or raking leaf litter or decomposing plant matter.

When to Refer

- Refer the patient to a board-certified allergist
  - If skin testing is needed to identify sensitization to inhalant allergens.
  - If immunotherapy is being considered.
- Refer the family for a home environmental assessment
  - If an environmental trigger is suspected for a severe lung disease but not identifiable from the history alone
  - For additional help with identifying and reducing exposure to relevant environmental triggers
  - If the local health department or the child's managed care program care manager may be able to arrange for the home assessment, especially if the child has severe lung disease. Quality of services, if available, can vary. Pediatricians should be aware of available resources in their community. To avoid adverse incentives, it is prudent to not have the same companies perform both assessment and remediation.
  - If a home assessment visit cannot be accomplished, asking for pictures of the home (indoor and outdoor) may help to identify potential environmental triggers.
- Refer the family to social services or relevant community resources if needed to address problems with housing quality or homelessness.

Resources for Families

- AirNow: Air Quality Monitoring (U.S. Environmental Protection Agency). www.airnow.gov
- Formaldehyde (U.S. Environmental Protection Agency). www.epa.gov/formaldehyde
- Manage Environmental Asthma Triggers (U.S. Environmental Protection Agency). www.epa.gov/asthma/manage-environmental-asthma-triggers
- National Allergy Bureau (American Academy of Asthma, Allergy, and Immunology). www.aaaai.org/global/nab-pollen-counts?ipb=1

Clinical Pearls

- How you breathe starts with what you breathe. Routinely inquire about a child's environmental exposures when treating respiratory disease.
- Respiratory disease can be caused or exacerbated by irritants (does not require prior sensitization) and allergens (only after prior sensitization).
- Relevant exposures can occur at any location the child frequents, including home, day care, school, recreation facilities, and work.
- Tobacco dependence is a treatable, severe chronic illness. Pediatricians should inquire about and address parent and/or caregiver tobacco dependence to protect the child's health.

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Chapter 4

Office Pulmonary Function Testing

James W. Stout, MD, MPH, FAAP

Introduction

- Spirometry is an office test used to assess lung function—specifically, the flow and volume of a patient's full and forceful inhaled and exhaled breath, compared to normal tidal breathing.
- In primary care, the focus is typically on the exhaled breath to be able to diagnose and manage obstructive lung diseases, rather than more sophisticated testing, such as lung volume measures and carbon monoxide diffusing capacity.
- In pediatrics, spirometry is used most commonly for the diagnosis and ongoing management of asthma.
  - However, spirometry does not provide information about the remaining (residual) volume of air in the lungs—in other words, a reduced total lung volume—which is required for diagnosing restrictive lung diseases.
  - A plethysmograph, also known as a *full-body box,* is required to measure this residual volume to determine total lung capacity and should be used in a pulmonary function testing laboratory, with supervision of testing and interpretation of findings performed by a specialist.

Spirometry in the Management of Asthma: The Clinical Case

Spirometry permits an objective measurement of the *degree* of airway obstruction (impairment and risk). This is important because

- Patients' perceptions of obstruction are notoriously inaccurate.
- Clinically significant obstruction can be present even when the chest appears to be clear at physical examination.
- Clinical symptoms alone will lead to underestimation of asthma severity approximately 30% of the time in primary care.
- Peak flow testing alone is highly variable, is not a very sensitive measure of obstruction, and is no longer recommended for diagnosis. However, it may have a role in monitoring.

Use of Spirometry for Asthma Care in the Primary Care Setting

- Use of spirometry enables accurate diagnosis and management of asthma.
- Roughly half of U.S. primary care offices report using spirometry for pediatric patients with asthma, representing a significant gap in usage.
- Spirometry should not be performed during an asthma exacerbation but rather when patients are in their usual state of health.
- Spirometry is easy to perform poorly, but with training and feedback, it is not hard to do well.
- Spirometry is a potent tool for improving planned asthma care, thus reducing morbidity and lowering hospitalization rates and reducing emergency department visits.
- Spirometry has several indications in primary care pediatrics. These include
  - Diagnosis and severity assessment of asthma in patients ≥5 years of age
  - Follow-up of asthma control (especially when changing medications)
  - Evaluation of chronic cough
  - Evaluation of shortness of breath and other chronic respiratory complaints
  - Evaluation of baseline lung function in a patient with exercise-induced bronchospasm
- Routine use of good-quality office spirometry can improve provider and patient satisfaction with care and should also lead to better health outcomes.
- Spirometry is a reimbursable procedure. The *Current Procedural Terminology*® codes are as follows:
  - 94010 for simple office spirometry
  - 94060 for pre- or postbronchodilator spirometry

Spirometry and the Expert Panel Report 3, or EPR-3, Asthma Guidelines

Establishing asthma severity and control is the foundation of preventive asthma care.

Assessing Asthma Severity

- Assessment is based on
  - Age
  - Impairment (frequency and intensity of symptoms, lung function, functional limitations over the past 2–4 weeks)
  - Risk (exacerbations over the past year)

- Levels of severity
  - Intermittent
  - Persistent and mild
  - Persistent and moderate
  - Persistent and severe

Assessing Asthma Control

- Control is assessed on the basis of severity metrics obtained over time, once treatment is initiated.
- Metrics include
  - Age
  - Impairment (frequency and intensity of symptoms; lung function; functional limitations over the past 2–4 weeks; use of a questionnaire for patients and parents, depending on the child's age, such as the Childhood Asthma Control Test ("C-ACT") for children 4–11 years of age and the Asthma Control Test ("ACT") for children aged 12 through adulthood
  - Risk (exacerbations, reduced lung growth, adverse effects of medications)
- Levels of control
  - Well controlled
  - Not well controlled
  - Poorly controlled

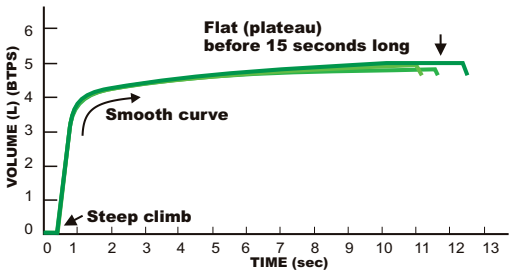
How to Use Spirometry in Primary Care

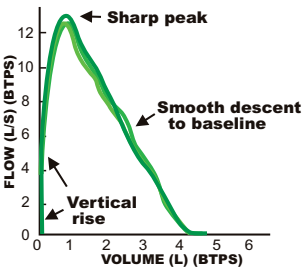
- The goal of spirometry in a general pediatrician's office should be to identify and manage reversible airway obstruction, which defines asthma.
  - Is the test acceptable and reproducible? (Figure 4-1, Figure 4-2)
  - Is lung function normal? (Figure 4-3)
  - If not, is there an obstructive pattern? (Figure 4-4)
  - If obstructed, is it reversible? (Figure 4-5)
  - Is lung function suspicious for something besides obstruction? (Figure 4-6)
    - If so, refer the patient to a specialist.
- In general, in primary care
  - Pre- and postbronchodilator office spirometry only needs to be performed once to establish the reversibility of lung function, supporting the diagnosis of asthma.
  - The forced expiratory maneuver (where obstruction is found) should be the focus of testing. If a chronic inspiratory problem is suspected, the forced inspiratory maneuver and consequent workup are best addressed in a specialist's office.

Get Valid Spirometry Results EVERY Time

A Valid Test has:
3 or More Good Curves
and Repeatable FVC and FEV1*

*Use most current American Thoracic Society/ European Respiratory Society (ATS/ERS) standards

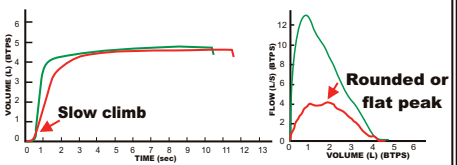




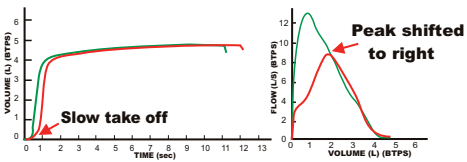
KEY
Green = Good Curve
Red = Error

HOW TO CORRECT TEST ERRORS

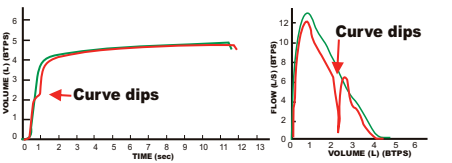
Poor Initial Blast
Coach: Blast air out HARDER



Hesitation; Slow Start; Large Extrapolated Volume
Delete Curve; Coach: Blast FASTER



Cough in First Second
Delete Curve; Correction: Try a drink of water



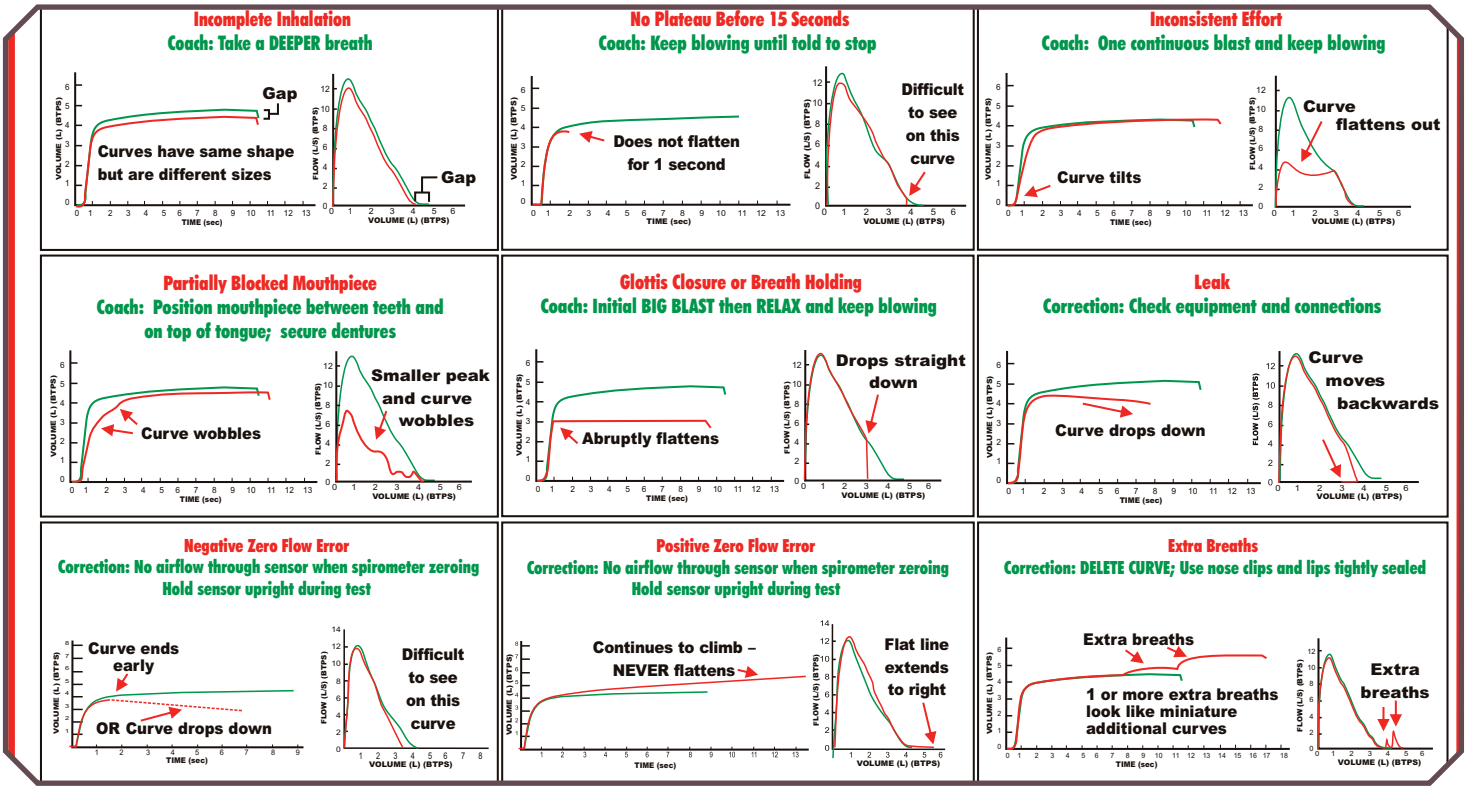


Figure 4-1. The National Institute for Occupational Safety and Health (NIOSH). Get Valid Spirometry Results Every Time. NIOSH publication no. 2011-135. www.cdc.gov/niosh/docs/2011-135. Accessed November 12, 2013.

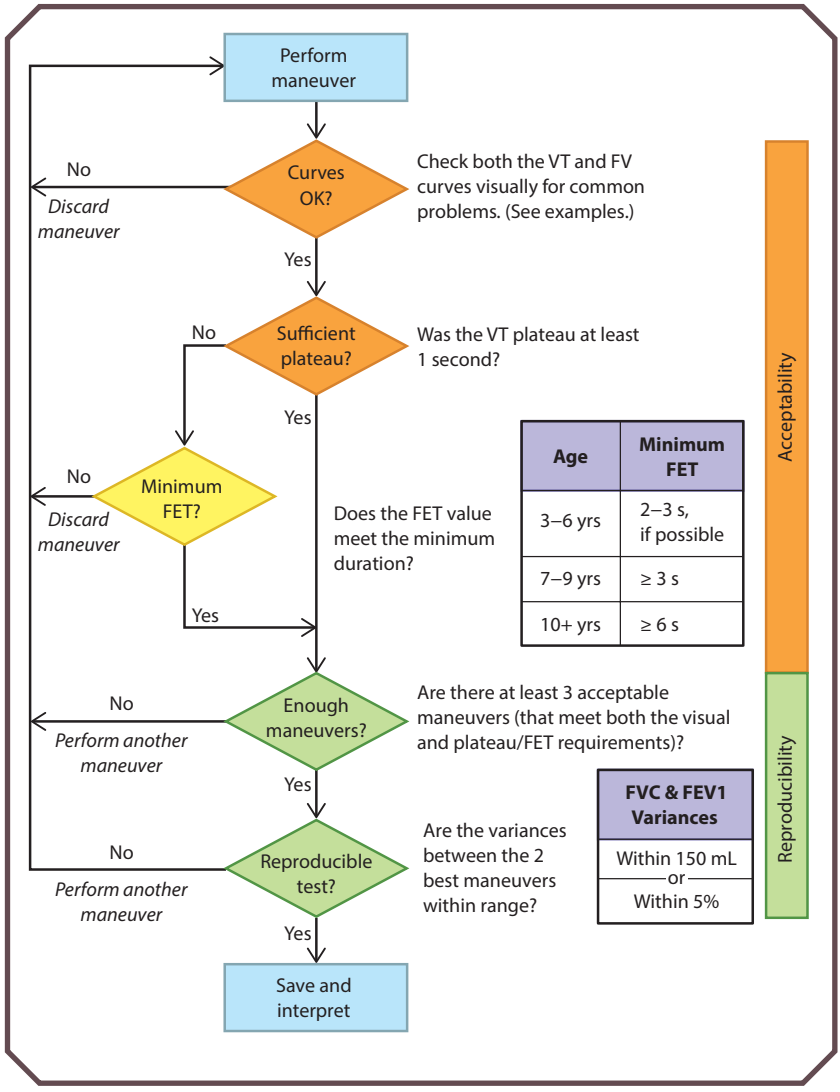


Figure 4-2. Spirometry 360. Spirometry test algorithm. Interactive Medical Training Resources. www.spirometry360.org/spiro360resources. Published January 9, 2013. Accessed November 12, 2013. FET = forced expiratory time, FEV1 = forced expiratory volume in 1 second, FV = flow volume, FVC = forced vital capacity, VT = volume-time.

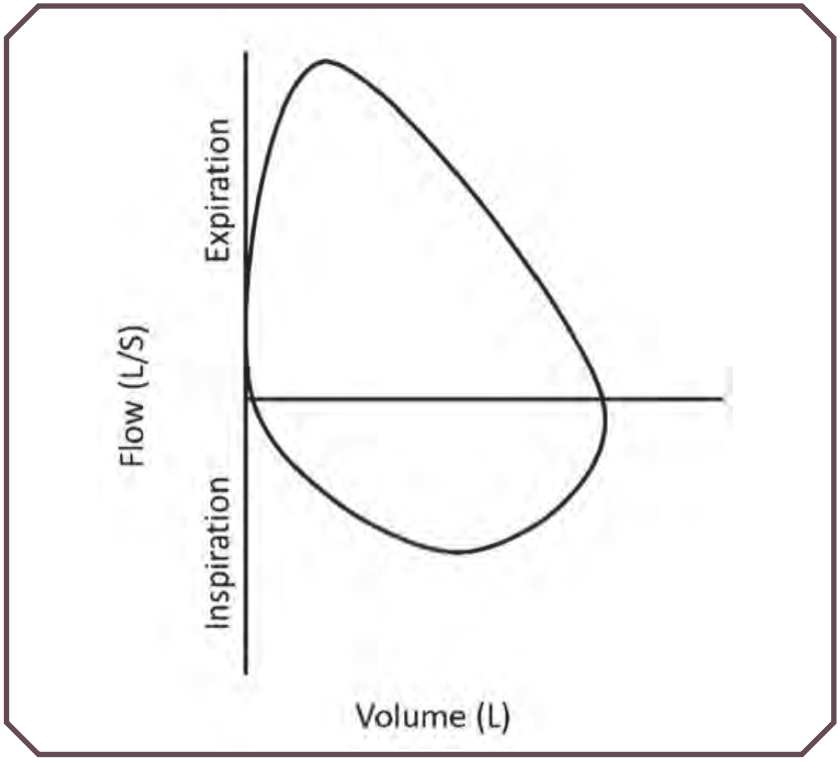
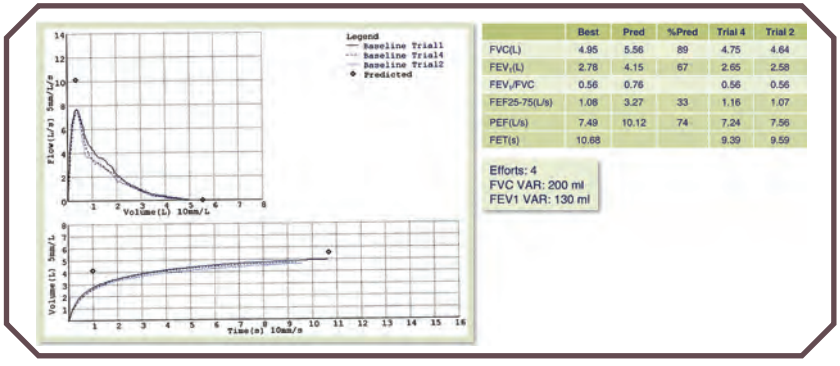


Figure 4-3. Normal flow volume loop from a pediatric patient. From Link HW. Pediatric asthma in a nutshell. *Pediatr Rev*. 2014;35(7):287–298.

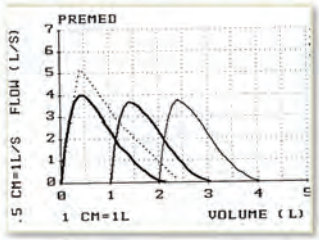


	Best	Pred	%Pred	Trial 4	Trial 2
FVC(L)	4.95	5.56	89	4.75	4.64
FEV_1(L)	2.78	4.15	67	2.65	2.58
FEV_1/FVC	0.56	0.76		0.56	0.56
FEF25-75(L/s)	1.08	3.27	33	1.16	1.07
PEF(L/s)	7.49	10.12	74	7.24	7.56
FET(s)	10.68			9.39	9.59

Figure 4-4. Results from a 16-year-old male adolescent with asthma, without wheeze. FEF = forced expiratory flow, FET = forced expiratory time, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, PEF = peak expiratory flow, VAR = variability, %Pred = percentage predicted.

Pre	Best	%Pred
FVC(L)	2.14	87
FEV_1(L)	1.73	77
FEV_1/FVC	0.81	
FEF25-75(L/s)	1.67	61
PEF(L/s)	4.21	79
FET(s)	7.67	
Efforts: 5		
FVC VAR: 78ml		
FEV1 VAR: 52ml		

Pre	Best	%Pred	%Chg
FVC(L)	2.34	95	9
FEV_1(L)	1.96	87	12
FEV_1/FVC	0.84		3
FEF25-75(L/s)	2.13	77	26
PEF(L/s)	4.16	78	-1
FET(s)	6.46		
Efforts: 6			
FVC VAR: 82ml			
FEV1 VAR: 55ml			



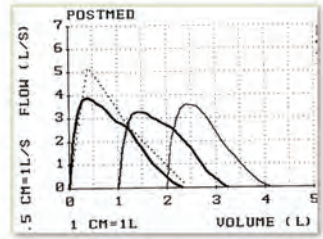
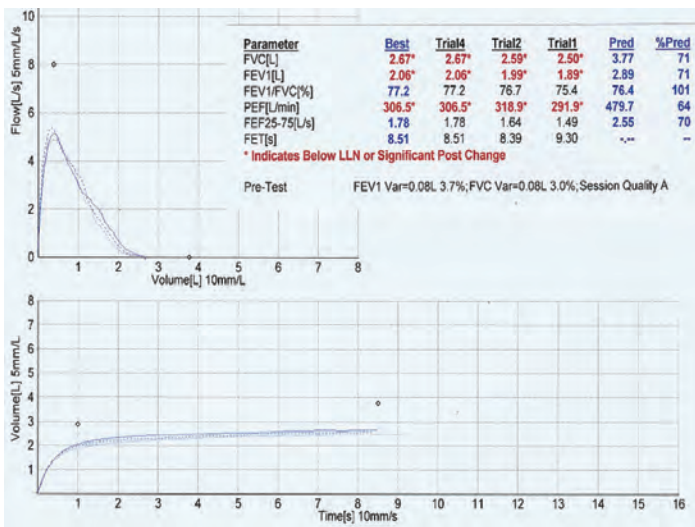


Figure 4-5. Results from a 12-year-old male patient who had no history of asthma but had recurrent croup as an infant and now has the occasional "chest cold." He has had a chronic daily morning cough for 1–2 months but is otherwise healthy. FEF = forced expiratory flow, FET = forced expiratory time, FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity, PEF = peak expiratory flow, VAR = variability, %Chg = percentage change, %Pred = percentage predicted.



Parameter	Best	Trial4	Trial2	Trial1	Pred	%Pred
FVC[L]	2.67*	2.67*	2.59*	2.50*	3.77	71
FEV1[L]	2.06*	2.06*	1.99*	1.89*	2.89	71
FEV1/FVC[%]	77.2	77.2	76.7	75.4	76.4	101
PEF[L/min]	306.5*	306.5*	318.9*	291.9*	479.7	64
FEF25-75[L/s]	1.78	1.78	1.64	1.49	2.55	70
FET[s]	8.51	8.51	8.39	9.30	-.--	--

* Indicates Below LLN or Significant Post Change

Pre-Test FEV1 Var=0.08L 3.7%;FVC Var=0.08L 3.0%;Session Quality A

Figure 4-6. Results from a 16-year-old female patient who experiences shortness of breath on exertion, without wheezing. Further specialist evaluation is indicated to explore whether low forced vital capacity represents a restrictive condition. FEF = forced expiratory flow, FET = forced expiratory time, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, LLN = lower limit of normal, PEF = peak expiratory flow, Pred = predicted, Var = variability, %Pred = percentage predicted.

- Changes to make in practice
  - — Get a spirometer; numerous portable spirometers exist that meet American Thoracic Society standards. Additionally, consultation with local pulmonary specialists or a pediatric pulmonary laboratory may be useful.
  - — Acceptable spirometry can be performed by office personnel, but training is necessary.
  - — Emphasize support staff training. Usually, a limited number of interested and motivated staff should be involved in testing.

Available Training Resources

- Hands-on workshops
- In-person 2-day National Institute for Occupational Safety and Health training
- Local pulmonologist and/or respiratory therapist (the American Association for Respiratory Care website [www.aarc.org] can help to locate providers)
- Spirometry 360 online training and feedback. www.spirometry360.org

Resources for Families

- How to Perform Spirometry: A Video Guide (San Francisco Asthma Task Force). www.spirometry360.org/otherresources

Clinical Pearls

- Peak flow testing is inadequate for assigning a diagnosis of asthma, although it may still have a role in home monitoring for patients established to have asthma.
- As many as 1 in 3 children and teens with asthma show obstruction at spirometric testing yet report lack of symptoms.
- Spirometry should not be performed for diagnostic purposes during an asthma exacerbation in the primary care setting.
- Obstructive lung disease is common, and restrictive lung disease is rare in pediatric populations; suspected restriction should be further evaluated by a specialist.
- Obstructive lung disease is identified in the expiratory limb of the flow volume loop, so this should be the focus of spirometry in primary care.
- Spirometry is a technique-dependent procedure that typically requires training and feedback regarding performance and clinical interpretation.

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Chapter 5

Complete Pulmonary Function Tests

Clement L. Ren, MD, MS

Introduction

- Assessment of respiratory function is an important component of the care of children with pediatric respiratory disease.
- There are multiple options available for pulmonary function tests (PFTs), but in most cases, primary care physicians will use spirometry, with or without a bronchodilator.
- However, it is still useful for any clinician involved in the care of children with respiratory disease to be familiar with other PFTs.

Lung Volumes

- The space in the lungs can be divided into several different volumes and capacities (capacities are the sums of 2 or more volumes). Figure 5-1 shows the subdivision of lung volumes and capacities.
- Some of the important subdivisions include the following.
  - *Tidal volume* is the volume inspired and expired with each normal breath.
  - *Vital capacity* is the maximal volume that can be expired after starting at full inspiration. If this is done during forced expiration, then it is called the *forced vital capacity (FVC)*.
  - *Residual volume* is the amount of gas remaining in the lungs at the end of a vital capacity maneuver. Because of collapse of the small airways during expiration and the compliance of the chest wall, there will always be some residual volume remaining in the lungs, even after a maximal forced expiratory maneuver.
  - *Total lung capacity (TLC)* is the sum of vital capacity and residual volume, representing the maximal volume of gas that can be held in the lungs at end-inspiration.
  - *Functional residual capacity (FRC)* is the volume of gas in the lungs at the end of relaxed expiration.

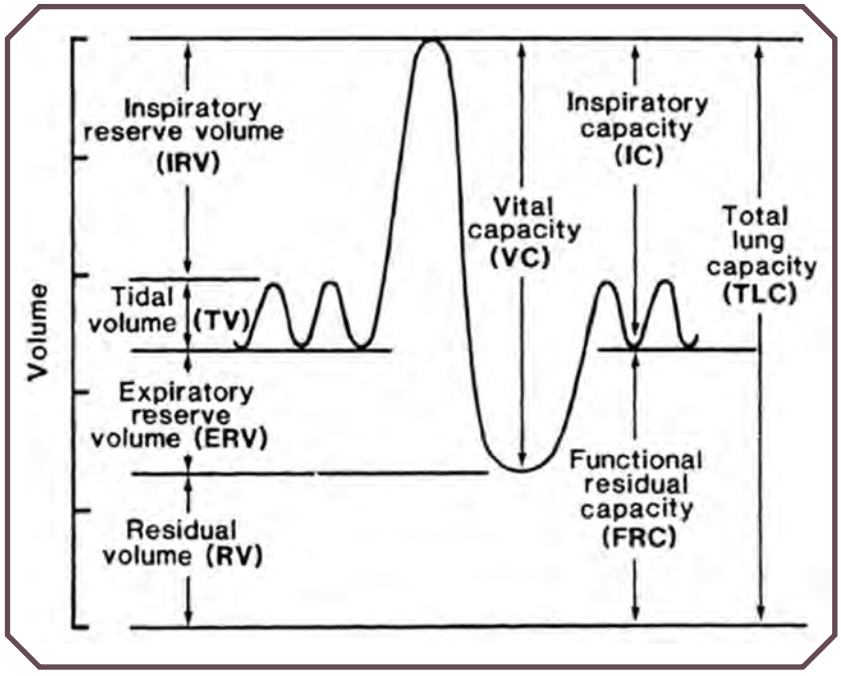

Figure 5-1. The subdivisions of lung volume. From Loughlin GM, Eigen H, eds. *Respiratory Disease in Children: Diagnosis and Management.* Baltimore, MD: Williams & Wilkins; 1994:79.

Spirometry

- Spirometry, the most commonly used PFT, involves measurement of flows and volumes during a maximal forced expiratory maneuver.
- Although spirometry is a simple test, quality data acquisition is still critical to ensure that the test results can be appropriately interpreted.

Spirometric Measurements

- The following are the most commonly used measurements obtained through spirometry. There are other values that can be reported, but they add little to clinical management.
  - FVC is the forced vital capacity.
  - FEV_1 is the volume forcefully exhaled in the first second.
  - FEV_1/FVC ratio is the emptying constant of the respiratory system.
  - $FEF_{25\%-75\%}$ is the forced expiratory flow between 25% and 75% of vital capacity. Because $FEF_{25\%-75\%}$ is dependent on FVC, it is much more variable than FEV_1 and FVC. $FEF_{25\%-75\%}$ was previously thought to reflect small-airway flow, but in reality, it is dependent on many other factors; it should not be considered a direct measure of small-airway function. Additionally, it may not provide any additional information beyond that obtained with FEV_1 and FVC.

Interpretation of Spirometry Results

- Traditionally, lung diseases have been divided into 2 categories: obstructive and restrictive.
- Obstructive diseases are more commonly encountered and are characterized by reduced flow rates. Examples include asthma and cystic fibrosis.
- Restrictive diseases are characterized by reduced lung volumes, because of either musculoskeletal factors or decreased lung compliance. Examples of restrictive disease include kyphoscoliosis and interstitial lung disease.
- Table 5-1 summarizes the usual PFT findings in obstructive versus restrictive disease.
- In children, FEV_1 is frequently normal in obstructive diseases early on in the disease process, and FEV_1/FVC ratio is a more sensitive measure of obstruction.
- FEV_1/FVC ratio varies with age, and it can be as high as 0.85 in young children and as low as 0.65 in elderly patients.
  - — Therefore, interpreting the FEV_1/FVC ratio requires identifying the lower limit of normal based on the patient's age, sex, race, and height.
  - — A ratio less than the 5th percentile (the lower limit of normal) or >2 standard deviations (SDs) below the mean for age signifies obstruction.

Table 5-1. Typical Pulmonary Function Test Findings in Obstructive Versus Restrictive Disease

Disease Type	FVC	FEV_1	FEV_1/FVC	Total Lung Capacity	Residual Volume
Obstructive	Normal or ↓	↓	↓	↑	↑
Restrictive	↓	↓	Normal	↓	↓

FVC is usually normal in obstruction—especially in mild obstruction—but with severe obstruction, it may be reduced. FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Reference Equations

- Just as with growth curves, the values obtained with spirometry and other PFTs must be normalized for the patient's age, sex, race, and height.
- The selection of reference equations can have a substantial effect on the interpretation of PFT results.
  - — Older reference equations included relatively small numbers of nonwhite subjects and tended to cause overestimation of values in younger, shorter children.
  - — Some equations did not include data on subjects younger than 8 years, and extrapolation below that age resulted in substantial error.
  - — Other equations contained discontinuities in the adolescent age range.
- More recently, the Global Lung Function Initiative has developed reference equations that span the age range of 3 to 95 years and include both male and female subjects and multiple racial groups.

- The Global Lung Function Initiative reference equations should be used whenever possible, but not all commercial spirometry devices contain them yet.
- According to historical convention, spirometry results are often reported as the percentage predicted of the mean—that is, an FEV_1 of 90% predicted means that the value is below the mean of patients matched for height, race, and sex.
- While percentage predicted provides a useful comparison to the normal mean, the threshold for the lower limit of normal will depend on the variability of the spirometric measurement in question.
  - For example, an FEV_1 of 80% predicted is approximately 2 SDs below the mean, and values below that are considered abnormal.
  - In contrast, measurements such as $FEF_{25\%-75\%}$ are much more variable, and values of 70% or even 65% predicted may still fall within 2 SDs of the mean.
  - It is therefore important to be familiar with the variability of the measurement when interpreting percentage predicted spirometric values.
- An alternative to using percentage predicted is to report results as the number of SDs (z scores) from the mean predicted value.
  - This takes into account the variability of the different measurements, as well as the covariates of age, sex, and height.
  - A z score of 0 corresponds to the mean predicted value, and a z score of –1.645 corresponds to the fifth percentile, often taken as the lower limit of normal.

Quality Control

- Acceptable spirometric data require that the patient inspires completely to TLC, exhales fully to residual volume, and maintains maximal effort throughout the expiratory maneuver.
- This latter element ensures that flow limitation is achieved, which in turn reduces the variability of the measurements.
- The quality of a patient's spirometric maneuvers can be determined by analyzing the flow volume and volume-time curves that are generated.
- Figure 5-2 shows an example of acceptable flow volume and volume-time curves.
- Common reasons for unacceptable spirometry results are shown in Figure 5-3 and include
  - Incomplete expiration or early termination. This can result in underestimation of FVC.
  - Poor start of test. The patient may not have started with maximal effort.
  - Glottic closure. Some patients may involuntarily abduct their vocal cord during forced expiration, resulting in airflow limitation.
  - Inconsistent expiratory effort. The patient failed to maintain maximal effort throughout the forced expiratory maneuver.

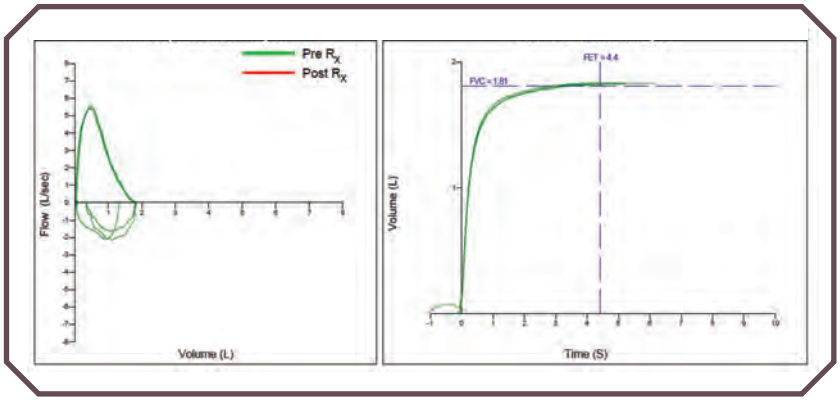

Figure 5-2. An acceptable spirogram. The volume-time graph (right panel) depicts the volume of air exhaled over the duration of the exhalation effort. It shows a good start of the test, with a rapid increase in volume at the beginning of exhalation, and there is complete exhalation, as demonstrated by the plateau in volume nearing the end of exhalation. The flow-volume curve (left panel) shows the rate of air flow compared to the volume of air that is displaced; expiration is demonstrated above the x-axis, and inspiration is shown below the x-axis. This curve has a nice, sharp peak expiratory flow. Flow continues throughout the expiratory maneuver and does not terminate abruptly. Note how all the curves overlay each other completely, demonstrating excellent reproducibility. FET = forced expiratory time, FVC = forced vital capacity, R_x = medication.

Reproducibility

- In addition to quality data, the other requirement for acceptable spirometry is reproducibility, defined as a minimum of 3 maneuvers with ≤10% difference between FVC and FEV_1.
- For young children 3–5 years old, 2 reproducible maneuvers can be acceptable.

Age

- In general, 6 years is the threshold at which most clinicians believe that children can perform acceptable spirometry.
- However, some young children are able to meet the requirements for high-quality spirometry data, whereas there are children >6 years of age who are still not able to perform maximal forced expiratory maneuvers.

Peak Flow Meters

- Peak expiratory flow (PEF) reflects flow at a single point in the flow-volume curve that occurs early in expiration.
- Measurement of PEF can be performed by using much simpler equipment than a spirometer.
- PEF is highly effort dependent, so low values may not be specific for obstruction.

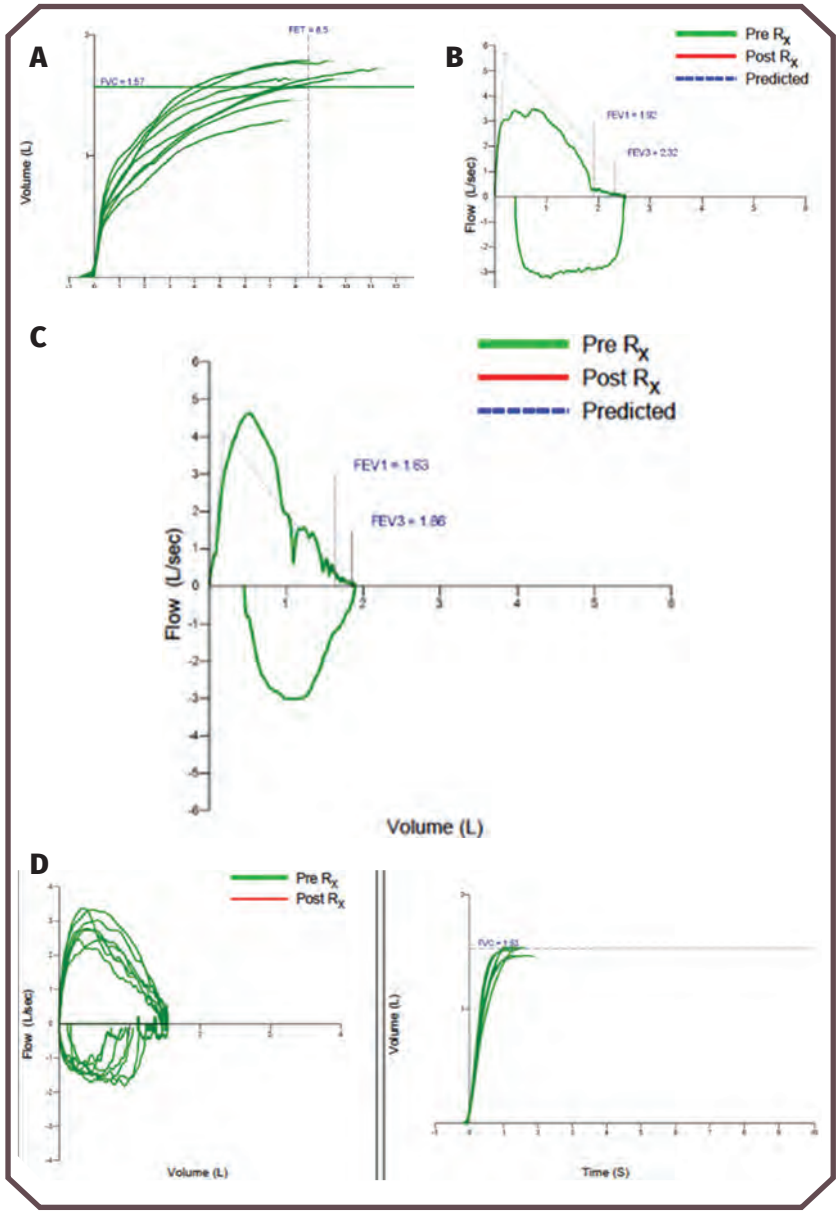

Figure 5-3. Examples of unacceptable spirometry tests. A. Poor start of test. Note also how the curves are not reproducible. B. Glottic closure. Note how the early part of the expiratory portion of the flow-volume curve is flattened. C. Coughing during the forced expiratory maneuver. This accounts for the jagged lines in the flow-volume curve. D. Early termination. Note how the flows drop abruptly in the flow-volume curve. A clear plateau cannot be seen on the volume-time curve. FET = forced expiratory time, FEV1 = forced expiratory volume in 1 second, FEV3 = forced expiratory volume in 3 seconds, FVC = forced vital capacity, R_x = medication.

- PEF can be relatively preserved in the presence of obstruction; normal values lack sensitivity.
- The National Heart, Lung, and Blood Institute Asthma Guidelines recommend considering the use of PEF meters for some patients who have trouble sensing airflow obstruction or prefer objective measures of expiratory flow.
- However, this recommendation was based on the lowest level of evidence quality (category D), which represents panel consensus judgment in the absence of published data supporting the recommendation.

Exercise Testing

- Exercise testing can be useful in the evaluation of dyspnea to rule out a cardiopulmonary limitation to physical activity or to identify the presence of exercise-induced bronchoconstriction (EIB).
- Patients can exercise on a treadmill or cycle ergometer; the latter allows for more precise calculation of power output.
- By measuring expired CO_2 and O_2 consumption during a graded increase in exercise, the maximal oxygen consumption (VO_{2max}) and anaerobic threshold can be calculated; a low VO_{2max} is evidence of deconditioning.
- EIB may be assessed by using serial spirometry after a rapid increase in work intensity; EIB is demonstrated by ≥20% decrease in FEV_1 after maximal exercise capacity has been achieved.

Gas Dilution

- Spirometry cannot be used to measure the residual gas remaining in the lungs at the end of the forced expiratory maneuver; therefore, it cannot be used to measure residual volume, FRC, or TLC. To measure FRC (and calculate other volumes), other methods must be used.
- Gas dilution methods are used to measure the dilution of a tracer gas—usually helium—by the gas in the lungs.
- By starting with a known concentration of helium and measuring the concentration after mixing with the gas in the lungs during quiet tidal breathing, the volume needed to dilute the concentration can be calculated.
- Alternatively, the resident nitrogen in the lungs can be washed out by inspiring 100% O_2 and dividing the total expired volume needed to wash out all the nitrogen by the concentration difference.
- Because gas dilution techniques require complete mixing of all the lung units with the tracer gas, they can potentially underestimate lung volumes owing to areas of the lung that are poorly ventilated or obstructed.

Body Plethysmography

- Body plethysmograpy allows measurement of the entire volume of the lung, regardless of whether there are areas of poor or no ventilation.
- Body plethysmograpy relies on Boyle's law, which states that the product of pressure and volume is a constant, assuming the temperature is stable.

- To perform body plethysmograpy, patients pant (breathe very quickly) against a closed tube, generating changes in pressure and volume that can be used in the application of Boyle's law.
- Body plethysmograpy requires a large, airtight chamber or box in which the patient can be contained. This equipment is expensive and requires regular maintenance and calibration.
- Some degree of coordination is also required to generate pants that are not too fast or slow and that do not result in overly large pressure swings. Many young children cannot adequately perform this maneuver.

Bronchoprovocation

- The hallmark of asthma is bronchial hyperresponsiveness (BHR), which is a tendency for airways to more easily constrict in response to a bronchoconstrictor.
- BHR can be quantitatively determined by having patients inhale progressively higher concentrations of the bronchoconstrictive agent methacholine.
- The PC_{20} is the provocative concentration of methacholine required to lower the FEV_1 by 20% from baseline.
- The lower the PC_{20}, the more sensitive the airways are to methacholine (increased BHR is present).
- A PC_{20} of ≤1 mg/mL methacholine is evidence of severe BHR and is suggestive of asthma.
- Bronchoprovocation can be helpful in situations where the diagnosis of asthma is being considered and there is a desire to objectively document BHR.
- The demonstration of BHR does not indicate a diagnosis of asthma, since there can be other causes of BHR.

Assessment of Respiratory Muscle Strength

- In patients with neuromuscular diseases, measurement of maximal inspiratory and expiratory pressures and peak cough flow can be helpful in assessing respiratory muscle strength and serially monitoring and tracking changes in muscle strength.
- Generally, assisted cough devices are used when a patient's respiratory muscle strength is markedly reduced.

Diffusion Capacity of the Lung to Carbon Monoxide

- Gas exchange occurs through diffusion of oxygen and CO_2 across the alveolar capillary membrane.
- Conditions such as interstitial lung disease or pulmonary edema, which result in thickening of the alveolar capillary membrane, will also lead to decreased efficiency of gas exchange.

- The diffusion capacity of the lung can be measured by using carbon monoxide (CO), a tracer gas that diffuses readily across the alveolar capillary membrane but is retained in the pulmonary circulation through its avid binding to hemoglobin.
- In clinical practice, diffusion capacity of the lung to CO (DLCO) is measured by using the following single-breath technique:
  - A patient inspires a gas mixture that contains a small amount of CO (typically 0.3%), holds his or her breath for 10 seconds, and then exhales.
  - By measuring the concentration of exhaled CO, the diffusion capacity can be calculated.
- Although this measurement is referred to as the *DLCO,* factors other than diffusion capacity, such as pulmonary vascular perfusion and hemoglobin concentration, also contribute to the DLCO value. Nonetheless, the DLCO is a good reflection of the gas exchange capacity of the lung.

Infant PFTs

- Infants cannot perform the forced expiratory maneuvers required for standard spirometry.
- Adult-type spirometry can be replicated by using the single-breath occlusion method or the raised-volume rapid thoracoabdominal compression technique.
  - Raised-volume rapid thoracoabdominal compression technique
    - The method is safe and generates forced expiratory flow data similar to those of standard spirometry.
    - It is time and labor intensive, and it does require sedation.
  - Single-breath occlusion method
    - The method relies on triggering the Hering-Breuer reflex, which is a brief apneic pause that occurs in response to airway occlusion.
    - It can be performed in sleeping infants, as well as sedated ones.
- Infant pulmonary function testing is usually available to subspecialists in pediatric pulmonology. While it may have some clinical applications, it is more often used in the research setting.

Preschool PFTs

- Although many children aged 3–5 years can perform acceptable spirometry with achievement of flow limitation, even with less stringent criteria, the success rate ranges from 50% to 80%. Other methods for preschool PFTs have been developed that require less patient cooperation.
- The forced oscillation technique and the interrupter technique are methods of measuring pulmonary function in younger children.
  - Children performing the forced oscillation technique do not need to perform forced expiratory maneuvers; they simply need to maintain steady tidal breathing.

  - With the interrupter technique, a brief occlusion is applied while children passively exhale through the interrupter device.
- There are commercially available devices for both techniques, and normal reference data have been published.
- Availability generally remains limited to subspecialists' offices. The need for accurate lung function testing in young children may constitute a reason for referral.

Multiple-Breath Washout

- The degree of ventilation inhomogeneity present during a gas dilution test can be quantified through multiple-breath washout.
- The lung clearance index (LCI) represents the number of FRC volumes needed to completely wash out a tracer gas (either helium or sulfur hexafluoride) or the resident nitrogen in the lungs.
- The higher the LCI, the greater the amount of ventilation inhomogeneity.
- A substantial advantage of this technique is that it requires only quiet, tidal breathing.
- In young children with cystic fibrosis, LCI is increased even when spirometric measures are normal; LCI is being studied as a method to detect early disease and as an outcome measure in studies of treatment of children with mild cystic fibrosis lung disease.

Exhaled Nitric Oxide

- Allergic airway inflammation mediated by type 2 helper T cell cytokines, such as interleukin 4 and 5, induces the production of nitric oxide (NO) in the airways of children with atopic asthma.
- Measurement of the fraction of exhaled NO can be used to assess allergic airway inflammation, and commercial, Food and Drug Administration–cleared devices to measure fraction of exhaled NO are currently available.
- Studies have shown that in general, routine measurement of fraction of exhaled NO and medication protocols driven by this parameter have not resulted in improved asthma control.
- Fraction of exhaled NO may still have a role in the diagnosis of asthma, assessing adherence to inhaled corticosteroid therapy in asthmatic children, and the management of severe asthma.

Clinical Pearls

- PFTs provide objective evidence of lung function in patients with lung diseases such as asthma or cystic fibrosis.
- Spirometry is the most commonly used PFT, but obtaining good spirometry data requires careful attention to technique and quality control.
- More specialized PFTs are available and are usually performed by specialists such as pediatric pulmonologists.

Chapter 6

Imaging

Sabah Servaes, MD, FAAP

Overview of Modalities

Imaging permits screening, diagnosis, and identification of complications of infections and other disorders of the respiratory system.

- Chest radiography is the most commonly ordered imaging modality. It is quick, easy to perform, relatively inexpensive, and involves a small amount of radiation. It is widely available and portable and can be performed at the patient's bedside.
- Ultrasonography (US) requires a moderate amount of time, depending on the examination and experience level of the sonographer. The cost is low to moderate, and the examination involves no ionizing radiation. It is widely available (although specialized pediatric sonographers are not as widely available) and can be performed portably, as well.
- Computed tomography (CT) is widely available and provides excellent spatial resolution with a quick examination time at a moderate cost. Radiation can be decreased by use of pediatric dose parameters (CT performed at a center with American College of Radiology CT accreditation is ideal). Sedation may be needed in uncooperative children, especially those 1–3 years of age. CT is excellent for characterization of lung parenchyma and osseous structures.
- Magnetic resonance (MR) imaging provides the best soft-tissue resolution with no ionizing radiation, but the examination is lengthy, may require sedation, is costly, and is less widely available than other modalities. It has limited value in the assessment of lung parenchyma.
- Positron emission tomography (PET)/CT and PET/MR imaging are typically used for oncologic applications but are also used occasionally for infectious or inflammatory entities. The examinations are lengthy, frequently require sedation (especially in children under 6 years of age), are costly, and are not widely available.
- Fluoroscopy is a dynamic examination involving low to moderate levels of ionizing radiation. It is performed in a fluoroscopy suite to image real-time changes in the airways, diaphragm, and thoracic cavity. It may be used in conjunction with a speech pathologist for swallow function studies or in conjunction with an upper gastrointestinal examination performed by a radiologist (both studies are reliant on patient compliance).

Chest Radiography

- Chest imaging is most commonly performed with chest radiography (Figure 6-1).
- Technical factors to remember include the following.
  - The frontal projection is obtained with a posteroanterior radiation beam.
  - In patients who are unable to stand or follow instructions (eg, in an intensive care unit or, if very young, typically <5 years old), the frontal (anteroposterior [AP]) projection is obtained, which makes anterior thoracic structures, such as the heart, appear larger.
- Common findings include the following.
  - Atelectasis: focal opacity due to loss of lung volume that may appear and resolve rapidly (Figure 6-2).
  - Pneumonia (Figure 6-3)
    - Focal consolidation is seen without volume loss.
    - Follow-up radiography is rarely necessary.
    - Radiographic findings of pneumonia can persist for days or weeks, despite clinical improvement.
  - Pleural effusion (Figure 6-4) manifests as fluid between the lung and the chest wall. Radiographically, it blunts the diaphragm margin and may be seen tracking along the chest wall. Noncomplicated effusion is free flowing and more easily observed with the patient in a lateral position (decubitus views). However, decubitus radiographs are rarely obtained in lieu of US, which can demonstrate the effusion without additional radiation exposure.
  - Bronchiectasis
    - Dilated bronchi typically indicate chronic airway disease
    - Commonly seen in cystic fibrosis, primary ciliary dyskinesia, or immunodeficiency or after severe infection
  - Acute chest syndrome
    - Diffuse, acute, patchy lung opacity in children with sickle cell disease
    - Associated with hypoxemia and respiratory distress
    - May initially be a subtle opacity on chest radiographs
    - May progress rapidly to complete unilateral or bilateral opacification of the lungs
    - Imaging does not allow infection to be distinguished from acute chest syndrome
  - Hyperinflation
    - Flattened hemidiaphragms, typically bilaterally
    - Often seen with asthma, viral illness in infants, or other obstructive lung disorders
  - Pneumothorax
    - Manifests as air within the pleural space, between the chest wall and the lung.

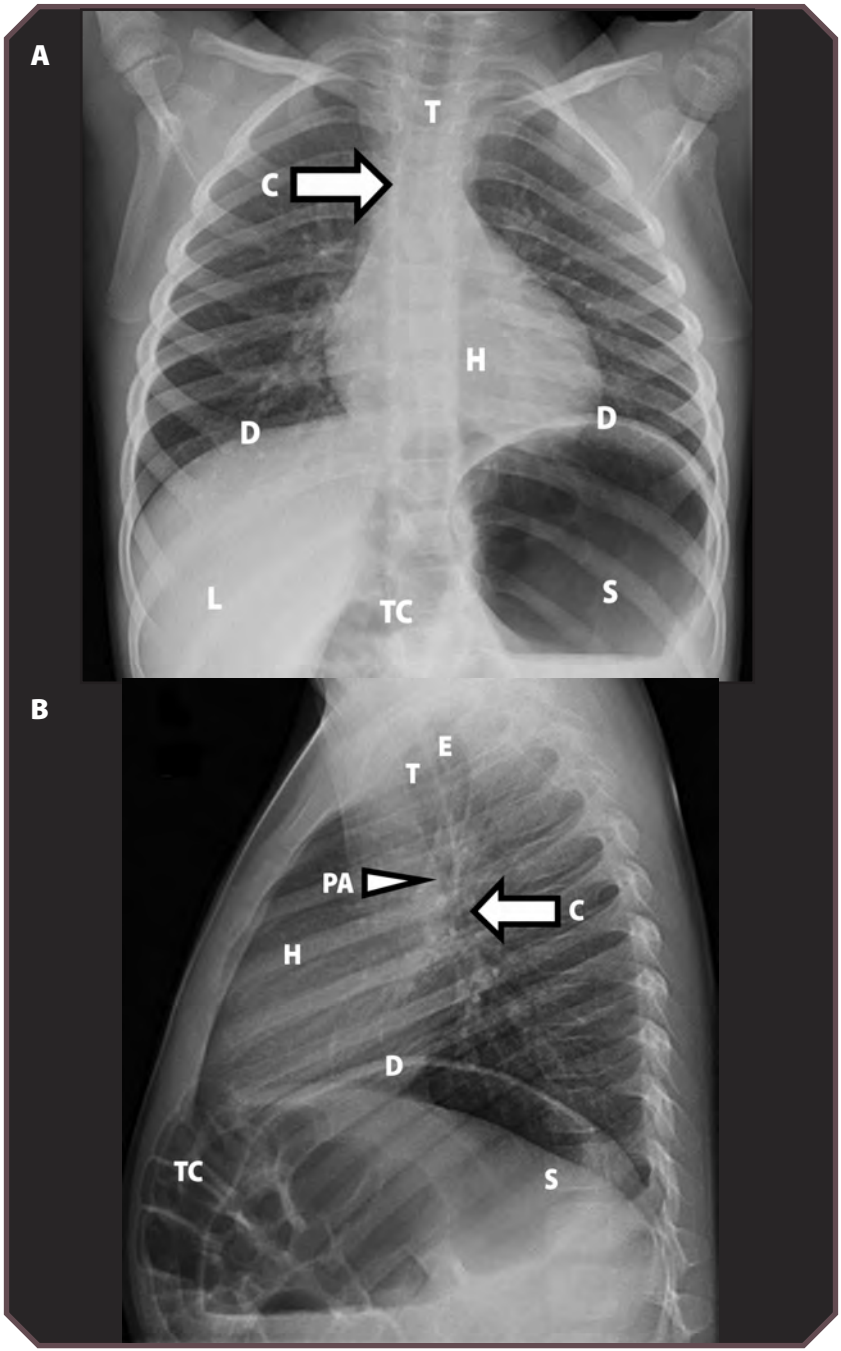

Figure 6-1. Normal chest radiographs in a 3-year-old boy. A. Frontal and B. lateral views show a normally sized heart *(H)*, trachea *(T)*, carina (*C*, arrows on A and B), stomach *(S)*, diaphragm *(D)*, liver *(L)*, pulmonary artery (*PA*, arrowhead on B), esophagus *(E)*, and transverse colon *(TC)*.

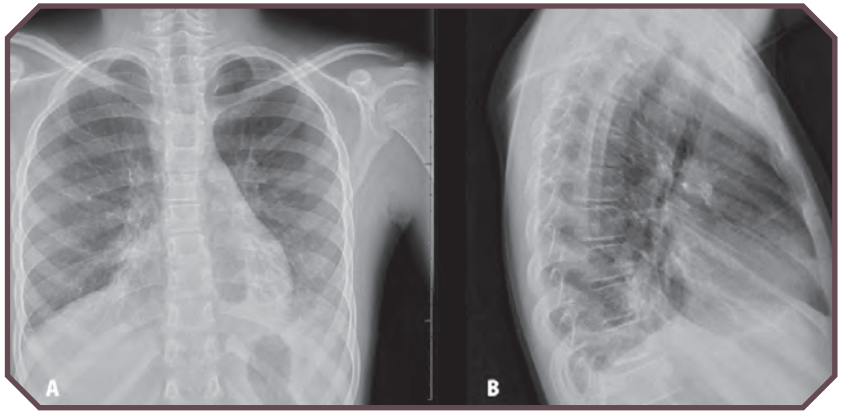

Figure 6-2. Bibasilar atelectasis in a 13-year-old boy with asthma. A chest radiograph with normal findings was obtained a few days earlier. A. Anteroposterior (frontal) and B. lateral views of the chest demonstrate tenting of the hemidiaphragms, secondary to volume loss.

- Small pneumothoraces show a thin, dark edge identified without lung markings beyond. Decubitus views or cross-table lateral views better demonstrate the pleural line.
- Larger pneumothoraces are often easier to identify but can be subtle when the lungs are hyperinflated and clear (Figure 6-5).
- Mediastinal shift indicates a tension pneumothorax, which requires emergent intervention.

— Croup
- Chest radiographs show subglottic narrowing, described as a steeple sign (Figure 6-6).
- Croup is most easily evaluated with soft-tissue airway radiographs.

— Foreign body (Figure 6-7)
- At radiography, opaque foreign bodies can typically be seen in the airway (turned sideways) or the esophagus (facing forward).
- Button batteries have a lucent ring at the periphery, forming a beveled edge. They usually lodge in the esophagus, where they face forward on the frontal radiograph and sideways on the lateral radiograph.
- Foreign bodies in the airway that are not opaque at radiography are more difficult to diagnose. Findings include differential aeration of the lungs with unilateral hyperinflation.
- Decubitus radiographs, which have the advantage of not requiring patient cooperation, are used for diagnosis. Inspiratory-expiratory radiographs serve the same purpose in cooperative children.
- Both techniques demonstrate unchanged lung volume on the obstructed side due to air trapping.
- Button batteries have a high rate of complications, including corrosive strictures, tracheoesophageal fistulas, and mediastinal perforations.

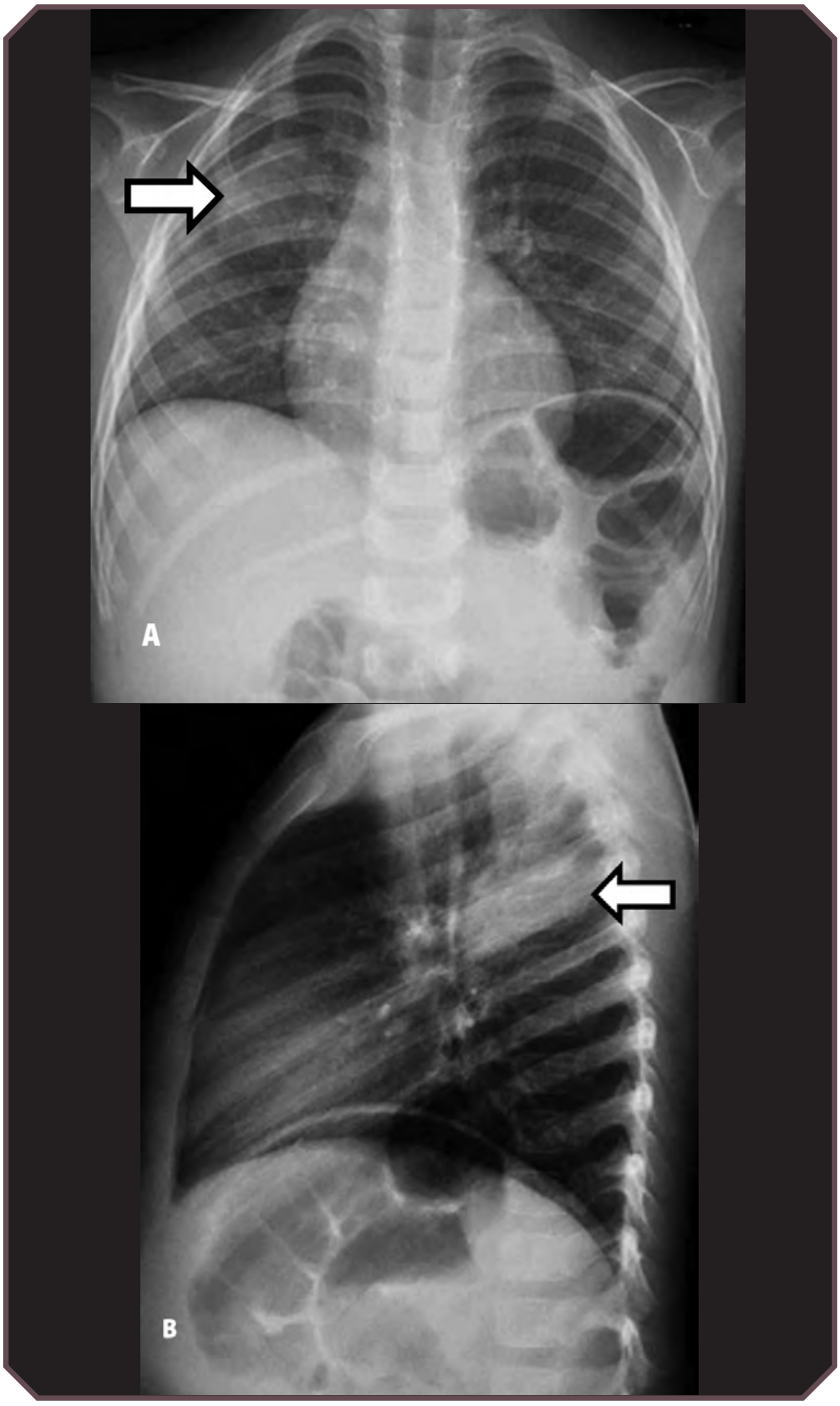

Figure 6-3. Right upper-lobe pneumonia in a 3-year-old girl. A. Frontal and B. lateral chest radiographs demonstrate focal consolidation in the right upper lobe (arrows).

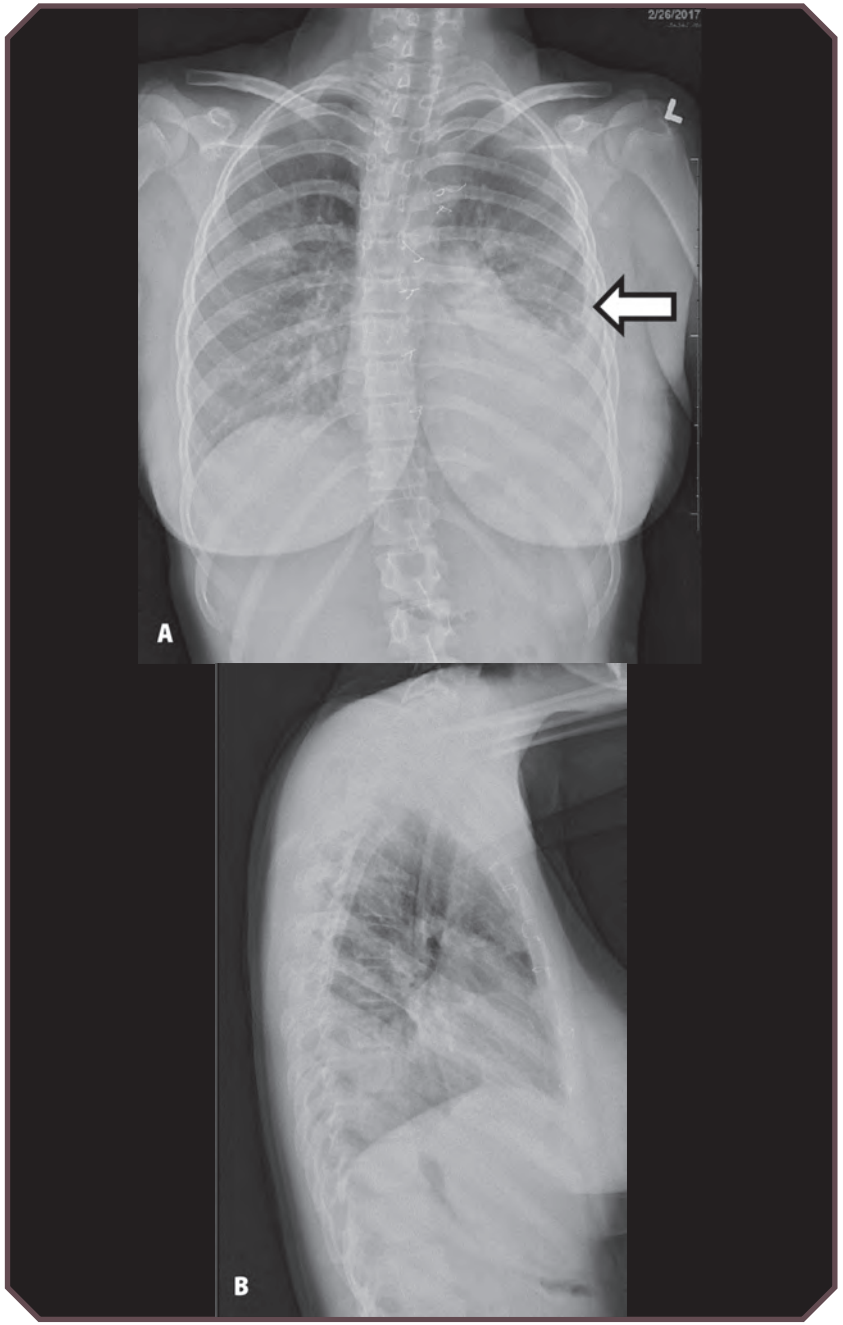

Figure 6-4. Left lower-lobe pneumonia with effusion. A. Frontal and B. lateral chest radiographs show focal opacity with air bronchograms and obscuration of the left hemidiaphragm. On A, a subtle effusion is seen tracking along the left pleural margin (arrow). Sternotomy wires from old surgical repair of congenital heart anomaly are incidentally noted.

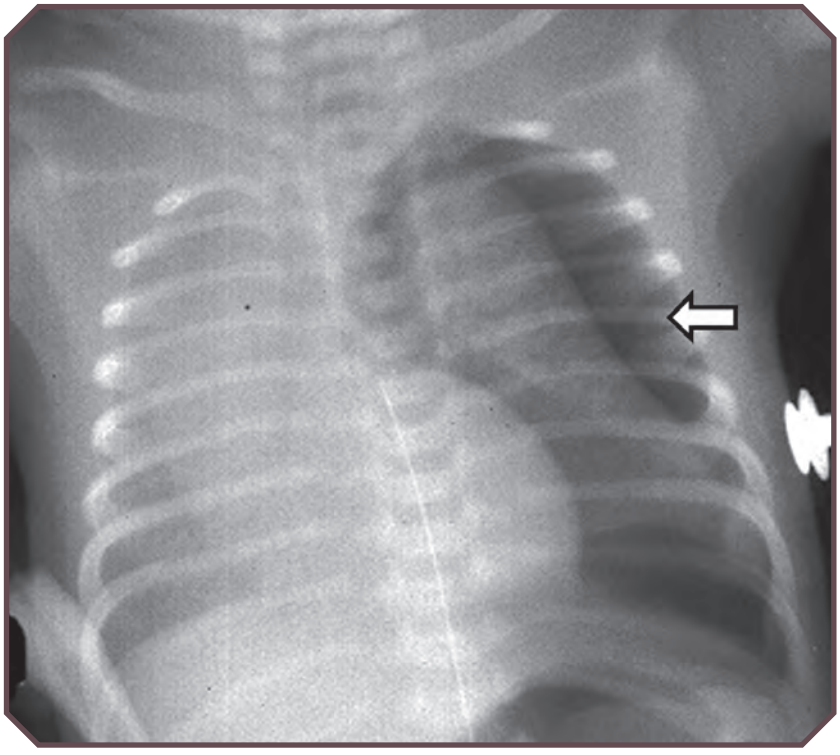

Figure 6-5. Frontal portable radiograph obtained in a premature newborn with surfactant deficiency and worsened respiratory distress shows diffuse fine granular alveolar opacities, in addition to a left pneumothorax (arrow). Also, noted is a small amount of left-to-right shift and an umbilical catheter.

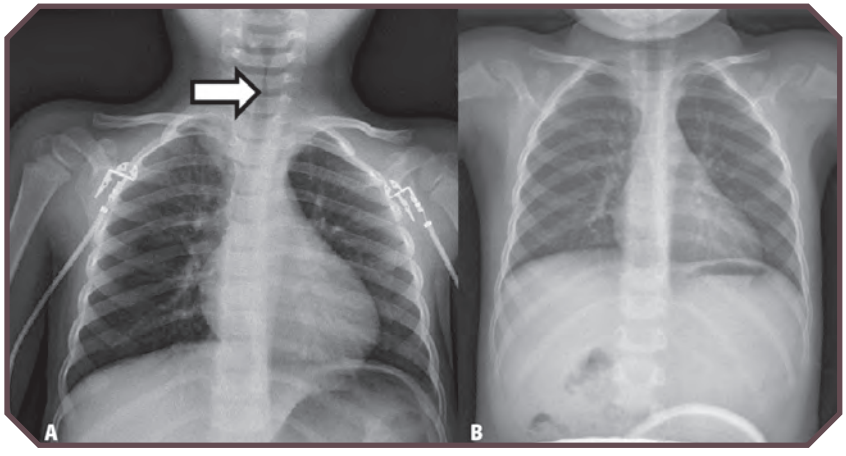

Figure 6-6. Croup. A. Anteroposterior (AP) chest radiograph in a 4-year-old girl demonstrates subglottic narrowing (arrow). B. Note the normal trachea in the same child on a previous AP radiograph.

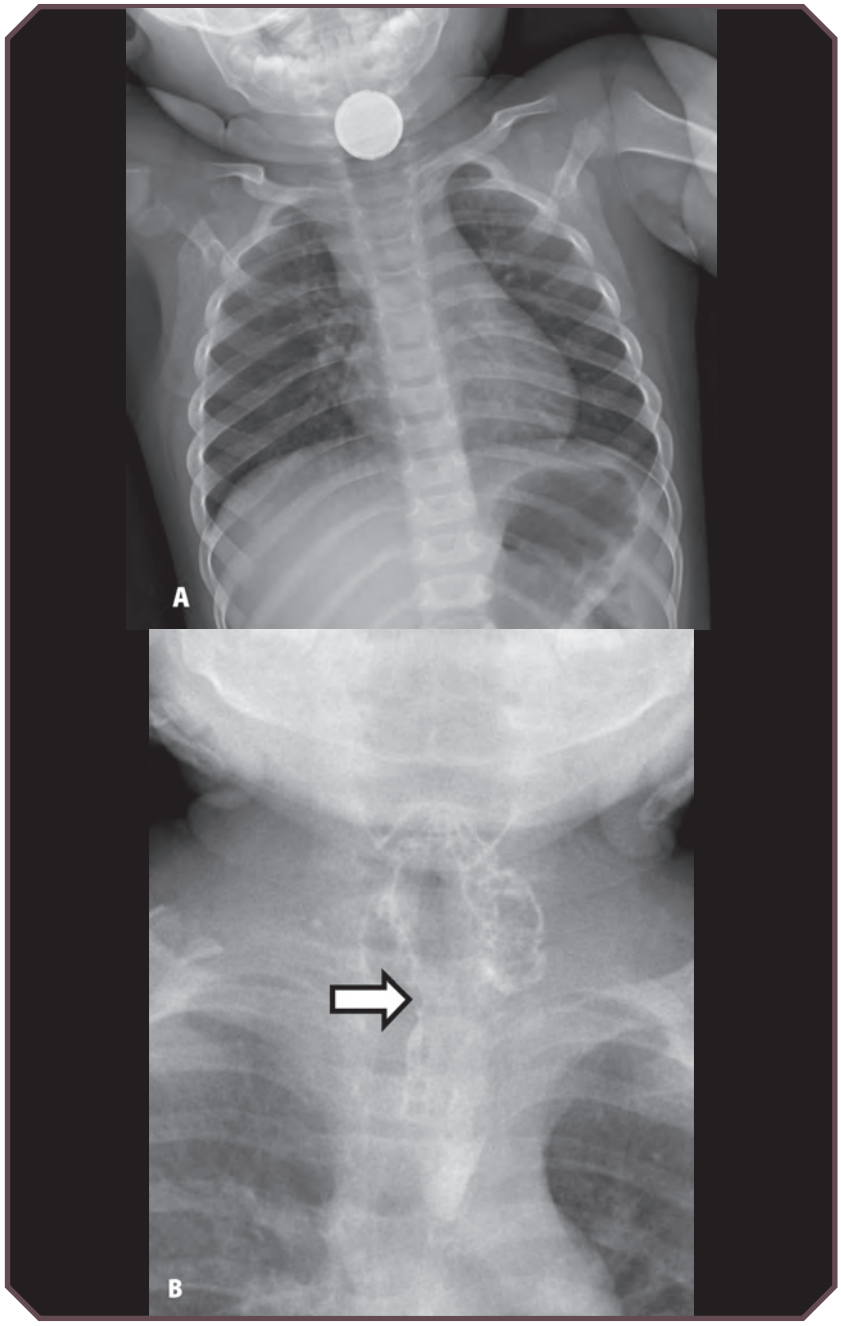

Figure 6-7. Button battery ingested by a 1-year-old girl with associated esophageal stricture. A. Frontal radiograph shows a circular, forward-facing, esophageal foreign body with a peripheral beveled edge. Note the subtle lucent foci along the battery edges, indicating corrosion. B. Frontal esophagram obtained after battery removal shows focal esophageal narrowing (arrow).

Ultrasonography

- US is most often used to identify and characterize pleural effusions (Figure 6-8).
- Simple effusions are dark, whereas complex effusions contain septations and debris.
- US can also be used to assess the degree and symmetry of diaphragmatic motion.
- US facilitates obtaining pleural fluid for diagnosis and placement of chest tube drainage if necessary.

Computed Tomography

Detailed imaging of the lung in 3 dimensions allows discrimination of a variety of lesions.

- Nodules
  - CT is the most sensitive modality for detection.
  - CT demonstrates soft-tissue (eg, presence of calcification) and osseous structures.
  - Serial examinations can be performed to document changing size or number of lesions.

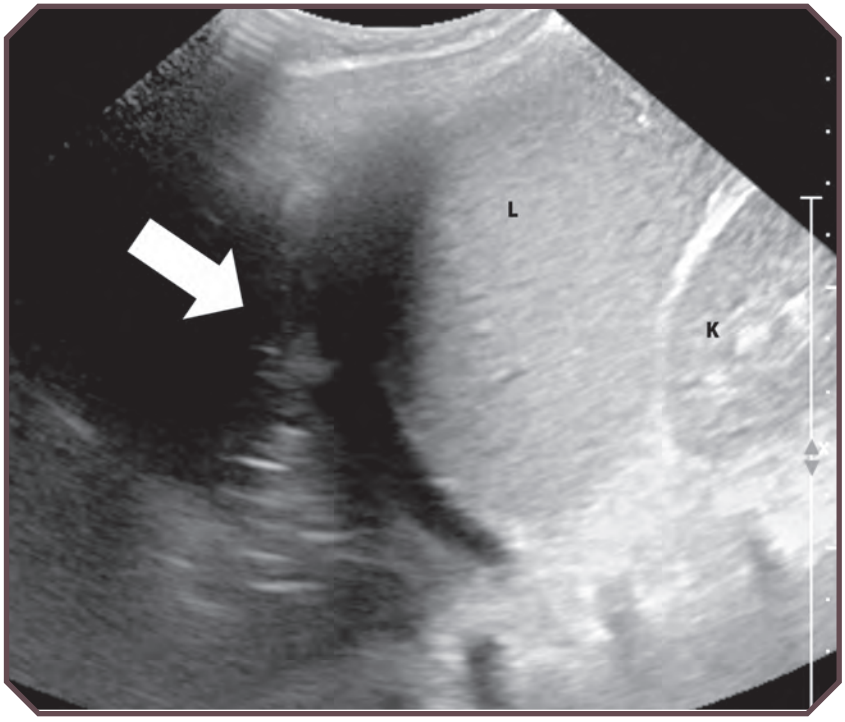

Figure 6-8. Pleural effusion. Sagittal ultrasonographic image demonstrates a left pleural effusion (arrow). Normal liver *(L)* and right kidney *(K)* are partially visualized.

- Parenchymal disease
  - CT is able to demonstrate changes associated with a variety of thoracic disorders.
    - Consolidation may be seen with infection.
    - Hilar adenopathy is seen with granulomatous infections and, less commonly, in children with malignancy.
    - Peripheral and mediastinal calcifications are most commonly seen with granulomatous infection and in the Mississippi River valley, overwhelmingly due to *Histoplasma capsulatum*.
    - Ground-glass air space disease suggests active inflammation in the lung parenchyma.
    - Bronchiectasis is diagnosed when the bronchi are larger than the adjacent vessel (signet ring sign) and is easiest to visualize at CT.
  - Hyperlucent lesions may be seen in a variety of conditions.
    - Congenital cysts
    - Congenital lobar emphysema
    - Congenital pulmonary airway malformations
    - Acute abscesses—often partially opacified by fluid
    - Postinfectious cysts and pneumatoceles
- Mediastinal masses and lymphadenopathy
  - Mediastinal masses (nodes, congenital cysts, vascular lesions, and lymphadenopathy) are evaluated easily with CT (Figures 6-9 and 6-10).
  - Hilar nodes are more easily distinguished when intravenous contrast material is used.
  - Axillary and cervical nodes may also be visualized.
- Vascular anatomy
  - Intravenous contrast material is required for complete visualization.
  - CT can be used to detect aberrant anatomy, vascular anomalies (eg, aneurysm), and emboli.
- Pectus excavatum
  - Convex indentation of the sternum that narrows the AP diameter of the chest
  - May be quantified by using a measure called the *Haller index*. The Haller index is the maximal transverse diameter or narrowest AP length of chest. The normal index is 2.5, and indexes >3.25 are typically clinically significant enough to warrant consideration of surgical correction on the basis of accompanying symptoms.
  - The degree of cardiac compression is also important to consider.

Fluoroscopy

- Fluoroscopy is used for dynamic airway assessment to evaluate the following:
  - Diaphragmatic motion
  - Tracheomalacia and laryngomalacia
  - Airway obstruction in suspected foreign bodies

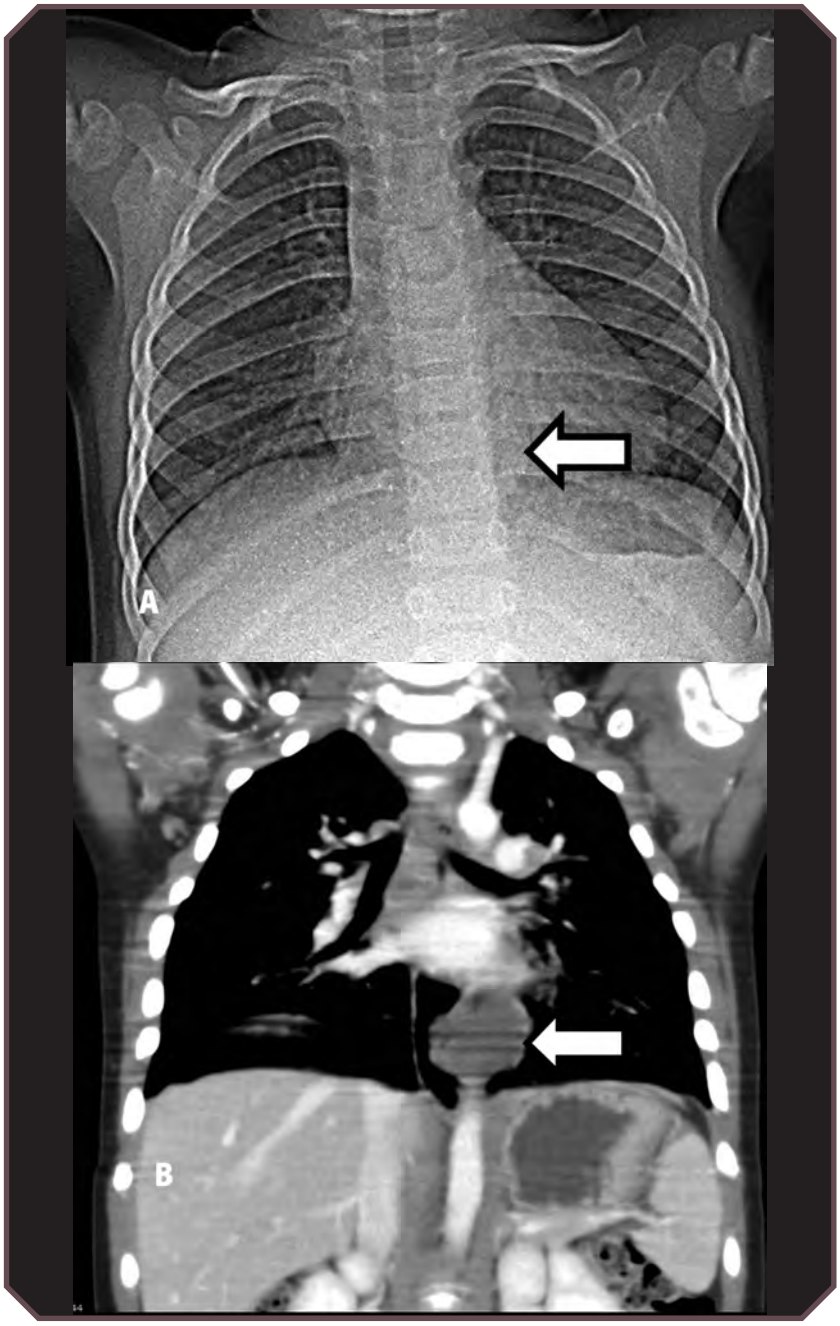

Figure 6-9. Esophageal duplication cyst in a 2-year-old girl. A. Posteroanterior radiograph of the chest shows a subtle, well-defined retrocardiac opacity (arrow). B. Coronal reconstruction from contrast-enhanced computed tomography confirms a low-attenuation lesion (arrow) typical for a duplication cyst. The cyst was surgically resected.

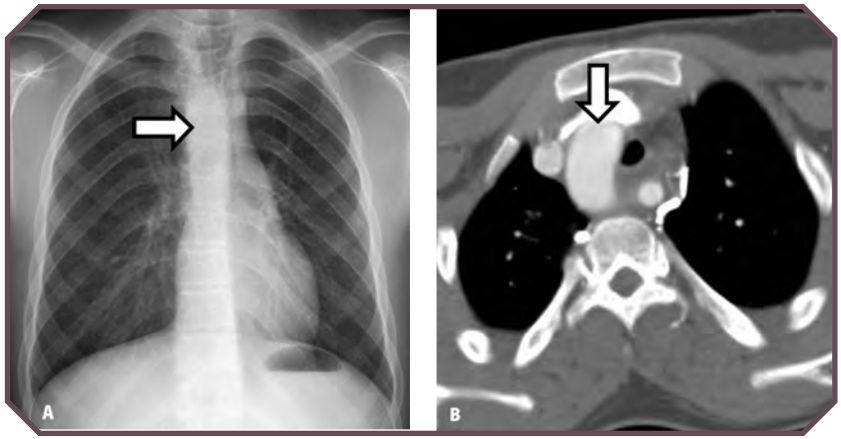

Figure 6-10. Right aortic arch in a 14-year-old female patient. A. Posteroanterior chest radiograph shows a soft-tissue density (arrow) along the right side of the trachea. B. Axial contrast-enhanced computed tomographic image confirms a right aortic arch (arrow).

- Fluoroscopy may also be 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

MR Imaging

- MR imaging is used to detect masses, such as venous and lymphatic malformations of the mediastinum (Figure 6-11).

PET/CT and PET/MR Imaging

- PET is a functional examination combined with an anatomic modality, CT or MR imaging, used most often to evaluate the activity of neoplastic cells (Figure 6-12).

Resources for Families

- Children's (Pediatric) Imaging (Radiological Society of North America). www.radiologyinfo.org/en/submenu.cfm?pg=ped
- What Can I Do as a Parent? (Image Gently). www.imagegently.org/Roles-What-can-I-do/Parent

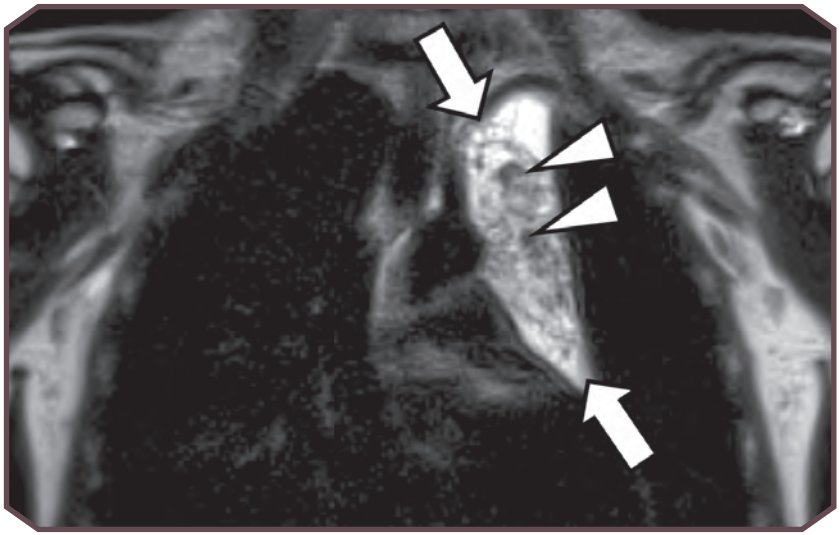

Figure 6-11. Coronal T2-weighted magnetic resonance image illustrates a left mediastinal venous malformation, which is predominantly high in signal intensity (arrows). Dark foci likely correspond to internal septations and phleboliths, which are calcifications within the veins (arrowheads).

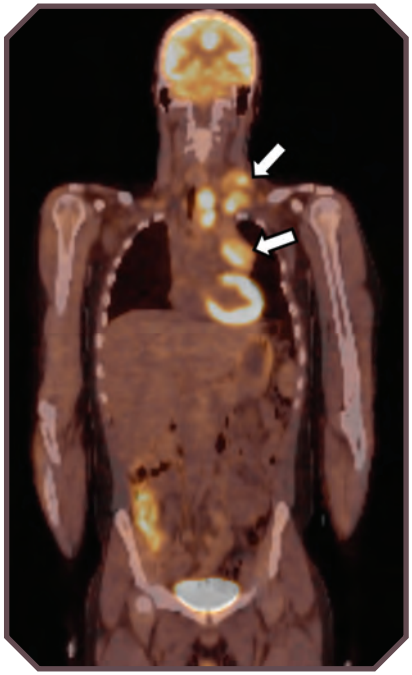

Figure 6-12. Hodgkin lymphoma. Coronal positron emission tomography/computed tomography image demonstrates increased fluorodeoxyglucose uptake in the mediastinum and left lower neck, which corresponds to an active neoplasm (arrows). Normal uptake is noted in the brain, bowel, and bladder.

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Chapter 7

Allergy Testing

David Stukus, MD

Indications for Allergy Testing

- Persistent symptoms, despite regular use of medications, such as antihistamines and/or nasal steroid sprays
- Exposure to potential allergens with ongoing symptoms (eg, cat or dog inside the home)
- Consideration of allergen immunotherapy for severe refractory symptoms
- Children with persistent asthma who
  - Require more than 1 controller medication
  - Have ongoing symptoms despite adherence to therapy
  - Require help to determine a prognosis
- Need to establish the proper diagnosis and best treatment options

Appropriate Age for Allergy Testing

- There is no age limitation in the application of allergy testing or interpretation of the results. If a child is old enough to develop immunoglobulin E (IgE)–mediated inhalant allergies, then he or she is old enough to undergo allergy testing to detect specific IgE.
- Younger children often have negative allergy test results because their symptoms are not caused by IgE-mediated allergies.
- Perennial allergic rhinitis (caused by exposure to dogs, cats, dust mites, cockroaches, or rodents) typically does not develop until at least 12 months of age and can begin anytime thereafter.
- Seasonal allergic rhinitis (caused by exposure to trees, grasses, weeds, ragweed, or mold spores) develops as follows:
  - Typically not until at least 2–3 years of age
  - Unlikely in children <18 months of age

Skin Prick Testing

- Skin prick testing involves the introduction of a small amount of allergen percutaneously, through the use of a prick device.
- Test samples should be placed on the upper back or volar aspect of the forearm.
- If the patient has specific IgE attached to localized mast cells, the skin prick test for an allergen will result in a localized wheal (bump) and flare (erythema) response.

- Test results should be interpreted 15 minutes after application.
- The mean diameter of the wheal is measured to determine sensitization to that particular allergen. A positive (histamine) and negative (saline) control sample should always be placed and used for comparison and interpretation of specific allergen wheal diameters.
- A wheal ≥3 mm larger than the negative control sample is consistent with the presence of allergic sensitization.
- The size of the skin prick test result does not correlate with severity of symptoms but does correlate with likelihood of the test result being clinically relevant.
- Medications can interfere with test results (Table 7-1); antihistamines should be discontinued at least 3–5 days prior to testing.

Table 7-1. Differences Among Serum-Specific Immunogloblulin E Diagnostic Tests

	Skin Prick Test	Serum-Specific Immunoglobulin E
Sensitivity	High	High
Specificity	Low	Low
Medications that may interfere with results	• Antihistamines • Tricyclic antidepressants • H_2 histamine blockers • Long-term systemic corticosteroids (>2 wks)	None
Adverse effect	• Localized pruritus, discomfort • Very low risk for anaphylaxis	• No risk for allergic reaction • Localized trauma from venipuncture
Timing of results	15–20 min	Hours to days, depending on the laboratory

Serum-Specific IgE Testing

- Immunoassay is used to measure levels of specific IgE toward an allergen through routine venipuncture.
- Results are reported as a range from 0.1 to 100 kU/L.
- Similar to skin prick testing, the level of specific IgE does not correlate with severity of symptoms but does correlate with the likelihood that allergy is present.
- Many laboratories also report arbitrary classes assigned to certain ranges; these have no clinical relevance and should not be used in the interpretation of results.
- Serum IgE results are not affected by any medications; patients do not need to discontinue antihistamines prior to testing (Table 7-1).

- Many commercial laboratories offer panels of allergens that can be measured on the same sample. This often combines food allergens with inhalant allergens. These panels should be used rarely, if ever, because they often introduce unnecessary testing or may not contain desired allergens. Individual allergens should be assessed and ordered accordingly.

Total IgE Levels

- Total IgE levels are not diagnostic for any condition and should not be obtained routinely.
- Atopic conditions, such as atopic dermatitis, allergic rhinitis, and asthma, are generally associated with higher total IgE levels.
- There are 2 scenarios in which a total IgE level is indicated and useful:
  - — To determine if allergic bronchopulmonary mycosis (aspergillosis) is present, in which total IgE levels often double or increase substantially during an acute flare
  - — To determine dosing of omalizumab (anti-IgE monoclonal antibody) for patients with moderate to severe asthma who are candidates for this therapy

Interpretation of IgE Results

- Both skin prick and serum IgE tests are associated with high negative predictive values but poor positive predictive values. Neither test can be used as a screening tool or as a predictor of future allergy.
- The size of the test result does not correlate with severity of symptoms, only the likelihood that allergy is present.
- For inhalant allergens, predictive values are not well established for any indoor or outdoor inhalant allergens. Interpretation relies on clinical history, pretest probability, and exposure history.
- For food allergens, predictive values have only been established for the 8 most common food allergens: milk, egg, wheat, soy, peanut, tree nuts, fish, and shellfish. Determination of food allergy relies on clinical history, pretest probability, and size of the test result.
- *Foods should never be removed from the diet solely on the basis of IgE test results*. Owing to high rates of falsely increased and clinically insignificant results, a thorough history should be obtained to elicit reproducible, immediate-onset symptoms consistent with IgE-mediated food allergy prior to ordering any food allergen IgE testing or interpreting the results.

Indications for Repeat Testing

- Repeat testing is rarely necessary any sooner than 12 months after the last test, unless new symptoms develop.

- Inhalant allergy testing should be repeated if symptoms at the time of the original test have persisted or progressed despite medical management. If new symptoms arise, if new exposures occur (eg, a new pet at home), or if consideration for allergen immunotherapy arises, then repeat testing should be conducted.
- Food allergy testing should be repeated annually for anyone with physician-diagnosed food allergy who is strictly avoiding a certain food (or foods). Many children with food allergies will develop tolerance with age.
- Testing should *not* be repeated for these reasons:
  - To gauge effectiveness of immunotherapy or to determine when to discontinue immunotherapy. This is best determined through assessment of symptoms or predetermined time frames for maintenance immunotherapy (3–5 years).
  - To determine effectiveness of medical management. This is best approached through assessment of symptoms.

When to Refer

- Asthma or allergy symptoms persisting despite adherence to baseline daily therapy (antihistamines with or without nasal steroid sprays, inhaled steroids)
- Skin prick testing required
- Immunotherapy or use of monoclonal antibodies being considered in the management of severe refractory asthma
- Education or information needed for allergy diagnosis, allergen avoidance, prognosis, and additional treatment considerations
- Patient requires National Heart, Lung, and Blood Institute asthma guideline step 4 care or higher
- Assistance needed in the interpretation of previously obtained IgE test results

Resources for Families

- Allergy Testing (American Academy of Allergy, Asthma, and Immunology). www.aaaai.org/conditions-and-treatments/library/allergy-library/all-about-allergy-testing
- What You Need to Know About Food Allergy Testing (Kids With Food Allergies). www.kidswithfoodallergies.org/page/food-allergy-test-diagnosis-skin-prick-blood.aspx

Clinical Pearls

- Skin prick and serum IgE tests alone are not diagnostic for any allergies.
- The size of an allergy test result can help determine the likelihood of allergy being present, as determined by the clinical history.
- Allergy testing for inhalant allergens can help identify the cause of nasal and ocular symptoms, appropriate treatment strategies, avoidance measures, and prognosis for children with asthma.

Chapter 8

Bronchoscopy

Shailendra Das, DO, FAAP

Introduction

- Flexible bronchoscopy allows for examination of the nose, pharynx, larynx, and tracheobronchial tree.
- Bronchoscopic developments, including smaller scope sizes and improvements in picture quality and video technology, have facilitated use in younger children and neonates.

Indications for Bronchoscopy

- Stridor (especially in the setting of failure to thrive or apneic spells)
- Persistent wheezing (especially if asthma therapies do not alleviate symptoms)
- Monophonic wheezing (suspicion of foreign body)
- Persistent wet cough
- Recurrent and/or persistent pneumonia
- Persistent abnormal chest radiographic and/or computed tomographic findings (atelectasis, infiltrate)
- Recurrent aspiration
- Foreign-body aspiration
- Hemoptysis and/or pulmonary hemorrhage
- Respiratory symptoms in an immunocompromised host
- Interstitial lung disease
- Tracheostomy evaluation
- Lung transplant surveillance
- Direct instillation of medications (deoxyribonuclease, hypertonic saline, N-acetylcysteine, sodium bicarbonate) to aid in thinning and removing mucus

Additional Tests

- Bronchoalveolar lavage
  - — Evaluation of alveolar cells via instillation of saline in a pulmonary lobe to obtain diagnostic information
  - — Indications
    - Microbial cultures (bacterial, fungal, viral, and mycobacterial) and rapid diagnostic tests
    - Cytologic analysis and cell count
    - Bleeding
    - Aspiration or gastroesophageal reflux

  - Cytologic findings in bronchoalveolar lavage
    - Normal: >80% macrophages
    - Inflammation and/or infection: increased numbers of neutrophils
    - Asthma: increased percentage of eosinophils
    - Alveolar or airway hemorrhage: presence of hemosiderin-laden macrophages
    - Aspiration and/or gastroesophageal reflux: presence of lipid-laden macrophages (sensitive, not specific)
    - Interstitial lung disease: increased numbers of lymphocytes, eosinophils, neutrophils
    - Sarcoidosis: increased lymphocyte count ($CD4^+$ cells)
    - Hypersensitivity pneumonitis: increased lymphocyte count ($CD8^+$ cells)
- Transbronchial biopsies: evaluation for acute cellular rejection in patients who underwent lung transplantation, sarcoidosis
- Endobronchial biopsies: evaluation of airway inflammation, potential malignant lesions, granulation tissue
- Endobronchial brush biopsies: evaluation of ciliary motility and cilia electron microscopy ultrastructure (primary ciliary dyskinesia)

Deciding Between Flexible and Rigid Bronchoscopy

- Flexible bronchoscopy
  - Usually performed by pulmonologists
  - Can be performed at the bedside (eg, in the pediatric intensive care unit) or in an outpatient procedure suite
  - Can be performed with moderate sedation or general anesthesia
- Rigid bronchoscopy
  - Usually performed by otolaryngologists or pediatric surgeons
  - Usually performed in an operating room
  - Requires general anesthesia
- Table 8-1 shows indications for flexible and rigid bronchoscopy.
- In general, flexible bronchoscopy
  - Allows for more maneuverability, giving a better view of the lower airways
  - Offers a more dynamic view of the airway
  - Provides the opportunity for sampling of the lower airways for microbial and cytologic testing
- Direct laryngoscopy (without endotracheal tube)
  - Allows for better examination of the posterior glottis
- Rigid bronchoscopy
  - Provides for controlled ventilation through the scope
  - Provides for a bigger working channel for removal of a foreign body (see Figure 8-1 for evaluation and/or management of a foreign body)
  - Essential for ruling out suspected H-type tracheoesophageal fistula

Table 8-1. Choosing Between Flexible and Rigid Bronchoscopy		
Area of Interest or Evaluation	**Flexible**	**Rigid**
Nasopharynx	✓	
Larynx[a]	✓	✓
Vocal cord function and/or movement	✓	
Subglottis		✓
Trachea	✓	✓
Laryngomalacia	✓	
Tracheobronchomalacia	✓	✓
Diagnostic workup (microbial, cytologic analysis)	✓	
Mainstem bronchi	✓	✓
Lobar, segmental, and subsegmental bronchi	✓	
Endobronchial biopsy	✓	✓
Foreign-body removal		✓
Diagnosis of foreign body	✓	✓
Control of bleeding		✓

[a] If a laryngeal cleft is suspected, direct laryngoscopy must be performed, with palpation of the interarytenoid space.

Findings

- Upper-airway lesions
  - Vocal cord paralysis
  - Vocal cord dysfunction
  - Laryngomalacia
  - Laryngeal web
  - Laryngeal cleft
  - Subglottic stenosis
  - Subglottic cysts
- Lower-airway lesions
  - Tracheomalacia
  - Tracheal stenosis and/or complete tracheal rings
  - External (vascular) compression of the airway
  - Tracheal bronchus
  - Tracheoesophageal fistula
  - Protracted bacterial bronchitis
  - Endobronchial foreign body
  - Endobronchial mass
  - Bronchomalacia

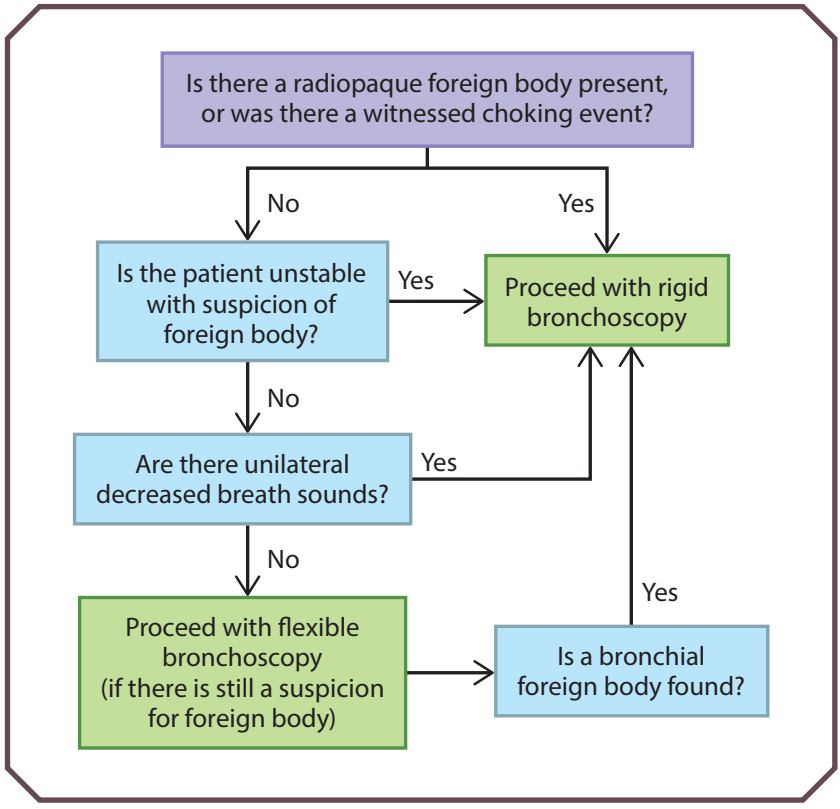

Figure 8-1. Algorithm for assessment of foreign body.

Complications of Bronchoscopy

- Common complications
  - — Cough
  - — Low-grade fever
  - — Transient hypoxemia, due to either sedation or obstruction of the airway by the scope itself
  - — Minor airway and/or nasal bleeding, due to local trauma
  - — Local trauma during rigid endoscopy procedures
    - ▪ Abrasions of the lips or gingiva
    - ▪ Chipped teeth
- Rare complications
  - — Laryngospasm: avoided by using topical laryngeal anesthesia
  - — Bacteremia: caused by spread of infection
  - — Pneumothorax: incidence increased when transbronchial biopsy performed
  - — Hemorrhage: incidence increased when transbronchial biopsy performed
  - — Airway obstruction: can occur during removal of a foreign body

Resources for Families

- Flexible Bronchoscopy (Airway Endoscopy) (American Thoracic Society). www.thoracic.org/patients/patient-resources/resources/flexible-bronchoscopy.pdf

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Chapter 9

Oximetry and Capnography

Sankaran Krishnan, MD, MPH

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.

Principles of Pulse Oximetry

- Pulse oximetry is used to measure oxygen saturation (Spo_2) by relying on the differential absorption spectra of deoxyhemoglobin (red light, 660 nm) and oxyhemoglobin (infrared light, 940 nm) (Figure 9-1).
- The comparative ratio of light absorbance at these 2 wavelengths is calculated and calibrated against direct measurements of arterial oxygen saturation (Sao_2) via blood gas measurements. This establishes the pulse oximeter's measure of arterial saturation (Spo_2).

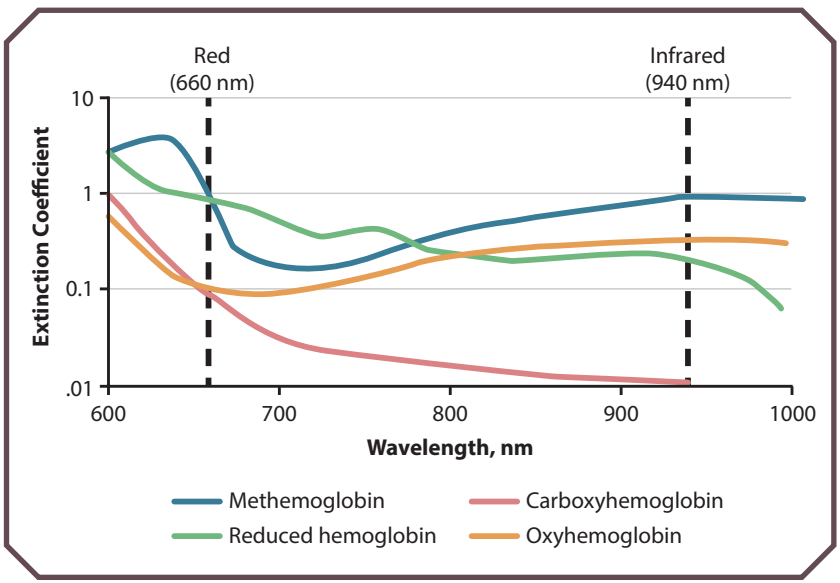

Figure 9-1. Absorption spectra of human hemoglobins. Adapted from Miller RD. *Miller's Anesthesia.* 8th ed. Philadelphia, PA: Elsevier; 2015. Copyright 2015, with permission from Elsevier.

- Pulse oximeters typically consist of 2 light-emitting diodes, 1 emitting at the red spectrum and the other at the infrared spectrum. At the other end of the diodes, a detector is used to measure nonabsorbed energy. A microprocessor is used to subtract 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 is thus a marker of pulse or heart rate.
- Spo_2 is calculated by converting the absorption ratios with dedicated calibration algorithms stored in the microprocessor of the device. These algorithms were derived from blood gas measurements obtained in healthy volunteers who were breathing standard oxygen concentrations.
- These algorithms are not useful below an Spo_2 level of 75% because it is unethical to expose volunteers to oxygen concentrations that lead to lower Spo_2 levels.
- 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.
- Masimo technology (Irvine, CA) uses a patented signal extraction technique to smooth out motion artifacts. Pulse oximeters equipped with this technology tend to more accurately reflect Spo_2 in young infants and children.

Normal Spo_2 Values

- Normal Spo_2 values in children are not well established.
- Readings vary with age and altitude.
  - Typical Spo_2 values in healthy children at sea level range from 97% to 99%.
  - In neonates and young infants, typical values are lower, ranging from 93% to 100%.
  - Values are lower at higher altitudes.
  - Spo_2 values demonstrate diurnal fluctuation, with lower readings in the early morning and peak readings in late afternoon.

Utility of Pulse Oximetry

- Monitoring in respiratory disorders associated with hypoxemia (eg, bronchiolitis, asthma, pneumonia)
- Monitoring during resuscitation
- Neonatal screening for congenital heart disease
- Prevention of hyperoxia, especially in neonates
- It is important to emphasize that pulse oximetry is not used to measure "oxygen level in the blood." Rather, it is a measure of how well the hemoglobin is saturated with oxygen. There is no established "safe value" to discharge a child from the hospital. Clinical consideration is needed, and a child may be discharged from the hospital with a lower than normal Spo_2 value as long as he or she is clinically well otherwise.

Limitations of Pulse Oximetry

- Erroneous readings may occur in the presence of any of the following:
  - — Abnormal hemoglobins, such as methemoglobin or carboxyhemoglobin (see Figure 9-1)
  - — Nail polish (may need to be removed before testing), skin pigmentation
    - ▪ Darker skin pigmentation can lead to erroneously lower values of Spo_2
  - — Ambient (white) light interference
  - — Poor perfusion states (decreased cardiac output, marked hypothermia)
  - — Severe anemia
  - — Intravenous dyes (like methylene blue)
  - — Suboptimal probe positioning
  - — Motion artifact
- Pulse oximetry is inaccurate below an Spo_2 level of 75%
- It is not a good reflector of O_2 status beyond 100% (see Figure 9-2)

Capnography

Principles of Capnography

- Capnography is the noninvasive monitoring of the concentration of carbon dioxide (CO_2) in expired respiratory gases, presented in a continuous waveform display.
- It may be worthwhile (and cost-effective) for offices, especially those that deal with a large volume of technology-dependent children, to have this modality available in the office to enhance monitoring.
- Infrared spectrometry is the most commonly used method of capnography.
  - — Infrared radiation passing through the sample chamber is absorbed by CO_2.
  - — The remaining unabsorbed radiation is detected by a semiconductor, which converts it into a continuously displayed electrical signal that is directly proportional to the concentration of CO_2.
- Since CO_2 is produced in the tissues, transported in the blood, exchanged in the lungs, and expired through the airways, capnography is an integrated indicator of the functions of the respiratory, cardiovascular, and metabolic systems.
- Though frequently used by anesthesiologists as a tool to monitor the adequacy of ventilation in the surgical setting, capnography continues to develop wider applications outside the perioperative setting.
- The capnogram obtained during expiration is described in 3 phases (Figure 9-3).
  - — Phase zero represents the gas from the anatomic dead space (trachea) that contains no CO_2.

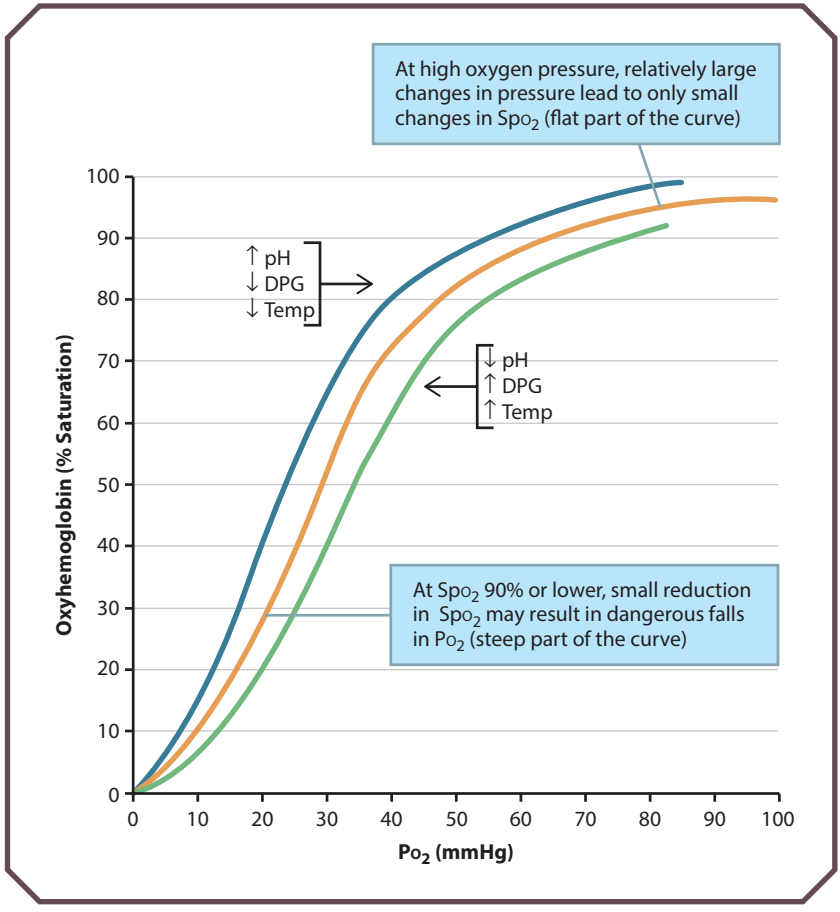

Figure 9-2. The oxygen dissociation curve demonstrates the relationship between partial pressure of oxygen (Po_2) and the percentage of hemoglobin saturation with oxygen (Spo_2). As can be seen from the curve, the relationship between Po_2 and Spo_2 is not linear but S-shaped. At higher Po_2 levels, the curve flattens out, indicating that there is little incremental increase in Spo_2. Fever, acidosis, and increased levels of diphosphoglycerate (DPG) reduce affinity for hemoglobin with oxygen, demonstrating a "shift to the right" for the curve, which leads to unloading of O_2 to the tissues.

— In phase 2, the curve increases sharply as CO_2-containing alveolar gas mixes with dead space. As expiration continues, more and more of the alveoli empty, and CO_2 concentration increases rapidly.
— In phase 3, a plateau is reached as end-expiration is reached.
— As the next inspiration begins, the CO_2 level decreases sharply to zero. The point at which the plateau ends, just before inspiration, is referred to as the *end-tidal CO_2 concentration.*

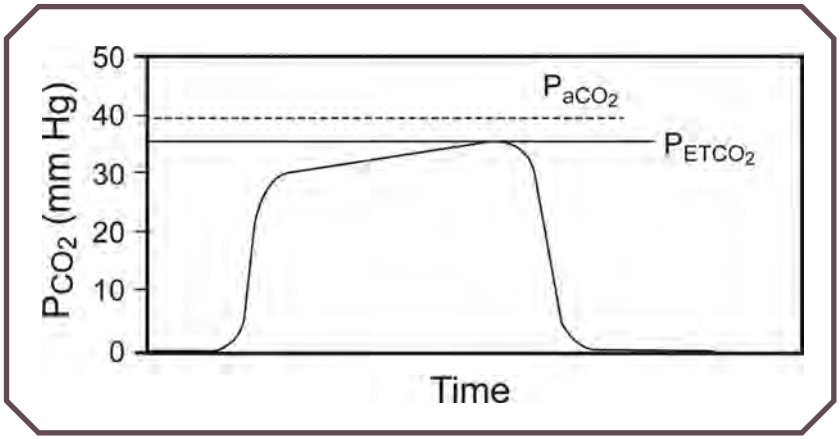

Figure 9-3. Sample capnogram. $PETCO_2$ = end-tidal CO_2 concentration.

Clinical Applications of End-Tidal CO_2 Concentration Monitoring

- Confirming endotracheal intubation
- Assessing effectiveness of cardiopulmonary resuscitation
- Monitoring real-time alveolar ventilation in the intensive care unit setting
- Monitoring ventilation in the home ventilator setting (ventilator setting adjustments)
- Monitoring changes in dead space while the patient is receiving ventilator support (eg, mucus plugging, bronchospasm)

Resources for Families

- 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

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Part II. Anatomic Disorders and Congenital Anomalies of the Airway, Lungs, Pulmonary Vessels, and Chest Wall

Associate Editor: Mary E. Cataletto, MD, MMM, FAAP, FCCP

SECTION 1. CONGENITAL ANOMALIES OF THE AIRWAY

SECTION 2. DEVELOPMENTAL ANOMALIES OF THE LUNG AND PULMONARY VESSELS

SECTION 3. STRUCTURAL ABNORMALITIES OF THE CHEST WALL

Section 1. Congenital Anomalies of the Airway

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Chapter 10

Choanal Atresia

Nathan S. Alexander, MD, and James W. Schroeder, Jr, MD, FACS, FAAP

Introduction/Etiology/Epidemiology

- Choanal atresia is a relatively rare congenital craniofacial defect characterized by the obstruction of the posterior nasal passages.
- The incidence rate has been noted to range between 1 in 5,000 and 1 in 10,000 live births. Although it had long been thought that a 2:1 ratio favored both female to male patients and unilateral to bilateral cases, extensive literature reviews have shown that the ratio is closer to 1:1 for both relationships.
- Unilateral cases are likely to be isolated (unrelated to other congenital anomalies); bilateral cases are likely to be associated with specific disorders or multiple congenital anomalies (98%).

Pathogenesis

- The pathogenesis of choanal atresia is not fully understood.
- The most widely accepted theory is that affected individuals have either an abnormal persistence of the buccopharyngeal membrane from the foregut or persistence of the nasobuccal membrane of Hochstetter, which typically resorbs around the sixth week of gestation.

Clinical Features

- Neonates are classically thought to be obligate nose breathers, though some newborns are better able to switch to mouth breathing when required.
  - — By 4–6 weeks of life, almost all infants are able to manage mouth breathing well.
- As such, presentation of choanal atresia can look very different between bilateral and unilateral atresia, given the degree of airway obstruction.
  - — Bilateral choanal atresia is often diagnosed soon after birth and appears with complete nasal obstruction, which manifests with apnea and results in decreased oxygen saturation, which is subsequently relieved by crying (cyclic cyanosis). This can represent a medical emergency. Feeding difficulty can also be the alerting event, where a newborn's suck-swallow-breathe reflex is severely impaired by the bilateral nasal obstruction.

— Unilateral choanal atresia may present later in infancy. These patients typically do not present with neonatal respiratory distress but instead present later in life (usually at 5–24 months of age, sometimes closer to 5 years of age, and rarely in adulthood). The most common presentation in these patients is chronic unilateral nasal obstruction, persistent rhinorrhea, or chronic sinusitis.

Differential Diagnosis

- Rhinitis—viral, bacterial
- Deviated nasal septum (may be from birth trauma)
- Nasal foreign body
- Nasal turbinate hypertrophy
- Pyriform aperture stenosis (congenital narrowing of the anterior nasal cavity)
- Adenoid hypertrophy (unlikely in a neonate)

Diagnostic Considerations

- Diagnosis is determined in a stepwise fashion.
- First, physical examination is performed specifically to look for fogging of a mirror or a cold speculum held under the nare during exhalation. Movement of a cotton wisp under the nare may also be helpful.
- Second, passage of a 5-F to 8-F flexible suction catheter through the nose may help establish patency of the nasal passage.
  — Resistance within 1–2 cm of the alar rim may imply misdirection toward the superior nasal cavity or deflection from the turbinate(s) or piriform aperture stenosis.
  — Resistance at 32–35 mm indicates an issue with potential obstruction at the level of the choana.
- Third, referral to a pediatric otolaryngologist for flexible nasal endoscopy after mucosal decongestion is necessary to visualize the actual point of resistance and establish the diagnosis.
- Finally, unenhanced computed tomography of the facial bones and sinuses with 2–5-mm sections is performed with proper prescanning preparation of the nasal cavity (to include decongestion of the nasal mucosa and suctioning of the nasal secretions). The scan should be ordered in consultation with a pediatric otolaryngologist to ensure that the proper study and timing are scheduled to prevent unnecessary radiation exposure. This facilitates assessment of the thickness of the atresia plate and the degree of lateral pterygoid plate and medial vomerine involvement, as well as planning for surgical intervention (Figure 10-1).

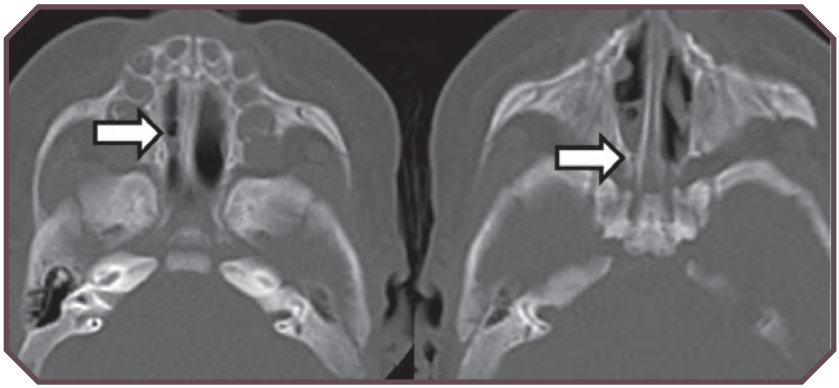

Figure 10-1. Choanal atresia in a 1-day-old female neonate with difficulty breathing. Axial computed tomographic bone window images show narrowing of the right nasal canal (arrows).

Management

- In the case of a neonate with bilateral choanal atresia in respiratory distress, initial treatment includes placement of an oral airway, a McGovern nipple (a standard nipple with an enlarged hole, secured with a tracheostomy tie), or oral intubation.
- Nutritional support can be provided with an orogastric feeding tube placed alongside the McGovern nipple or oral airway.

Surgical Repair

Transnasal Puncture

- The classic technique involves using a curved trocar while protecting the skull base with a finger in the mouth. Progressively larger dilators then enlarge the opening.
- This method has fallen out of favor for its high restenosis rate, inability to visualize the surgical field, and inability to allow resection of the posterior vomer.
- This technique has been refined to improve visualization by using laryngeal mirrors and nasal endoscopes (Figure10-2). More recently, balloon dilation has been used for initial dilations, as well as revisions.
- The transnasal puncture technique is not recommended for a thick bony atretic plate or patients with CHARGE syndrome (coloboma of the eye, heart anomaly, choanal atresia, retardation, and genital and ear anomalies).

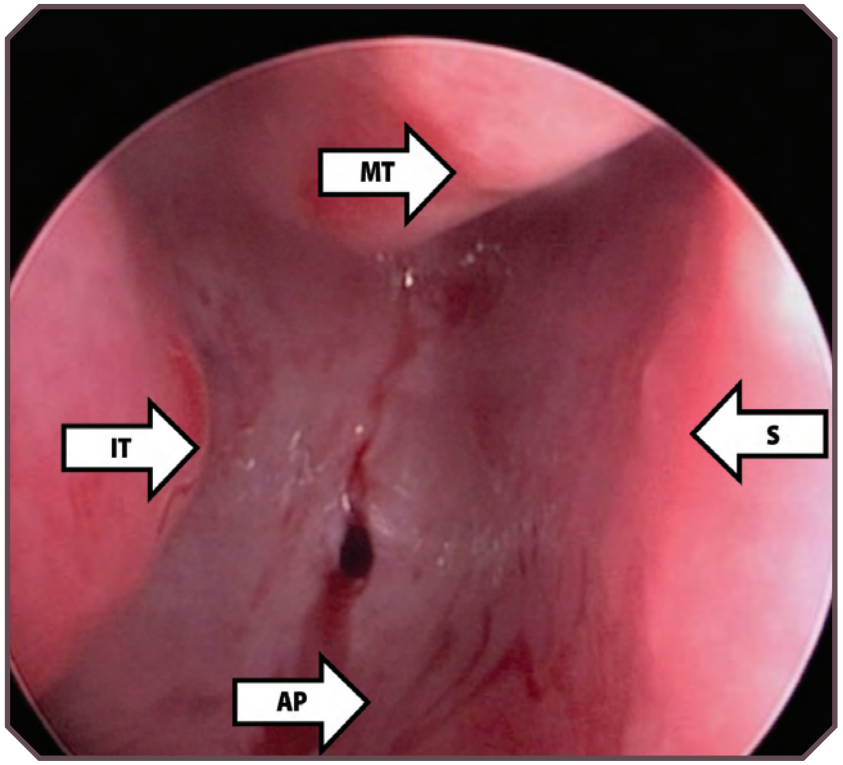

Figure 10-2. The right choanal atresia plate is demonstrated after endoscopic transnasal puncture, prior to dilation. AP = atretic plate, IT = inferior turbinate, MT = middle turbinate, S = septum.

Transpalatal Repair

- Transpalatal repair (Figure 10-3) involves a U-shaped mucosal incision along the alveolar arch. A mucosal flap is developed on the basis of the greater palatine vessels. The atresia plates are drilled by using a diamond burr.
- Despite success rates of approximately 84%, this technique has fallen out of favor, given its increased risk of impairment of palatal growth, which can subsequently lead to maxillary development abnormality and crossbite (52% risk). Palatal fistula, postoperative pain, and flap breakdown are more serious potential complications from the procedure.

Transnasal Endoscopic Repair

- Transnasal endoscopic repair has become the primary and preferred surgery for the repair of choanal atresia by most pediatric otolaryngologists.
- This technique involves the use of a Hopkins rod telescope placed through the nasal cavity to evaluate the atretic plate. A 120° Hopkins rod-lens telescope is placed transorally to view the choana from the

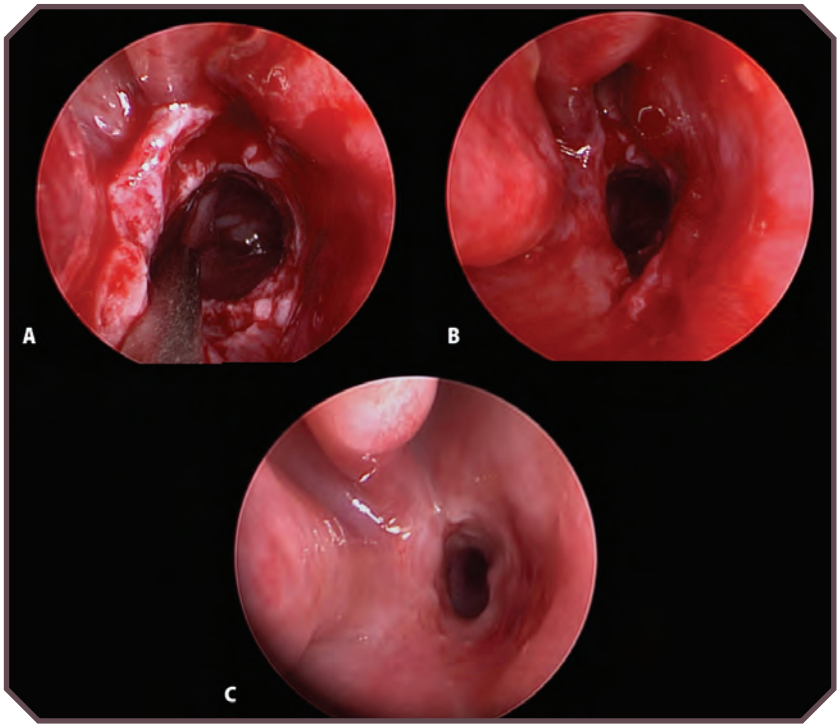

Figure 10-3. Endoscopic images of right choanal atresia repair. A. The mucosal flap has been elevated on the lateral wall to create space for the drill-out of the vomer and lateral nasal wall. B. The flap has been laid in position. C. Postoperative image obtained 1 month after the procedure.

nasopharynx. This allows for the controlled puncture of the atretic plate under direct vision endoscopically. Once this controlled puncture is performed, that aperture within the atretic plate can be enlarged with urethral sounds and/or balloons. Use of a backbiter nasal punch, microdebrider, curette, and drill may also be used.

Controversies

- **Postoperative stent placement:** After the creation of a patent choana, there has long been the theory that to reduce the risk of restenosis, a postoperative stent should be placed. However, some surgeons will opt not to place a postoperative stent. Most surgeons will require those who have undergone choanal atresia repair to return for postoperative debridement and dilation either in the office or in the operating room with anesthesia.
- **Mitomycin C:** An antitumor aminoglycoside antibiotic, mitomycin C inhibits fibroblast proliferation and migration. Topical application has shown some improvement in outcomes after choanal atresia repair.

Treating Associated Conditions

- Associated congenital anomalies are seen in 50%–70% of cases of choanal atresia.
- The most commonly seen associated abnormalities are those that occur with CHARGE syndrome (Box 10-1).
- Given the prevalence and association with CHARGE syndrome, consultations with personnel from ophthalmology, cardiology, neurology, nephrology, otolaryngology, and genetics are appropriate. In children who present with the defects of CHARGE syndrome, 50% will have some form of choanal atresia.

Expected Outcomes/Prognosis

- Surgical success in repairing choanal atresia is dependent on the technique used.
- Transnasal endoscopic repair is reported to have a success rate of approximately 85%.
- Children with bilateral atresia (who often undergo surgery early in life), CHARGE syndrome, or other craniofacial abnormalities may require multiple surgeries to decrease restenosis.

Box 10-1. Diagnostic Criteria for CHARGE Syndrome

Major	Minor	Diagnosis
Ocular coloboma	Cardiovascular malformations	Typical CHARGE: 4 major elements or 3 major elements and 3 elements
Choanal atresia	Genital hypoplasia	
Characteristic ear abnormalities	Cleft lip and/or palate	
Cranial nerve abnormalities, including SNHL	Tracheoesophageal fistula	
	Hypothalamic-hypophyseal dysfunction	
	Distinctive CHARGE facies	
	Developmental delay	

CHARGE, coloboma of the eye, heart anomaly, choanal atresia, retardation, and genital and ear anomalies; SNHL, sensory nerve hearing loss.

From Ramsden JD, Campisi P, Forte V. Choanal atresia and choanal stenosis. *Otolaryngol Clin North Am.* 2009;42(2):339–352. Copyright 2009, with permission from Elsevier.

- Some children who present with severe respiratory distress may also require a temporary tracheostomy in addition to the surgical correction of choanal atresia.

When to Refer

- Children with unilateral nasal obstruction with or without unilateral rhinorrhea should be referred for evaluation by a pediatric otolaryngologist. A nasal foreign body must be ruled out in cases of acute-onset unilateral nasal obstruction.
- Newborns with bilateral nasal obstruction, failure to thrive, feeding difficulty (marked by frequent pauses to breathe), and obstructive sleep apnea should be evaluated for bilateral choanal atresia.
- When a newborn with signs of nasal obstruction (chronic mouth breathing, snoring, poor feeding, failure to thrive) cannot accommodate the passage of a 6-F flexible catheter placed through the nasal cavity and into the nasopharynx (6 cm), then a referral to a pediatric otolaryngologist should be initiated.

When to Admit

- A newborn with bilateral nasal obstruction should be admitted until choanal atresia can be ruled out.
- A newborn with symptoms suggestive of CHARGE syndrome (Box 10-1) should be admitted for workup.
- Children with unilateral choanal atresia may be relatively asymptomatic. In these cases, surgical intervention to address the unilateral nasal obstruction can be delayed until the child is older (up to but preferably prior to reaching school age). In these cases, surgery is typically performed on an outpatient basis.

Prevention

- Regarding environmental risk factors, several models have been studied, including the role of retinoic acid deficiency, the role of thioamides (commonly used to treat hyperthyroidism), and the actual state of increased thyroid-stimulating hormone levels.
- Regarding genetic risk factors, the strongest link is within the subgroup associated with CHARGE syndrome—most commonly associated with a new mutation of the dominant gene *CHD7*.

Resources for Families

- About Choanal Atresia (Children's Hospital of Philadelphia). www.chop.edu/conditions-diseases/choanal-atresia/about
- The CHARGE Syndrome Foundation. www.chargesyndrome.org
- Choanal Atresia: Bilateral (The Hospital for Sick Children). www.aboutkidshealth.ca/en/healthaz/conditionsanddiseases/earnoseandthroatdisorders/pages/choanal-atresia-bilateral.aspx

Clinical Pearls

- Choanal atresia is a relatively rare congenital craniofacial defect characterized by the obstruction of the posterior nasal passage.
- Unilateral cases are likely to be isolated (unrelated to other congenital anomalies); bilateral cases are likely to be associated with specific disorders or multiple congenital anomalies (98%).
- Bilateral choanal atresia is often diagnosed soon after birth and appears with complete nasal obstruction at presentation.
- Unilateral choanal atresia may appear later in infancy.
- Associated congenital anomalies are seen in 50%–70% of cases of choanal atresia.
- The most commonly seen associated abnormalities are those that are seen with CHARGE syndrome.
- When a newborn shows signs of nasal obstruction (chronic mouth breathing, snoring, poor feeding, and failure to thrive) and cannot accommodate the passage of a 6-F flexible catheter placed through the nasal cavity and into the nasopharynx (6 cm), then a referral to a pediatric otolaryngologist should be initiated.

Chapter 11

Laryngomalacia

Mary E. Cataletto, MD, MMM, FAAP, FCCP

Introduction/Etiology/Epidemiology

- Laryngomalacia (LM) is the most common cause of stridor in newborns and the most common laryngeal disease of infancy.
- LM is defined as collapse of supraglottic structures (epiglottis and/or arytenoids) during inspiration.
- LM is thought to be caused by neuromuscular alteration in laryngeal tone and resultant prolapse of the supra-arytenoid tissue and supraglottic collapse, which causes airflow obstruction.
- The epidemiology of LM is poorly defined.
- In a 2012 systematic review of LM and acid reflux, Hartl and Chadha identified an almost 10-fold increase in reflux prevalence in infants with moderate to severe LM, as compared to those with mild LM. The prevalence rate for gastroesophageal reflux in infants with severe LM was 65% in this review. However, direct causality has not been established.
- Acquired LM can also occur and should be considered in children who present with sleep-associated stridor, upper airway obstruction, and apnea.

Signs and Symptoms

Stridor

- See Chapter 2, The Pediatric Pulmonary Physical Examination, for evaluation of stridor.
- Timing is predominantly inspiratory but may also be biphasic.
- Quality is high pitched, musical, and vibrating.
- Approximately 10% of infants may have respiratory distress, aspiration, apnea, cyanotic episodes, or poor weight gain with difficulty feeding.
- Stridor of LM often worsens with agitation, crying, feeding, and lying in the supine position.

Associated Findings and Comorbidities

- Feeding difficulty can occur with coughing, choking, regurgitation, vomiting, and slow oral intake. Aspiration or cyanotic episodes can also occur.
- Gastroesophageal reflux disease (GERD) and laryngopharyngeal reflux disease (LPRD) may be present.

- Excluding GERD and LPRD, 25%–50% of patients will have an additional comorbidity (eg, neurological disease, congenital heart disease, genetic syndromes, or the presence of a secondary airway lesion).

Clinical Course

- Clinical course is affected by multiple factors, including laryngeal anatomy and supraglottic tone, as well as the presence of mucosal edema and decreased airflow.
- The developmental changes in airway anatomy that predispose the young infant to LM are no longer evident by 18–24 months of age.
- The typical course of LM is
  - Onset within the first 2 weeks after birth
  - Increased symptoms between 4 and 8 months
  - Improvement between 8 and 12 months
  - Resolution by 12–24 months

Diagnostic Considerations

- Flexible laryngoscopy performed in the awake infant allows dynamic evaluation of the larynx, providing a diagnosis as well as demonstrating other causes of supraglottic obstruction.
  - Typical findings at direct laryngoscopy (Figure 11-1; see also Video 11-1 at https://www.aap.org/en-us/restricted/pediatric-pulmonology) include the following.
    - During expiration, the glottis is patent, and no abnormal sounds are heard.
    - During inspiration, the epiglottis and arytenoids collapse and compromise the glottic opening, causing inspiratory stridor.
  - CAUTION: In cases of severe LM, it is often difficult to visualize vocal cord mobility. It is prudent to visualize and assess the vocal cords so as not to miss vocal cord paralysis or dysfunction.

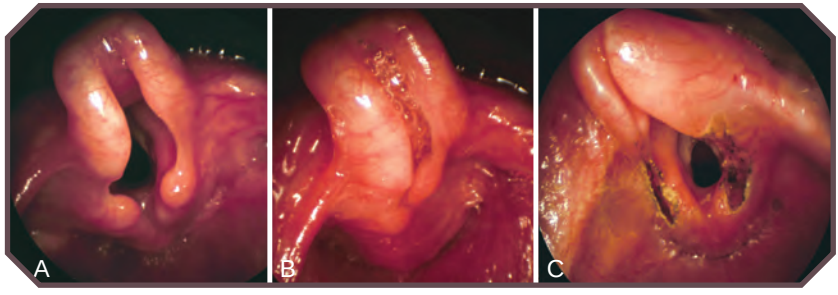

Figure 11-1. Laryngomalacia (LM) as seen at flexible laryngoscopy. A. During expiration the glottis is patent, and no abnormal sound is heard. B. During inspiration the epiglottis and arytenoids collapse and compromise the glottic opening, causing inspiratory stridor. C. In cases of severe LM, surgical resection of redundant tissue can improve glottic patency, even during inspiration. From Vicencio AG, Bent JP. Stridor. In: McInerny TK, Adam HM, Campbell DE, DeWitt TG, Foy JM, Kamat DM, eds. *American Academy of Pediatrics Textbook of Pediatric Care*. 2nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2017:1615–1620.

- Clinical examination and additional evaluation may be performed when necessary to identify comorbid conditions and/or syndromes.
- Rigid endoscopy performed with general anesthesia may be necessary. It is generally considered in patients with
  - Severe LM
  - Discrepancy between symptom severity and laryngoscopy
  - Scheduled surgical supraglottoplasty

Treatment

Medical

- In most infants with LM, it is managed conservatively.
- Feeding modification (pacing, thickened liquids and foods, upright positioning) may be helpful; however, many infants will require antireflux medications.
- Antireflux therapy is helpful in patients undergoing supraglottoplasty, in both the pre- and postoperative periods, until healing has occurred.

Surgical

- The preferred surgical intervention for infants with severe LM is supraglottoplasty, also known as *aryepiglottoplasty*. The procedure focuses on the infant's individual area of obstruction and may include *(a)* removal of redundant cuneiform cartilages or obstructing portions of the epiglottis or arytenoids and *(b)* lysis of tight aryepiglottic folds.
- Surgical decision-making is based on evaluation of clinical course with emphasis on growth, feeding, work of breathing, presence of episodes of cyanosis and/or apnea, hypoxia, aspiration with recurrent pneumonia, and pulmonary hypertension.

Prognosis

- Most cases of congenital LM are mild, and stridor resolves by 18–24 months.
- Approximately 10% of cases are severe and will require surgical intervention. The success rate of supraglottoplasty is about 94%.
- Tracheostomy is rare; it may be considered for those who have life-threatening symptoms and who do not improve after supraglottoplasty.
- Untreated, these infants can suffer from chronic hypoxia that leads to pulmonary hypertension and cor pulmonale.
- Synchronous airway lesions may occur and can cause additional airflow obstruction. Tracheomalacia and subglottic stenosis are the most common synchronous airway lesions.

When to Refer

- Flexible laryngoscopy performed while the patient is awake should be considered in any infant with stridor when a definitive diagnosis is desired, including when noisy breathing does not resolve within the expected time frame.
- Refer infants with LM and failure to thrive, feeding difficulty, episodes of respiratory distress, and apneic or cyanotic episodes for surgical consideration.

Resources for Families

- Coping With Laryngomalacia, Inc. www.copingwithlm.org
- Laryngomalacia (U.S. National Institutes of Health, Office of Rare Diseases Research). rarediseases.info.nih.gov/gard/6865/Laryngomalacia/resources/1

Clinical Pearls

- Listening for LM symptoms alone can be misleading and result in an incorrect diagnosis. The diagnosis of LM can only be established by means of direct visualization.
- It can be difficult to visualize the vocal cords in infants with severe LM. While an uncommon finding, it is prudent to consider concomitant bilateral vocal cord immobility.
- Pediatric aerodigestive programs offer an integrated and multidisciplinary approach to caring for infants and children with LM. These teams typically include pediatric pulmonologists, gastroenterologists, and otolaryngologists.

Chapter 12

Vocal Fold Paralysis

Marisa A. Earley, MD, and Max M. April, MD, FACS

Introduction/Etiology/Epidemiology

- Vocal fold paralysis in children is an uncommon and challenging problem.
- Vocal fold paralysis can be classified as unilateral vocal fold paralysis (UVFP) or bilateral vocal fold paralysis (BVFP).
  - UVFP
    - The leading cause is iatrogenic after cardiac surgery (most commonly patent ductus arteriosus ligation), tracheoesophageal fistula repair, transcervical excision of branchial anomalies, or thyroidectomy.
    - Additional causes include trauma, intubation, cardiovascular anomalies, peripheral neurological disease, infection, and idiopathic origins.
    - Left-sided paralysis (Figure 12-1; see also Video 12-1 at https://www.aap.org/en-us/restricted/pediatric-pulmonology) is more common secondary to recurrent laryngeal nerve (RLN) having a longer course from the brainstem, through the neck, into the chest, and around the aortic arch on the left. The right RLN has a similar descent but travels around the right subclavian artery. Both nerves then ascend in the neck to innervate the larynx.
  - BVFP
    - A neurological etiologic origin is encountered most frequently, with Arnold-Chiari malformation being the most common central nervous system cause.
    - Additional causes include idiopathic origins, followed by birth trauma (forceps, breach, or vertex delivery) and vincristine toxicity.
    - A more severe condition than UVFP, BVFP often requires intubation immediately after birth.

Clinical Features

- Stridor, with or without respiratory distress
  - Stridor occurs in nearly all children with BVFP and 75% of children with UVFP.
  - Airway obstruction that necessitates intervention is more common with BVFP.
- Dysphonia
  - Dysphonia occurs in 50% of children with UVFP.
  - It is less common in BVFP because the vocal folds are in the midline position, versus the paramedian position with UVFP.

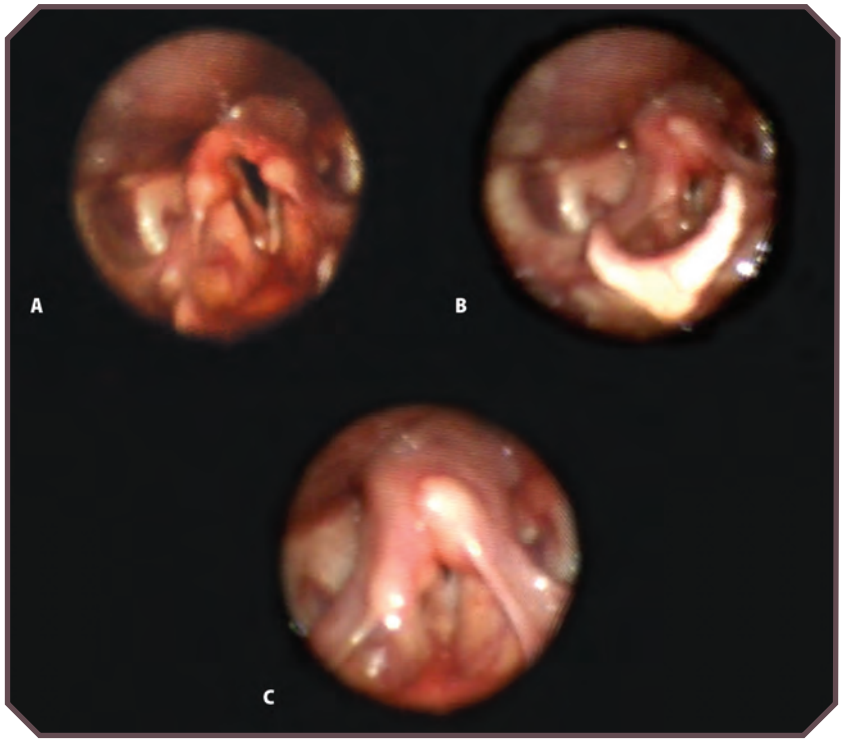

Figure 12-1. Flexible laryngoscopic images demonstrate unilateral vocal fold paralysis of the left vocal fold. A. On the image obtained during inspiration, the left vocal fold appears atrophic and pale but normal in length. B, C. During phonation, the left vocal fold is noted to be fixed in a paramedian position, with no change in position. The right vocal fold appears hyperemic secondary to trauma and from compensation for the left-sided paralysis.

  - It may cause social, academic, and behavioral problems as children age.
  - The child's family may "get used to" the dysphonic voice, the child may not speak at the physician's office, and children cannot articulate vocal concerns, which make this feature harder to diagnose.
- Feeding difficulty
  - Occurs in 25% of children with UVFP
  - Less common in BVFP unless secondary to underlying neurological disorder
- Aspiration
  - Secondary to poor glottic closure and/or competency in UVFP

Differential Diagnosis

- Laryngomalacia
- Glottic web
- Vocal fold nodules, cysts, or other vocal fold lesions
- Cricoarytenoid joint fixation or subluxation

- Subglottic stenosis
- Laryngeal cleft
- Intubation granuloma
- Infection

Diagnostic Considerations

- Flexible laryngoscopy may be performed in the office or at the bedside; ideally, it should be recorded for review and be used to follow the progress of the condition, which may resolve without intervention.
- Direct suspension microlaryngoscopy and bronchoscopy can be performed to rule out joint fixation and other laryngotracheal anomalies.
- Video fluoroscopic swallow study (modified barium swallow [MBS]) or fiber-optic endoscopic evaluation of swallowing may be conducted to assess swallowing dysfunction and rule out aspiration.
- Magnetic resonance (MR) imaging should be performed from the brain to the mediastinum in all cases of BVFP and in the absence of known iatrogenic causes of UVFP to image the brain and the full course of the RLN.
- Ultrasonography performed to assess vocal fold mobility has been described but is technician dependent.
- Laryngeal electromyography (LEMG) for UVFP
  - Performed with general anesthesia in the operating room
  - Can be used to assess the degree of abnormality when compared to the contralateral vocal fold (normal findings vs high-grade injury vs low-grade injury)
  - Good predictor of poor recovery; for instance, a high-grade injury has a low likelihood of spontaneous recovery
    - This can help eliminate long observation periods or unnecessary temporary procedures when a definitive one is needed.
  - Must wait at least 10–14 days after injury but otherwise may be performed at any time during the course of evaluation

Management

- Spontaneous recovery is possible; therefore, most clinicians observe the patient for 1–2 years after injury or diagnosis.
- Management is directed at symptoms: airway versus voice versus swallowing. Treatment of one may affect the others.
  - The focus for neonates and children younger than school age should be airway and feeding.
- Assess the need for urgent securing of the airway.
  - Patients with BVFP may require temporary tracheostomy tube placement.
- Aspiration prevention
  - Feeding modifications may be indicated, with or without injection laryngoplasty for UVFP.

- BVFP
  - Observation
  - Noninvasive positive pressure ventilation
    - May only be required at night and to prevent tracheostomy
  - Tracheostomy
  - Endoscopic procedures to improve airway: laser cordotomy, suture lateralization of vocal fold, arytenoidectomy, arytenoidopexy, posterior cricoid grafting
    - These procedures may increase the risk of aspiration.
  - Botox injected into the bilateral cricothyroid, sternothyroid, and sternohyoid muscles may improve the glottic airway.
  - Open airway procedures
    - Often reserved for older children
- UVFP
  - Observation, with or without speech therapy, is based on the child's disposition and maturity level.
  - Injection laryngoplasty (temporary)
    - Various injectable substances with different durations of improvement
      - ~ Collagen products, autologous fat, hydrated porcine gelatin, sodium carboxymethylcellulose aqueous gel, acellular cadaveric dermis, and calcium hydroxylapatite
    - Good voice function and voice handicap outcomes
    - Temporary (2 weeks to ≥6 months, depending on the substance used)
- Laryngeal framework surgery
  - Thyroplasty implants are inserted transcervically to medialize the vocal fold; this is for older adolescents, as the natural growth of the larynx may alter the position of the implant or require a change in size when performed in young children.
  - This surgery may be performed with local anesthesia to assess the voice and the medialization of the vocal fold during the procedure, which requires a calm, cooperative patient.
- Laryngeal reinnervation (ansa cervicalis to RLN anastomosis)
  - No need for the patient to be awake or cooperative
  - Good outcomes in children to date, but with limited data
  - Appears to lead to better and long-term improvements in voice quality, acoustic measures, and satisfaction when compared to injection laryngoplasty
  - RLN is sacrificed; therefore, no chance of spontaneous recovery

Treating Associated Conditions

- Case dependent
- Gastroesophageal reflux disease
  - May contribute to edema and inflammation of the larynx, resulting in airway or voicing difficulties

Expected Outcomes/Prognosis

- Spontaneous recovery may be seen within 2 years; some studies document longer time to recovery.
- Approximately 65% of patients with iatrogenic causes of UVFP will not spontaneously recover.
- Up to 61% of patients with BVFP will have full or partial recovery
  - If MR imaging demonstrates Arnold-Chiari malformation or hydrocephalus, BVFP may resolve when these conditions improve.
- LEMG may aid in identifying patients with poor prognosis sooner.

When to Refer

Refer patients to a pediatric otolaryngologist in the following cases:

- Neonate with stridor and/or respiratory distress.
- Dysphonic child, especially if there is any history of cardiothoracic or neck surgery or prematurity.
- Patient with stridor, dysphonia, feeding difficulty, or aspiration after cardiothoracic surgery.
- Child with recurrent pneumonia or silent aspiration at MBS—even a neurologically normal infant or child.

When to Admit

- Signs of acute respiratory distress
- Complications of aspiration (ie, pneumonia)

Resources for Families

- Vocal Cord Paralysis (American Speech-Language-Hearing Association). www.asha.org/public/speech/disorders/vfparalysis (also available in Spanish)
- Vocal Cord Paralysis (Stanford Children's Health). www.stanfordchildrens.org/en/service/ear-nose-throat/conditions/vocal-cord-paralysis
- Vocal Cord Paralysis (Speech Buddies). www.speechbuddy.com/blog/speech-disorders/vocal-cord-paralysis

Clinical Pearls

- Patients with UVFP can present with stridor.
- BVFP typically has more severe respiratory symptoms at presentation.
- Patients with BVFP may have a normal voice or cry.
- MR imaging should be included in the workup of all patients with BVFP.

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Chapter 13

Subglottic Stenosis

Claudia Fernandez, MD

Introduction/Etiology/Epidemiology

- Subglottic stenosis refers to a narrowing of the subglottic space that extends from just under the true vocal cords to the lower margin of the cricoid cartilage.
- The cricoid cartilage is a complete ring, as opposed to the trachea, where a posterior membrane allows for expansion of the lumen. The narrowest portion of the infant airway is the inferior cricoid ring.
- The normal subglottic area diameter in the term infant is 4–7 mm; in the preterm infant, it is 3.5–4.5 mm.
- A 1-mm circumferential reduction of diameter will reduce the cross-sectional area by 60% and markedly increase airway resistance.
- Subglottic stenosis is classified as either congenital or acquired.
  - Congenital
    - Congenital subglottic stenosis constitutes 5%–15% of all airway malformations.
    - It is the third most common laryngeal anomaly (after laryngomalacia and vocal cord paralysis).
    - It is one of the most common causes of stridor in neonates. The true frequency is unknown, since there is a high risk for fetal death or development of postintubation acquired stenosis due to respiratory distress at birth.
    - It is often associated with other congenital head and neck lesions.
    - There is increased prevalence in children with trisomy 21.
  - Acquired
    - The most common etiologic origin is scarring secondary to endotracheal intubation.
    - It is the third most common indication for tracheostomy in children.
- The degree of stenosis is classified with a staging system developed by Myer and Cotton (Figure 13-1). They proposed using different sizes of endotracheal tubes to measure the percentage relative reduction in the cross-sectional area of the lumen.

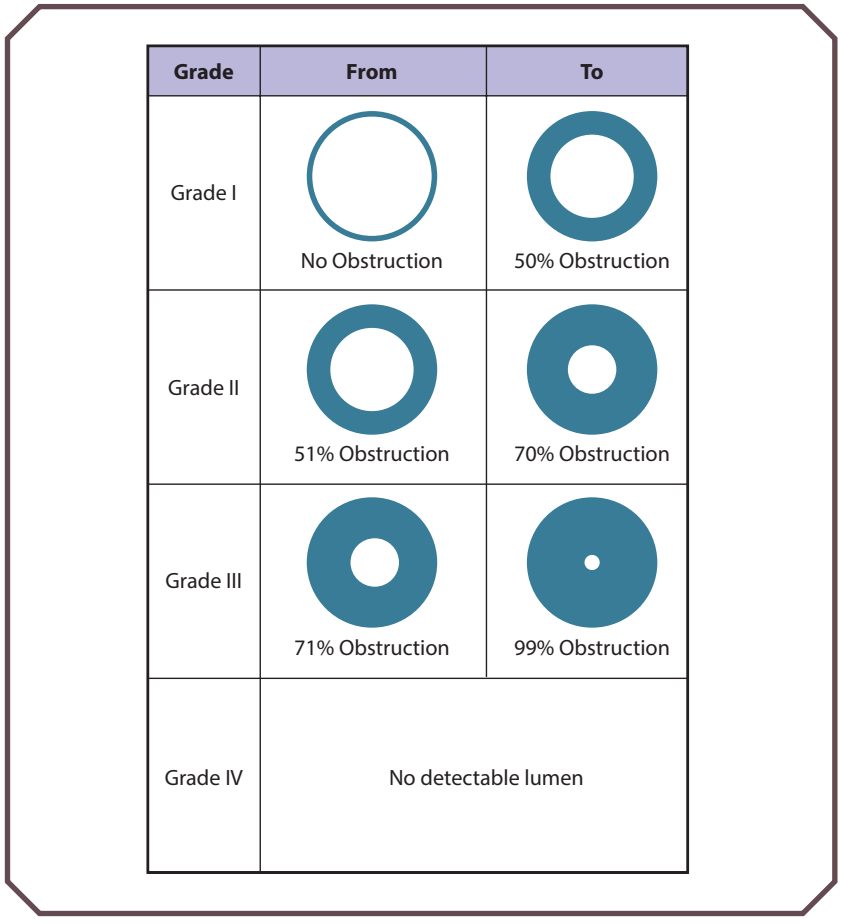

Figure 13-1. The Myer-Cotton staging system for subglottic stenosis. From Myer CM III, Hartley BE. Pediatric laryngotracheal surgery. *Laryngoscope.* 2000;110(11):1875–1883. Copyright © 2000 John Wiley & Sons, Inc.

Pathophysiology

- Congenital subglottic stenosis (CSS)
  - — Failure of the laryngeal lumen to canalize during embryogenesis
  - — Can be categorized into the following 2 types:
    - Membranous CSS (more common): There is fibrosis, submucosal gland hyperplasia, and granulation tissue formation in the subglottic area. Endoscopy demonstrates a circumferential and symmetrical shape.
    - Cartilaginous CSS: This refers to abnormal development of the cricoid cartilage. Endoscopy might show *(a)* a symmetrical lumen if the cricoid cartilage is small or *(b)* an asymmetrical lumen when the cricoid cartilage has an elliptical shape or when the submucosal cleft is associated with CSS.

  - Can occur as an isolated condition or as part of a syndrome in conjunction with other congenital anomalies
  - Laryngeal atresia is the most severe form
  - Trisomy 21 is associated with a higher incidence of CSS
- Acquired subglottic stenosis
  - The most common mechanism is mechanical trauma that leads to edema with subsequent infection. The pathophysiology after chemical trauma is similar. Sometimes CSS and acquired subglottic stenosis occur concurrently.
  - Risk factors include long-term intubation, recurrent intubation, inappropriately large endotracheal tube, prematurity, trauma, eosinophilic esophagitis, gastroesophageal reflux, bacterial laryngotracheitis, and trisomy 21.
  - A tracheostomy placed higher in the trachea may also lead to scarring in the subglottic area and cause acquired subglottic stenosis.

Clinical Features

- Biphasic stridor with or without respiratory distress is the most common presentation
- Brassy or barky cough
- Difficulty breathing, which may be present in more severe cases or appear intermittently during intercurrent viral infection
- Hoarseness
- Weak cry
- Fatigue with feeding
- Recurrent or prolonged croup in any child, particularly those presenting at <6 months of age or with a history of prolonged intubation
- Some infants may be asymptomatic for weeks or months, even in the presence of clinically significant stenosis

Differential Diagnosis

- Vascular malformation (eg, hemangiomas)
- Laryngomalacia and/or tracheomalacia
- Infectious croup
- Vocal cord immobility
- Tracheal stenosis
- Foreign body
- Gastroesophageal reflux
- Subglottic cyst
- Epiglottitis
- Bacterial tracheitis

Diagnostic Considerations

- Prenatal ultrasonography is helpful in the diagnosis of congenital high-airway obstruction syndrome that results from complete stenosis or atresia, which includes enlarged and echogenic lungs, flattened or inverted diaphragm, dilated tracheobronchial tree below the site of obstruction, and fetal ascites and/or hydrops.
- History can include prematurity, difficult or prolonged intubation, feeding difficulty associated with fatigue and sometimes failure to thrive, and syndromes associated with increased prevalence of subglottic stenosis, such as trisomy 21.
- At physical examination, perform careful characterization of stridor, work of breathing, nutritional status, and presence of associated anomalies, especially craniofacial (mandible size, hemangioma presence in a beard distribution).
- For airway imaging, high-kilovoltage airway radiographs, including posteroanterior and lateral views, show the typical bilateral narrowing (steeple sign) found in croup on a frontal view. The absence of concomitant tracheal stenosis should be noted in this view (Figure 13-2). Unilateral airway narrowing is more typical of masses, such as infantile hemangiomas (Figure 13-3).
- For direct visualization, flexible laryngoscopy and bronchoscopy are the standard of reference for diagnosis and for determining the degree of stenosis.

Management

- Determined by the symptoms, etiologic origin, and degree of stenosis
- Medical management
  - — At birth: If congenital high-airway obstruction syndrome is present prenatally, ex utero intrapartum treatment ("EXIT" procedure) may be lifesaving. It consists of performing a procedure such as tracheostomy while the baby is still attached to the placenta by the umbilical cord.
  - — After birth: In the asymptomatic infant, a conservative approach is generally recommended. Medical management of associated conditions such as gastroesophageal reflux disease is important to avoid scarring and worsening the degree of stenosis.
- Surgical management
  - — Endoscopic balloon dilation is most commonly used in mild but symptomatic cases. It may be followed by topical or injected steroids or topical mitomycin (Figures 13-4, 13-5). It is also used for temporary relief of severe stenosis until definitive surgery can be performed.
  - — Anterior cricoid cartilage split is indicated primarily in severe cases. An endotracheal tube is left as a stent in the airway while soft tissue forms in the gap, thus forming a larger subglottic lumen. The posterior cricoid cartilage may also be split. Some investigators report higher decannulation rates when compared to reconstruction.

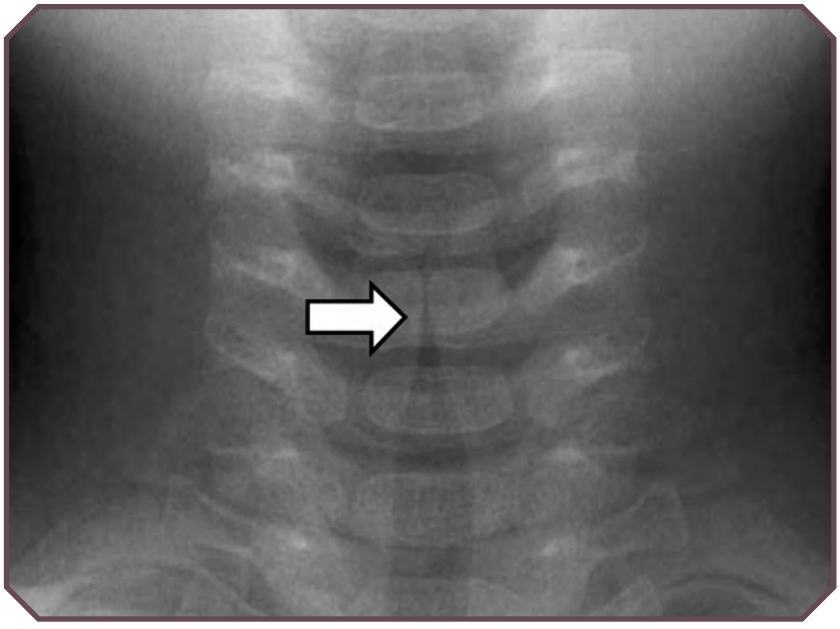

Figure 13-2. Croup in a 14-month-old girl with cough and stridor. Frontal radiograph demonstrates bilateral, symmetrical subglottic airway narrowing (arrow) consistent with the steeple sign of croup.

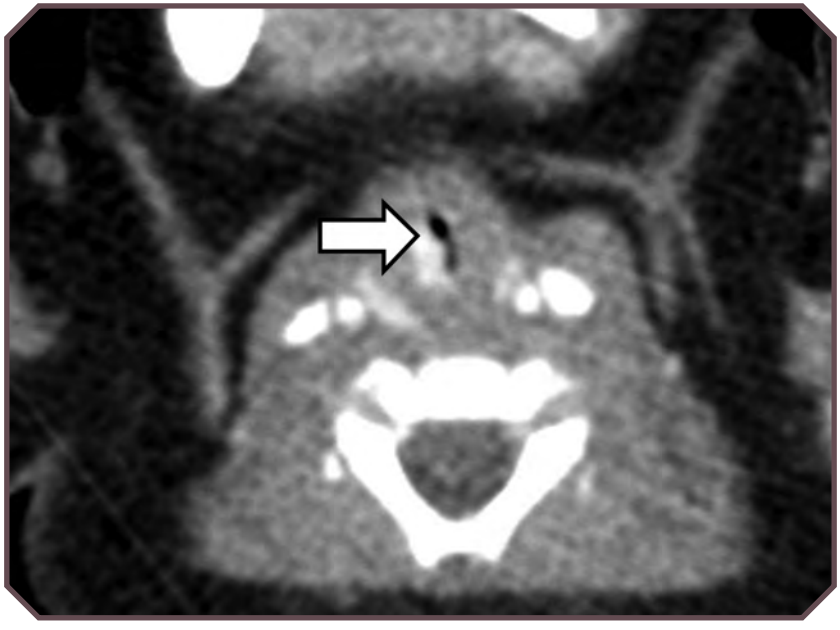

Figure 13-3. Infantile hemangioma in a 3-month-old male infant. Axial computed tomographic image demonstrates a mass with contrast material uptake along the right side of the airway (arrow) in this infant with multiple infantile hemangiomas.

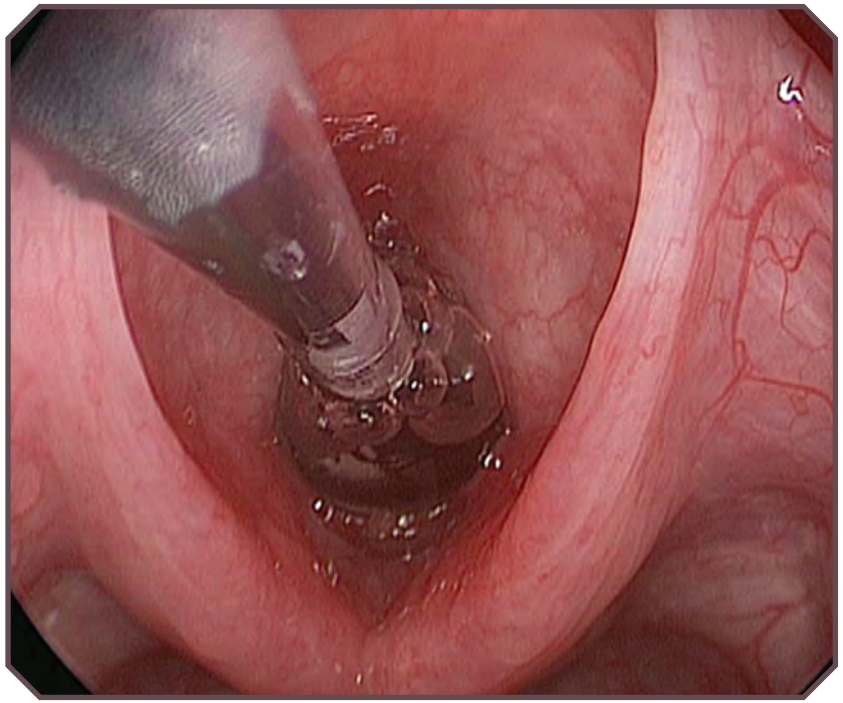

Figure 13-4. Balloon dilation of subglottic stenosis. Courtesy of Andres F. Orjuela, MD.

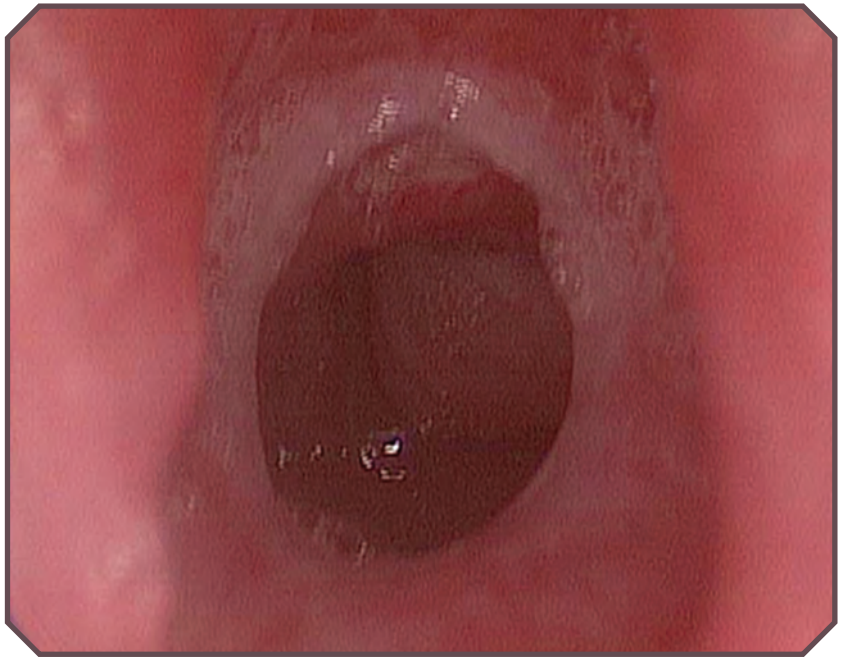

Figure 13-5. The subglottic area after dilation. Courtesy of Andres F. Orjuela, MD.

- Laryngotracheal reconstruction involves the placement of an anterior and/or posterior cartilage graft after splitting the cricoid cartilage. The graft source varies according to patient age and surgeon preference. The cartilage may come from the rib, thyroid, ala, ear, nasal septum, or a cadaver.
- Cricotracheal resection is an alternative for the most severe forms and depends on the location and length of the stenosed area. The anterior segment of the cricoid ring is removed, including the stenosed segment of the airway, followed by anastomosis of the trachea to the posterior segment of the cricoid cartilage left in place. This procedure has a greater risk for damaging the recurrent laryngeal nerve.

Treating Associated Conditions

- Gastroesophageal reflux can exacerbate edema and scarring, thereby worsening the stenotic area. Aggressive medical and surgical management should be considered, if appropriate.
- Airway granulomas involving the larynx have been described in granulomatosis with polyangiitis (previously known as *Wegener granulomatosis*). When present in the subglottic area, stenosis may improve or resolve with baseline disease management. Presentation is unusual in young children.

Expected Outcomes and/or Prognosis

- Restenosis can occur after intervention.
- Repeated bronchoscopies may be necessary to reassess the airway.
- Prognosis is related to both the degree of obstruction and the underlying pathologic condition as follows:
  - Degree of obstruction
    - Grade I–II is frequently asymptomatic and may not require intervention.
    - Grade III–IV is generally symptomatic; most patients will require surgical intervention. Tracheostomy may be required prior to surgery to bypass the stenotic segment.
  - Etiologic origin
    - CSS may resolve or improve with airway growth.
    - Acquired subglottic stenosis is unlikely to improve with airway growth.

When to Refer

- Any infant or child with airway symptoms should be referred for further evaluation and considered for endoscopic evaluation.
- Multidisciplinary teams can optimize care and may include a pediatric otorhinolaryngologist, pulmonologist, gastroenterologist, nutritionist, and speech and/or feeding therapist.

When to Admit

- In the face of respiratory viral infections, respiratory difficulty may occur in infants or children with subglottic stenosis, even those with mild stenosis.

Prevention

- Treat intubated patients with anti-reflux medication.
- The less time intubated, the less risk of subglottic stenosis. Recent reports showed that for every 5 days of intubation, risk increases by 50%.
- Use an appropriate size of endotracheal tube, particularly considering the smaller larynx size in patients with Down syndrome. Endotracheal tube size can be calculated as follows: (age in years + 4)/4.
- Minimize deep suctioning in children who are intubated or who have undergone tracheostomy.

Resources for Families

- Subglottic Stenosis (Cincinnati Children's). care.cincinnatichildrens.org/airway/subglottic-stenosis
- Subglottic Stenosis (Children's Hospital of Philadelphia). www.chop.edu/conditions-diseases/subglottic-stenosis
- Children With Down Syndrome: Health Care Information for Families (American Academy of Pediatrics). www.healthychildren.org/English/health-issues/conditions/developmental-disabilities/Pages/Children-with-Down-Syndrome-Health-Care-Information-for-Families.aspx
- Laryngotracheal Reconstruction (Mayo Clinic). www.mayoclinic.org/tests-procedures/laryngotracheal-reconstruction/home/ovc-20190706

Chapter 14

Tracheomalacia, Vascular Rings and Slings, and Bronchomalacia

Maria Teresa Santiago, MD

Tracheomalacia

Introduction/Etiology/Epidemiology

- Tracheomalacia is characterized by tracheal collapse during forced expiration. It may be congenital (primary) or acquired (secondary).
- Congenital tracheomalacia
  - It may be isolated but also occurs with airway abnormalities, including laryngomalacia, bronchomalacia, and laryngeal clefts.
  - The incidence rate is 1 in 2,100 children.
  - Proximal esophageal atresia with distal tracheoesophageal fistula is the most common associated congenital anomaly.
  - Tracheomalacia is seen with craniofacial anomalies, chromosomal defects, mucopolysaccharidoses, and inherited connective tissue disorders.
- Acquired tracheomalacia
  - Tracheotomy is the most common cause.
  - This condition affects 10% of patients who previously underwent tracheotomy and 16% of premature infants with bronchopulmonary dysplasia.

Pathophysiology

- Congenital tracheomalacia
  - This occurs when reduction and/or atrophy of cartilage rings causes softening of cartilage and/or decreased tone of the trachealis muscle.
  - Increased intrathoracic pressures during expiration cause airway collapse.
- Secondary tracheomalacia
  - This may occur after trauma, external compression, positive pressure ventilation, infection, and inflammation.
  - Premature infants are at increased risk, since airways are prone to deformation and injury when exposed to positive pressure.

Clinical Features

- Patients present with croupy, barklike or brassy cough, and shortness of breath with exercise.
- Recurrent pneumonia and/or atelectasis occurs because of impaired mucociliary clearance.
- Severe malacia causes apnea and cyanotic spells (particularly those that occur with feeding or reflex apnea).
- A monophonic wheeze or expiratory stridor can be observed in patients with intrathoracic tracheomalacia and biphasic stridor with extrathoracic tracheomalacia.

Differential Diagnosis

Differential diagnosis includes conditions associated with recurrent or persistent wheezing and airway obstruction.

- Bronchiolitis
- Asthma
- Bronchopulmonary dysplasia
- Cystic fibrosis
- Gastroesophageal reflux
- Bronchomalacia and/or stenosis
- Subglottic stenosis
- Bronchogenic cyst
- Vascular rings or slings

Diagnostic Considerations

- In children ≥5 years of age, spirometry may demonstrate expiratory flow limitation consistent with a variable intrathoracic obstruction.
- Tracheography, bronchography, and fluoroscopy may demonstrate expiratory airway narrowing.
- Multidetector computed tomography (CT) allows 3-dimensional (3D) reconstruction of the tracheobronchial tree (virtual bronchoscopy) and provides static images of tracheal narrowing.
- Dynamic magnetic resonance (MR) images show vascular compression of main airways but require patient cooperation and cannot be obtained in preschool-aged children.
- Direct airway visualization with flexible and/or rigid bronchoscopy demonstrates that >50% tracheal wall narrowing is the standard for diagnosis. Flexible bronchoscopy more effectively demonstrates airway dynamics, while rigid bronchoscopy can be used to evaluate associated anomalies. Widening of the posterior membrane with anterior collapse during expiration or "fish-mouthing" of the trachea is most commonly seen with congenital tracheomalacia associated with tracheoesophageal fistula and esophageal atresia (Figure 14-1). Malacia from external compression also results in flattening of the anterior cartilage. The ratio of the cartilage ring to the posterior membranous wall decreases from 4:1 or 5:1 to 2:1 or 3:1.

- The severity of tracheomalacia can be underappreciated if a child is given deep anesthesia during bronchoscopy.

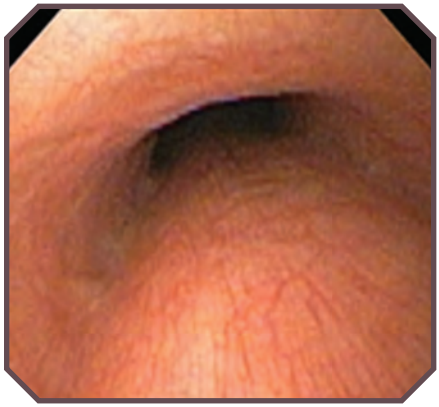

Figure 14-1. Tracheomalacia. Bronchoscopic image shows "fish-mouthing" of the trachea and anterior bowing of the trachealis muscle during expiration.

Treatment

- Symptoms associated with mild tracheomalacia usually resolve by 18 months to 2 years of age without treatment.
- Pharmacotherapy, positive pressure ventilation, and surgery may be considered for symptomatic patients.
- Pharmacotherapy treatment includes the following.
  - Bethanechol, a cholinergic agent delivered at doses of 0.1 to 0.2 mg per kilogram of body weight per dose 3–4 times daily, directly stimulates airway smooth muscle and improves airway mechanics.
  - In low doses, inhaled ipratropium bromide blocks presynaptic muscarinic receptors (M2), prolongs acetylcholine release at the neuromuscular junction, and stimulates smooth muscle contraction.
  - β-agonists such as albuterol may decrease airway smooth muscle tone, resulting in central airway collapse, and should therefore be used cautiously.
- Continuous positive airway pressure, introduced noninvasively or via endotracheal tube or tracheotomy, maintains central airway patency, decreases expiratory resistance, and increases lung volumes and maximal expiratory flow rates. Although tracheotomy can facilitate positive pressure ventilation and maintains patency of malacic segments, it will not bypass distal compression or obstruction.
- Surgical treatment includes the following.
  - An aortopexy is a procedure where peritracheal soft tissue, typically the aorta, is lifted anteriorly and sutured to the sternum. Occasionally, the innominate artery, pericardium, and/or trachea itself (anterior tracheopexy) may be sutured to the sternum. This remains the mainstay of surgical treatment for patients with severe malacia who have clinically significant respiratory distress or "death spells" or are failing to thrive.
  - Slide tracheoplasty has been used in severe malacia associated with tracheoesophageal fistula.

— Silicone or metal stents are rarely used in children. Stents may migrate, disrupt normal ciliary clearance, and require dilation, removal, or replacement as the child grows. There are case reports of success with newer 3D printed, bioresorbable, extraluminal stents.

Prognosis

- Symptoms of isolated congenital tracheomalacia and malacia from positive pressure ventilation improve markedly by 2 years of age, while malacia related to foregut abnormalities or external compression tends to persist into late childhood.

When to Refer

- Evaluation by a subspecialist for underlying anatomic tracheobronchial abnormalities should be considered in patients with recurrent croup and/or wheezing who are unresponsive to medications used to treat bronchospasm, such as bronchodilators, steroids, and/or leukotriene antagonists.
- Patients with "resistant asthma" and recurrent pneumonias or atelectasis, particularly if they are not thriving, should also be referred to a subspecialist for further evaluation.

When to Admit

- Admission should be considered for patients with respiratory distress and hypoxemia associated with viral illnesses.

Vascular Rings and Slings

Introduction/Etiology/Epidemiology

- Rare malformations occurring during embryonic aortic arch development represent approximately 1% of cardiovascular congenital anomalies.
- The spectrum and relative frequency of aortic arch abnormalities in children are listed in Table 14-1.
- "Vascular rings" are complete circumferential vascular anomalies.
  - Double aortic arch
    - This is the most common symptomatic vascular ring.
    - Persistent right and left fourth embryonic aortic arches encircle and compress the trachea and esophagus, producing respiratory distress and feeding difficulty in early infancy.
    - Ninety percent of patients are symptomatic and require surgical correction. The right arch is dominant in 70%–90% of cases. Determination of dominance is critical for deciding which side to ligate without causing cerebrovascular ischemia.
    - A double aortic arch may be associated with congenital heart defects such as transposition of the great arteries, ventricular septal defect, persistent truncus arteriosus, tetralogy of Fallot, and coarctation of the aorta.

Table 14-1. Classification and Relative Frequency of Aortic Arch Abnormalities That Cause Tracheoesophageal Compression in Children

Abnormality Type	Frequency
Complete vascular rings	
Double aortic arch	48%–55%
Right aortic arch	12%–15%
Incomplete vascular rings or slings	
Innominate artery compression syndrome	15%
Pulmonary artery sling	7%
Left aortic arch and aberrant subclavian artery	5%

  - Right-sided aortic arch
    - Two common variations are a concomitant aberrant retroesophageal left subclavian artery (65%) and mirror image branching (35%).
    - Ten percent to 50% of patients have associated congenital heart defects. Mirror image branching carries a 90% risk of congenital heart defects.
- "Slings" are incomplete or noncircumferential anomalies.
  - Aberrant right subclavian artery
    - Occurs in 0.5% of the population.
    - Presentation is variable, and most patients are asymptomatic.
    - Older children and adults may experience dysphagia due to esophageal compression.
    - There is increased incidence in patients who have Down syndrome with congenital heart defects (38%).
  - Pulmonary artery sling
    - The aberrant left pulmonary artery arises from the main pulmonary artery, dorsally encircles the right bronchus, and passes between the trachea and the esophagus before it enters the hilum of the left lung.
    - Although not a complete vascular ring, respiratory symptoms and feeding difficulties occur in infancy. Forty percent to 50% of patients have a "ring-sling complex" (a pulmonary artery sling with complete tracheal rings, causing tracheal stenosis).
    - These anomalies account for most fatalities associated with ring or sling defects.
    - Tracheobronchial abnormalities such as tracheomalacia, hypoplasia, and long-segment tracheal stenosis may be associated.
    - More than 50% of cases are associated with CHD.

— Innominate artery compression syndrome
  - This is usually an incidental bronchoscopic finding.
  - Symptoms relate to tracheomalacia from anterior tracheal compression and/or an associated esophageal atresia.

Pathophysiology

- The embryonic dorsal and ventral aortas are connected by 6 bilateral arches.
- During the fourth week of development, aortas fuse to form a single aorta with 6 adjoining arches that encircle the primitive trachea and esophagus.
- Normally the first, second, fifth, and right fourth arches involute, freeing the esophagus and trachea.
- Failure of embryonic arches to fuse or regress normally results in vascular anomalies.
- Errors in fourth arch development result in anomalies that form complete rings encircling and/or compressing the intrathoracic trachea and/or esophagus.
- Sixth arch anomalies usually do not form circumferential anomalies.

Clinical Manifestations

- Symptoms depend on the anatomic site of the ring, the degree of "tightness," and the site of compression.
- Children with complete rings often present early in infancy with progressive stridor, cyanosis, and dysphagia.
- At physical examination, biphasic stridor, monophonic wheezing, a croupy or brassy cough, and/or noisy breathing may be observed.
- Feeding difficulties such as dysphagia, slow feeding, and neck hyperextension may occur with introduction of solid foods. Dysphagia in association with respiratory symptoms is reported in 30% of patients at initial presentation but is an isolated symptom in 5%–15% of cases. Apnea or cyanosis may be precipitated by swallowing a solid food bolus that presses against a collapsible posterior trachea at the site of the anomaly.

Diagnostic Considerations

- Anteroposterior and lateral chest radiographs demonstrate tracheal deviation from a right-sided aortic arch. Lateral views demonstrate anterior bowing of the trachea and a retrotracheal density.
- More than 90% of vascular ring anomalies can be seen on esophagrams obtained with barium. Extrinsic posterior esophageal indentations from an aberrant subclavian artery, bilateral indentations from a double aortic arch, and anterior indentation from a pulmonary artery sling are readily demonstrable (Figure 14-2).

- In children >5 years of age, spirometry may demonstrate a fixed intrathoracic obstruction with flow limitation of expiratory and inspiratory flow volume curves. Expiratory flow rates do not improve after bronchodilator administration.
- Changes in the upper axial "3-vessel and trachea" view, along with color Doppler findings, may be seen at prenatal ultrasonography.
- Flexible bronchoscopy allows dynamic evaluation of the tracheobronchial tree and is used to assess the level and extent of tracheal narrowing and compression pre- and postoperatively (Figure 14-3).
- Echocardiography is not a dominant diagnostic tool for vascular anomalies but is essential for detecting associated CHDs, which occur in 12%–30% of cases.

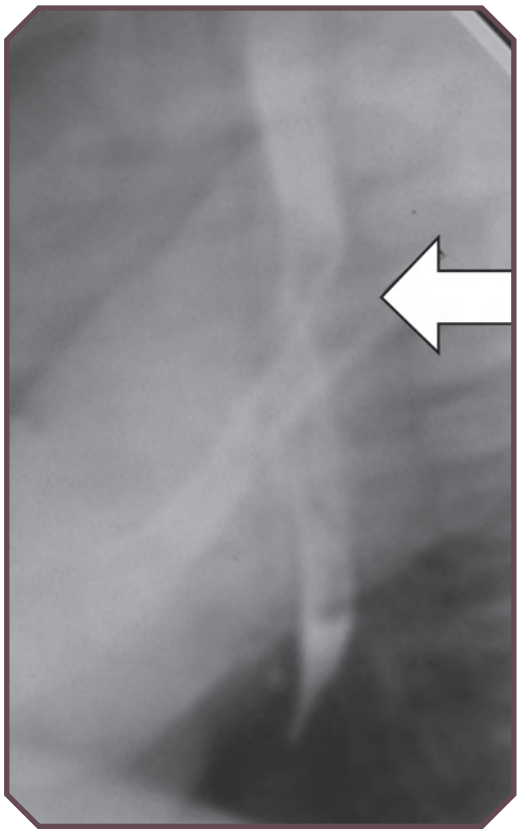

Figure 14-2. Esophagogram with arrow demonstrating posterior indentation of the esophagus in a patient with a right-sided aorta and ligamentum arteriosum.

- Definitive diagnosis and exact anatomy of an aortic arch malformation and relationship to adjacent structures require cross-sectional imaging with CT or MR imaging with angiography. Both techniques have equal diagnostic sensitivity.
  - — CT scans may not require sedation and allow 3D reconstruction (virtual bronchoscopy) but expose patients to higher levels of ionizing radiation and potentially nephrotoxic iodinated contrast material.
  - — MR imaging has the advantage of demonstrating intracardiac abnormalities, ventricular function, and intracardiac blood flow, as well as vascular anomalies and their relationship to the trachea and esophagus, without ionizing radiation or iodinated contrast material. However, it requires deep sedation, which could further compromise patients in respiratory distress.

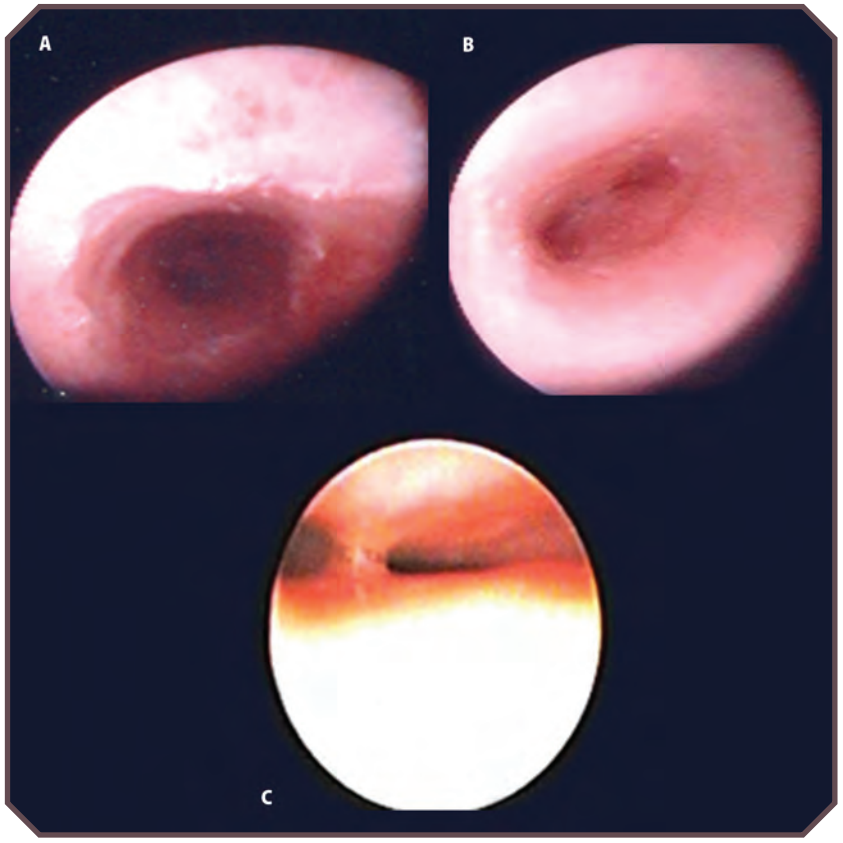

Figure 14-3. Bronchoscopic findings in vascular rings. A. The distal trachea is shown during inspiration. B. Dynamic collapse during expiration is shown in a patient with double aortic arch. C. Right main stem compression is shown from a right-sided aortic arch.

Treatment and Prognosis

- Many patients will be treated for airway obstruction but will receive minimal or no relief from bronchodilators or steroids.
- Patients with feeding difficulties benefit from feeding therapy and require intervention, depending on their aspiration risk and weight gain.
- Most patients with mild anomalies improve with airway growth.
- Symptomatic vascular rings require early surgical intervention to avoid prolonged airway vascular compression and decrease morbidity and mortality associated with hypoxic or apneic spells.
  - The surgical approach depends on the specific anomaly and usually requires open thoracotomy or video-assisted thoracic surgery.
  - Surgery has low mortality and morbidity rates and effectively relieves tracheoesophageal compression in >95% of infants.

- After surgery, patients with severe symptoms may have persistent airway obstruction for weeks to months.

When to Refer

- Pediatric subspecialty referral should be considered for patients with evidence of lower airway obstruction that is unresponsive to asthma therapy and for those with difficulty feeding and failure to thrive.

When to Admit

- Admission and inpatient workup should be pursued in infants with severe symptoms such as apnea, cyanosis, and "death spells."

Bronchial Wall Disorders

Congenital Tracheobronchomegaly (Mounier-Kuhn Syndrome)

- Tracheomalacia and bronchiectasis with markedly dilated major airways
- Types
  - The trachea and bronchi demonstrate symmetrical, diffuse enlargement.
  - The most common type is eccentric enlargement of the saccular diverticula between cartilages, with pronounced change to normal bronchial size.
  - The diverticula extend to the distal bronchi.
- Strong male predilection, with a ratio of 8:1; usually symptomatic in the third decade of life
- Associated with Ehlers-Danlos syndrome, Marfan syndrome, and cutis laxa, as well as rheumatologic disorders
- Signs and symptoms
  - Symptoms include chronic respiratory infections with dry cough, purulent sputum, dyspnea, and hemoptysis.
  - Crackles, wheezing, and digital clubbing are observed.
  - Bullous emphysema and pneumothoraces may be seen on radiographs.
- Gastroesophageal reflux may contribute to or exacerbate sleep apnea.
- Anesthesia and surgery may be complicated by large and weak airways, leading to endotracheal tube dislodgement, large air leaks, and postoperative tracheal collapse.
- Diagnosis
  - The diagnostic features may be missed on plain chest radiographs until the tracheal size exceeds the width of the vertebral column.
  - Increased tracheal diameter and expiratory collapse from tracheomalacia may be seen during flexible bronchoscopy.
  - Varying degrees of obstruction and increased residual capacity may be noted at pulmonary function testing.

  - Chest CT performed to assess tracheal size remains the standard of reference for confirming the diagnosis. Dynamic CT images demonstrate tracheal collapse.
- Therapy
  - Chest physiotherapy and antibiotics are the mainstays of therapy.
  - Successful airway stent placement and surgical tracheobronchoplasty procedures have been reported.
  - Endoscopic laser surgery causes submucosal tissue retraction, which can lead to increased rigidity of the membranous trachea.
  - Some patients have undergone lung transplantation.

Bronchomalacia

- Congenital bronchomalacia is often isolated and has a good prognosis.
- Bronchomalacia may be associated with connective tissue disorders and with Larsen syndrome and Fryns syndrome.
- Premature infants who require intubation and positive pressure ventilation are at increased risk.
- Clinical features
  - Patients present with persistent expiratory wheezing and cough.
  - Premature infants with chronic lung disease and severe malacia may fail extubation and weaning from ventilator support, have persistent infiltrates from atelectasis, and/or develop hypercapnic respiratory failure.
- Diagnosis is assigned by performing flexible bronchoscopy with the patient under light sedation, with spontaneous ventilation.
- Mild malacia improves with airway growth.
- Patients with more severe involvement may require long-term treatment with noninvasive positive pressure or tracheotomy and mechanical ventilation.
- A resorbable, extraluminal, custom-printed 3D stent has been used to treat an adult with severe bronchomalacia.

Williams-Campbell Syndrome

- This rare congenital syndrome is characterized by diffuse bronchomalacia secondary to defective or absent wall cartilage, usually in fourth- to sixth-generation bronchi.
- Patients have recurrent pneumonias, coughing, wheezing, bronchiectasis, and digital clubbing.
- Differential diagnosis includes more common causes of bronchiectasis, including aspiration, immune deficiency, cystic fibrosis, ciliary dyskinesia, postinfectious bronchiectasis, and allergic bronchopulmonary aspergillosis.

- Diagnosis is determined by obtaining chest CT scans, which demonstrate normal tracheal size, inspiratory ballooning of cylindrical bronchi beyond the third generation, and lung hyperinflation. During expiration, complete collapse of cystically dilated bronchi occurs. 3D reconstruction may demonstrate the absence of ring impressions, which suggests the presence of deficient cartilage rings.
- Therapy
  - Patients are treated with antibiotics for acute infections.
  - Exercise and inspiratory muscle training may improve quality of life and exercise tolerance.
  - Inhaled steroids may reduce sputum volume but do not reduce exacerbations.
  - No large randomized trials have been performed to demonstrate benefit with bronchodilators, anticholinergics, mucolytics, and/or chest physiotherapy.
  - Noninvasive positive pressure ventilation may be beneficial for patients with chronic respiratory failure.

Resources for Families

- Croup and Your Young Child (American Academy of Pediatrics). www.healthychildren.org/English/health-issues/conditions/chest-lungs/Pages/Croup-Treatment.aspx
- Tracheomalacia—Congenital (U.S. National Library of Medicine). www.nlm.nih.gov/medlineplus/ency/article/001084.htm

Clinical Pearls

- Primary or congenital tracheomalacia is most often associated with tracheoesophageal fistula.
- Most patients with congenital tracheomalacia usually improve by 2 years of age.
- Tracheal collapse during expiration is best demonstrated with bronchoscopy (flexible and/or rigid) but could be missed if the patient is deeply sedated.
- Surgical treatment may be considered for patients with severe symptoms from tracheomalacia, such as respiratory distress and "death spells."
- The pediatrician needs to maintain a strong index of suspicion for tracheobronchial abnormalities or tracheal compression from vascular abnormalities in patients with airway obstruction that does not improve with therapy for bronchospasm.
- Congenital abnormalities, such as tracheomegaly or congenital absence of bronchial cartilage, are rare and manifest with recurrent infections and bronchiectasis. They are diagnosed by obtaining chest CT scans.

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Chapter 15

Tracheoesophageal Fistulas

Jessica Van Beek–King, MD, and James W. Schroeder, Jr, MD, FACS, FAAP

Introduction/Etiology/Epidemiology

- A tracheoesophageal fistula (TEF) is an abnormal connection between the trachea and the esophagus.
  - — May be congenital or acquired
  - — No race or sex predilection
- May be associated with esophageal atresia (EA), whereby the esophagus ends in a blind pouch and does not connect to the stomach
- Congenital TEFs
  - — Incomplete separation of the esophagus from the laryngotracheal tube occurs during embryological development.
  - — Most cases have an unknown etiologic origin. EA and/or TEF associated with syndromes may have genetic associations. In isolation, EA and/or TEF is more likely multifactorial.
  - — Incidence ranges from 1 per 2,500 live births to 1 per 4,500 live births.
  - — There are 5 main types of EA and/or TEF. The first classification system, described by Vogt in 1929, included pure EA, which is extremely rare, as a sixth type. The system was modified by Gross in 1953 to the current 5-type classification. (See Figure 15-1.)
    - ▪ Type A: Proximal and distal esophageal bud, normal trachea, no TEF (8% of cases)
    - ▪ Type B: Proximal esophagus with TEF terminating at the lower trachea, distal esophageal bud (3% of cases)
    - ▪ Type C: Proximal EA, distal esophagus with TEF arising from the distal esophagus or carina (85% of cases)
    - ▪ Type D: Proximal esophagus forms a TEF that terminates in the distal trachea, and the distal esophagus arises as TEF from the carina (<1% of cases)
    - ▪ Type E (H-type): A variant of type D, whereby the proximal and distal esophagus is in continuity and a TEF is present near the distal tracheal (4% of cases)
- Acquired TEFs
  - — Nonmalignant
    - ▪ Blunt or open trauma, iatrogenic injury, irritation from endotracheal or tracheostomy tube, or cuff causing pressure necrosis

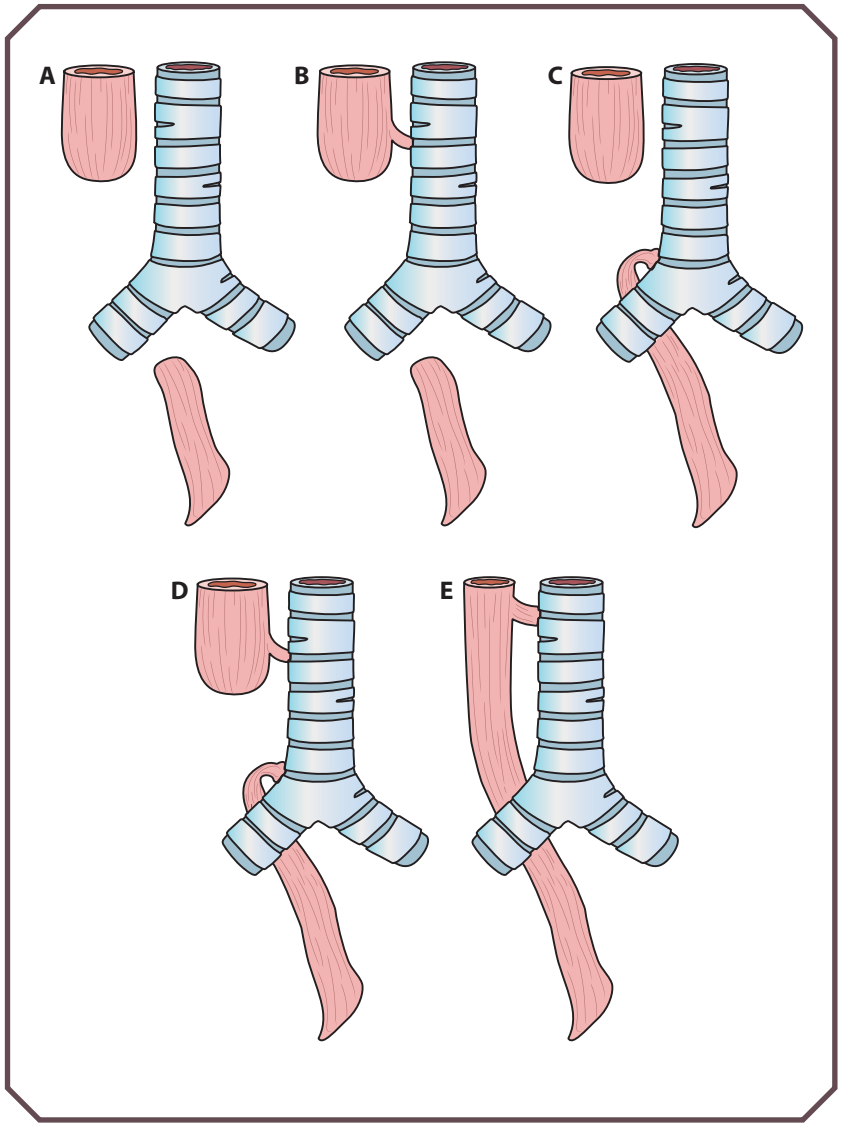

Figure 15-1. Gross classification of esophageal atresia with and without tracheoesophageal fistula. From Wootten CT, Myer CM. Congenital aerodigestive tract anomalies. In: Johnson JT, Rosen CA, eds. *Bailey's Head and Neck Surgery: Otolaryngology.* 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2014: 1306–1327.

    - Foreign-body ingestion
      - ~ The most common foreign body associated with acquired TEF is button batteries.
  - — Malignant
    - Uncommon in the pediatric population

Pathophysiology

- The esophagus and trachea both develop from the primitive foregut.
  - — During weeks 4–6 of gestation, a ventral diverticulum forms that evolves into the trachea.
  - — A longitudinal fold fuses to form a septum. Posterior deviation of this septum yields incomplete separation, resulting in a TEF.
- Esophageal motility is always affected secondary to abnormal innervation. Dysmotility is most commonly seen in the distal segment.
- The trachea is deficient of cartilage at the diseased segment and has increased width of the trachealis muscle, leading to tracheomalacia.
  - — Mild to moderate tracheomalacia may yield chronic cough and retained pulmonary secretions. More severe tracheomalacia may lead to respiratory distress that necessitates positive pressure or tracheostomy tube placement. (See Chapter 14, Tracheomalacia, Vascular Rings and Slings, and Bronchomalacia.)

Clinical Features

- Copious oral and nasal secretions
- Episodes of coughing, choking, and cyanosis that worsen with oral feedings
- Abdominal distention secondary to air in the stomach
- H-type fistulas often have a much different presentation, whereby the child has a long-standing history of recurrent aspiration and pneumonias.
- Approximately 50% of congenital TEFs are associated with other anomalies.
  - — Cardiovascular anomalies are most common (ventricular septal defect, tetralogy of Fallot).
  - — Abnormalities may be musculoskeletal, anorectal and intestinal, genitourinary, head and neck, mediastinal, or chromosomal.
  - — Associated conditions occur most commonly with isolated EA and least commonly with TEF without EA.
  - — Anomalies may be associated with syndromes and/or sequences.
    - Vertebral, anal, cardiac, tracheal, esophageal, renal, and limb ("VACTERL" syndrome)
    - Coloboma of the eye, heart anomaly, choanal atresia, retardation, and genital and ear anomalies ("CHARGE" syndrome); trisomy 13, 14, and 18; and Potter syndrome have also been described.

Differential Diagnosis

- Esophageal stenosis
- Esophageal malignancy
- Pharyngeal pseudodiverticulum
- Aspiration pneumonia and/or pneumonitis
- Laryngopharyngeal reflux
- Zenker diverticulum

Diagnostic Considerations

- Prenatal ultrasonography: EA may initially manifest in utero with polyhydramnios and absence of a gastric gas bubble. However, these findings only have a 44%–56% predictive value.
- Inability to pass a nasogastric tube (at birth): There is *(a)* an inability to pass a nasogastric tube beyond 10–12 cm or *(b)* coiling in the proximal esophageal pouch in TEF and/or EA.
- Chest imaging
  - Chest radiography with air contrast allows visualization of the proximal esophageal pouch. Distal TEFs will display air in the stomach with distention (Figure 15-2).
  - Contrast-enhanced esophagography or upper gastrointestinal series may be indicated.
    - Helpful in diagnosing H-type TEF, which is often diagnosed later than EA and/or TEF. Air is used instead of barium to avoid contrast material aspiration.
  - Tracheobronchoscopy and esophagoscopy
    - Allow direct visualization of the trachea and esophagus for identification of level of TEF and other anomalies
    - Especially important for identifying H-type, acquired nonmalignant, or malignant TEFs
    - Important for identifying secondary airway lesions
    - Repeat endoscopies may be necessary throughout the patient's life

Management

- Genetic counseling
- Multidisciplinary team management
  - Preoperative management
    - Supportive care
    - Monitoring and support of nutrition, oxygenation, and ventilation
    - Suctioning of the proximal esophageal pouch to minimize aspiration of oral secretions
    - Semiprone positioning to avoid reflux from the distal esophagus into the trachea

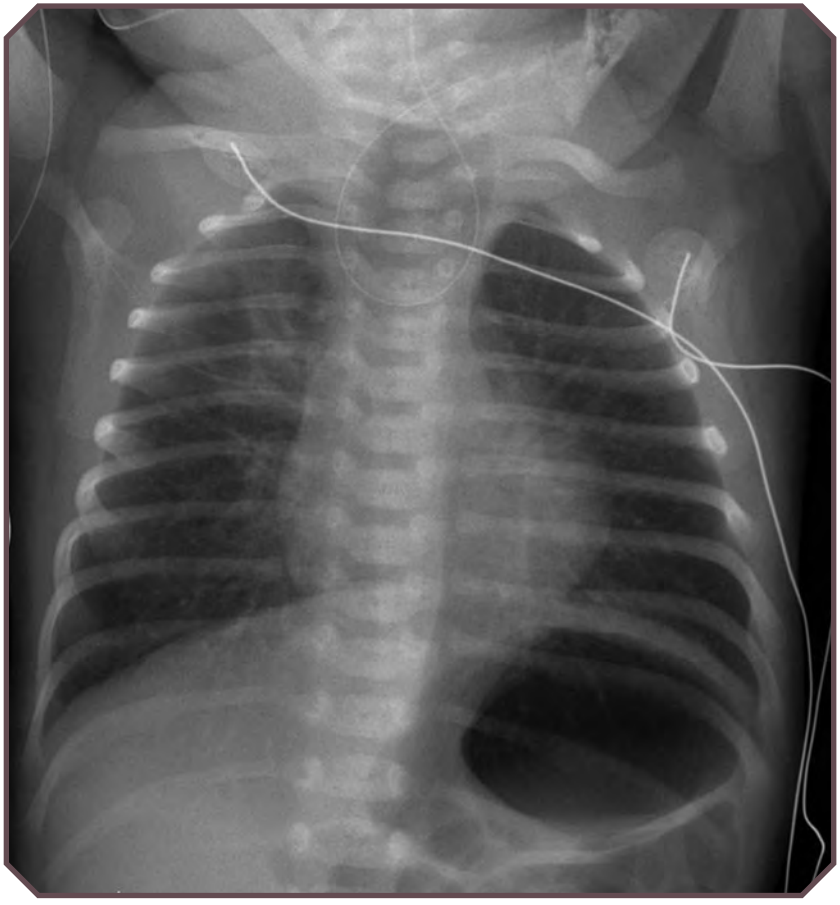

Figure 15-2. Esophageal atresia (type C) with distal fistula in a 2-day-old female neonate with difficulty feeding. Anteroposterior chest radiograph demonstrates a distended esophageal pouch containing a nasogastral tube that could not be passed. Air in the stomach indicates a distal tracheoesopohageal fistula.

— Surgical management
  - Urgent but not emergent, unless the infant is in respiratory distress
  - The goal of surgery is to establish reconnection of the esophagus and close the TEF.
    - ~ With short-segment EA, the ends of the esophagus may be repaired primarily.
    - ~ Native esophageal primary anastomosis is the preferred technique.
    - ~ Long-segment EA (>3 cm or 2 vertebral bodies) may require stretching prior to primary anastomosis. If stretching is inadequate, repair may be facilitated by using a colonic interposition graft, gastric pull-up, or jejunal free-flap procedure.

  - ~ Stretching is performed over a period of ≤3 months.
  - ~ Closure of the tracheal defect is performed primarily.
  - ~ With H-type fistulas, the fistula is identified with bronchoscopy. A Fogarty catheter is placed through the fistula to identify the defect in the esophagus. Esophageal and tracheal defects are closed primarily, and the local muscle flap is interposed.
  - ~ Endoscopic or open techniques are used, depending on the type and size of the fistula.
- — Postoperative management
  - ▪ Intensive care unit monitoring is indicated.
  - ▪ The neck is flexed to avoid tension on the anastomosis; in some cases, the patient may be paralyzed and sedated for a number of days to further limit mobility of the anastomosis while it is healing.
  - ▪ Nasogastric tube feedings may begin after 48 hours, and oral feedings may begin once the infant is able to tolerate secretions.
  - ▪ Potential short- and long-term complications include reflux, anastomotic leak, esophageal stenosis or dysmotility, dysphagia, fistula recurrence, scoliosis, deformities of the chest wall, tracheomalacia, tracheal stenosis, persistent cough and wheeze, and Barrett esophagus.

Treating Associated Conditions

- Once comorbid or associated conditions are identified, a multidisciplinary team approach should be used to treat these conditions as medically or surgically indicated.
- Esophageal dysmotility
  - — Swallow therapy may require video swallow or functional endoscopic evaluation of the swallow to determine the safety of oral feedings. Consistency variation of feedings is based on tolerance, aspiration, or penetration.
  - — A nasogastric or gastrostomy tube may be indicated if the patient is unable to safely take oral nutrition.
  - — Esophageal dilation for strictures may be indicated.
- Reflux
  - — Antisecretory therapy
- Tracheomalacia
  - — Mild to moderate symptoms should be treated with conservative therapy.
    - ▪ Humidified air, chest physical therapy, slow and careful feedings, and avoidance of infections
  - — Continuous positive airway pressure may be used for respiratory distress as a short-term intervention.
  - — Severe, diffuse tracheomalacia with failure of conservative therapy may necessitate tracheostomy tube placement or other treatment of the tracheomalacia.

- Chronic cough
  - See the reflux and tracheomalacia discussion earlier in the chapter.
  - Symptom management

Expected Outcomes/Prognosis

- Improved detection and advances in treatment have increased survival to >90%.
- If undetected, the TEF may lead to severe or fatal pulmonary complications.
- Acquired TEFs have higher mortality and morbidity rates.

When to Refer

- Once the diagnosis of EA and/or TEF is established, the patient should immediately be transferred to a facility with pediatric surgery specialists.

When to Admit

- Most diagnoses are established within the first 24 hours after birth, when the neonate is still an inpatient. The child should remain in the hospital or be transferred to a higher-level facility for monitoring and optimization prior to surgical correction.

Prevention

- Genetic counseling may be helpful in nonisolated or syndromic cases where there may be a genetic etiologic origin.
- In isolated EA and/or TEF, no specific gene or environmental factors have been conclusively identified as causative. Therefore, genetic counseling may be less beneficial.
- Acquired EA and/or TEF is preventable by being cautious of foreign-body ingestions, especially button batteries.

Resources for Families

- EA/TEF Esophageal Atresia/Tracheoesophageal Fistula Child and Family Support Connection. rarediseases.org/organizations/eatef-child-and-family-support-connection-inc
- Family and Parent Resource Center (American Pediatric Surgical Society). www.eapsa.org/parents

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Section 2. Developmental Anomalies of the Lung and Pulmonary Vessels

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Chapter 16

Pulmonary Hypoplasia

Brian P. O'Sullivan, MD

Introduction/Etiology/Epidemiology

- Pulmonary hypoplasia is arrested or impaired growth and development of the lung, airways, and pulmonary vessels.
- Overall incidence is 9–11 cases in 10,000 live births.
- Pulmonary hypoplasia may be primary or secondary, unilateral or bilateral.
  - — Primary pulmonary hypoplasia and familial occurrences are extremely rare.
  - — Secondary pulmonary hypoplasia is caused by a process that limits the space for lung development.
  - — The most common intrathoracic cause is congenital diaphragmatic hernia.
  - — The most common extrathoracic cause is severe oligohydramnios secondary to either genitourinary anomalies or midtrimester rupture of membranes.
  - — Pulmonary agenesis is an extreme variant.
    - ▪ Bilateral agenesis is incompatible with life.
    - ▪ Unilateral agenesis occurs with pulmonary artery agenesis or pulmonary venous anomalies (Figure 16-1).
    - ▪ Agenesis of the right lung is associated with respiratory symptoms caused by a mediastinal shift to the right, with distortion of major vessels and airways.
- Variations in bronchopulmonary vasculature are common.
- Associated anomalies of the diaphragm, heart, gastrointestinal tract, and bone occur at increased rates.

Pathophysiology

The following etiologic origins have been proposed:

- Pulmonary artery agenesis and/or anomalous venous drainage
  - — Pulmonary artery agenesis is a common cause of complete pulmonary agenesis.
  - — Scimitar syndrome consists of hypoplasia of the right lung with abnormal venous drainage to the inferior vena cava (Figure 16-2).
  - — Scimitar syndrome can be an asymptomatic incidental finding in adults but is often associated with severe cardiac defects, anomalous systemic arterial supply to the right lung, and pulmonary vein stenosis.

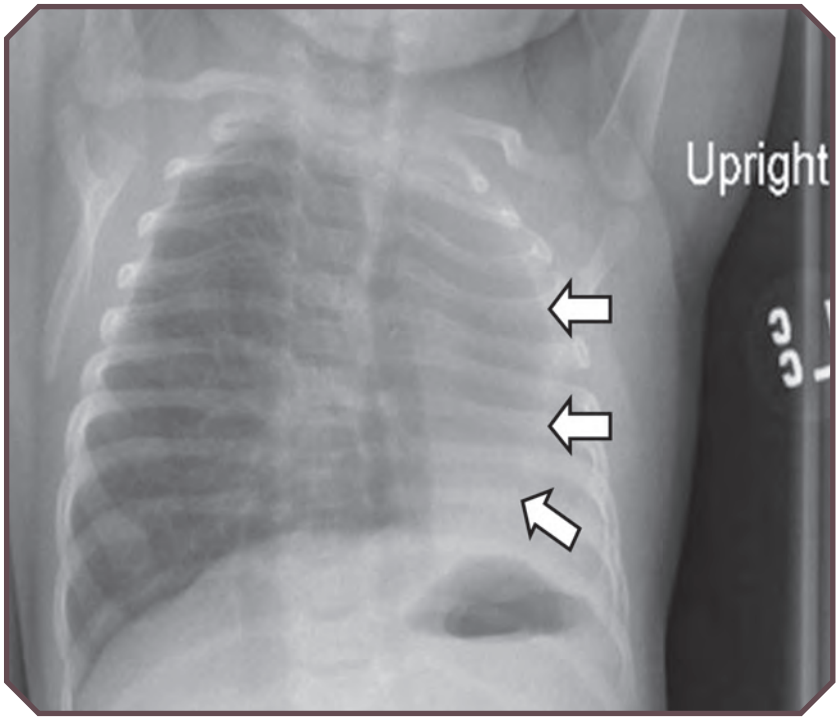

Figure 16-1. Frontal chest radiograph of a 1-month-old female infant with left pulmonary agenesis. Note the displacement of the heart and mediastinum into the left axillary line and herniation of the right lung into the left chest cavity (arrows).

- Chest wall abnormalities
  - Skeletal abnormalities that affect the chest wall and/or rib growth or position will restrict lung growth and lead to hypoplasia (eg, thanatophoric dysplasia, achondroplasia).
- Absent or disordered fetal breathing movements
  - Fetal breathing movements are imperative for normal lung development.
  - Lack of fetal breathing movements inhibits alveolar development.
  - This symptom can be caused by central nervous system abnormalities or phrenic nerve injury or agenesis.
- Amniotic fluid abnormalities
  - Fetal urination is the primary source of amniotic fluid.
  - Normal net movement of lung liquid is out of the lung and into the amniotic cavity, not movement of amniotic fluid into the lungs.
  - Oligohydramnios causes pulmonary hypoplasia because of compression of the chest wall by the maternal uterine wall and/or excess flow of fluid out of the lungs and into the amniotic cavity secondary to decreased amniotic fluid pressure.

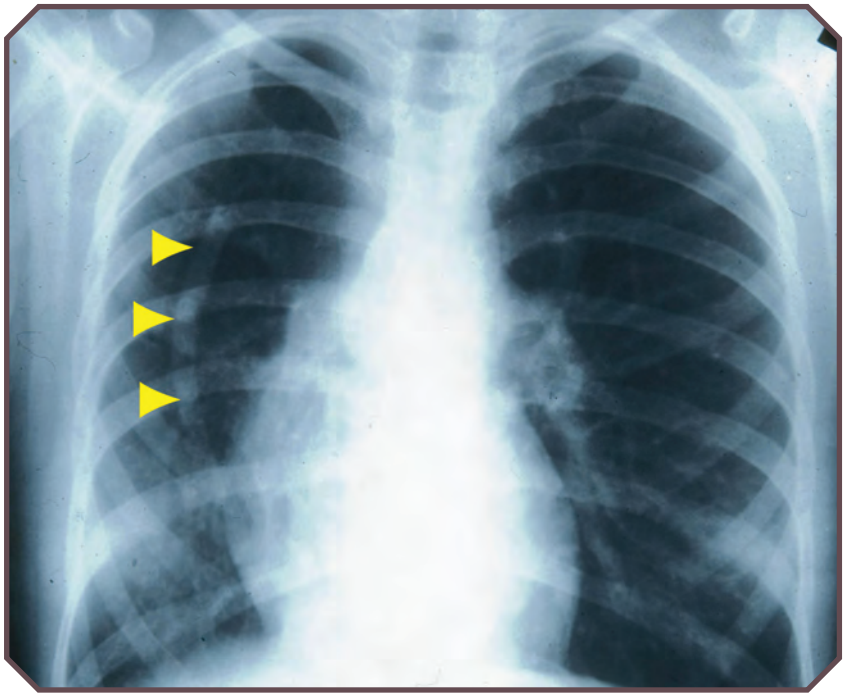

Figure 16-2. Frontal radiograph in a 2-year-old boy with Scimitar syndrome demonstrates hypoplasia of the right lung, dextroposition of the heart, and an anomalous draining vein (arrowheads).

  - Prenatal ultrasonography (US) is used to assess the amniotic fluid index and can alert the physician of the risk of pulmonary hypoplasia.
  - Lack of fetal urine output severely compromises lung growth because of lack of normal amniotic fluid volume.
  - Potter syndrome is an extreme variant, consisting of renal agenesis and severe pulmonary hypoplasia, along with facial and skeletal deformities.
  - If posterior urethral valves are the cause of decreased fetal urine output, surgical intervention prior to 20 weeks' gestation is recommended.
  - If oligohydramnios occurs prior to 16 weeks' gestation, both lung branching and acinar development are affected. If oligohydramnios occurs after 16 weeks, only acinar development is retarded.
  - Premature rupture of the fetal membranes late in pregnancy may have little or no effect on pulmonary function, since the lungs are nearly fully developed by this time.
- Congenital diaphragmatic hernia causes bilateral pulmonary hypoplasia secondary to the space-occupying mass (abdominal contents) in the chest cavity.
  - Hypoplasia is most severe on the side of the hernia.
  - Contralateral lung is also involved, more so the earlier in gestation the hernia appears (Figure 16-3).

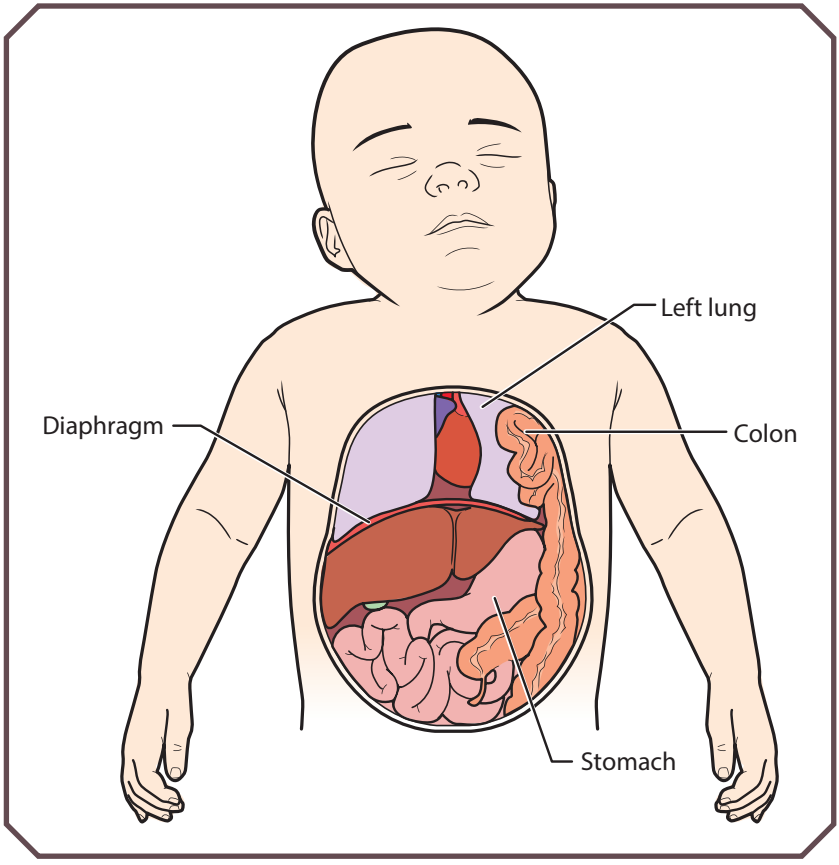

Figure 16-3. The degree of bilateral pulmonary hypoplasia is dependent on time and degree of displacement of abdominal contents. From https://ufhealth.org/uf-health-pediatric-surgery/congenital-diaphragmatic-hernia-cdh-program.

— Failure of diaphragm function because of phrenic nerve agenesis will have a similar effect.

Clinical Features

- Dependent on the degree of lung involvement
  - — At presentation, milder hypoplasia may appear with tachypnea that resolves over the first months of life.
- Clinical presentations may include
  - — Respiratory insufficiency
  - — Pulmonary hypertension
  - — Pulmonary hemorrhage
- Pulmonary hypertension with persistent fetal circulation may occur because of decreased cross-sectional area of pulmonary vessels.

Differential Diagnosis

- Congenital diaphragmatic hernia (CDH)
- Congenital pulmonary airway malformations
- Congenital lobar emphysema
- Congenital cardiac anomalies, such as situs inversus

Diagnostic Considerations

Multimodal imaging is frequently necessary.

- Steps to antenatal diagnosis
  - — Fetal 3-dimensional US: A lung area to head circumference ratio of <1 is associated with increased neonatal mortality.
  - — Doppler velocimetry may be helpful in detecting severe hypoplasia but remains experimental.
  - — Fetal magnetic resonance imaging complements fetal US and has been used to predict pulmonary hypoplasia.
- Steps to postnatal diagnosis
  - — Chest radiographs demonstrate
    - ▪ Reduced aeration
    - ▪ Volume reduction on the affected side
    - ▪ Ipsilateral mediastinal shift
    - ▪ Increased lucency of the affected lung
  - — Thoracic computed tomography (CT) demonstrates
    - ▪ Volume reduction on the affected side
    - ▪ Compensatory overinflation of the opposite side
    - ▪ Ipsilateral mediastinal shift
    - ▪ Hypoplastic airways
    - ▪ Potential abnormalities of the ribs and chest wall
  - — CT angiography
    - ▪ A complementary study to chest CT, CT angiography facilitates identification of aberrant vasculature and cardiac anomalies.
  - — Lung scintigraphy demonstrates
    - ▪ Reduced perfusion in the affected lung
- Lung biopsy is not routinely performed to assign the diagnosis.
- Postmortem examination of the lungs can be used to confirm the diagnosis in fatal cases.

Management

- If antenatal diagnosis:
  - — Work with the fetal medicine team (generally includes obstetrics, neonatal medicine, genetics, and pediatric surgery), together with the parents, during all phases of decision-making. In the event of a fetus with pulmonary hypoplasia, a pediatric pulmonologist should also be a member of the team.
  - — Anticipate delivery and make arrangements in a tertiary care center with neonatal and surgical teams available to care for the newborn.

- If postnatal diagnosis:
  - Be prepared to resuscitate and provide respiratory support.
  - Infants with CDH will require gastric and bowel decompression.
  - Obtaining a chest radiograph will aid in identifying the affected side and can indicate a specific diagnosis.
  - Identify and treat surgically correctable causes (eg, diaphragmatic hernia).
- Treating associated conditions
  - Associated renal, cardiac, and skeletal anomalies may require additional evaluation and therapy.
  - Examples include the following.
    - Genetics consultation for evaluation of associated syndromes is especially helpful in cases of unilateral agenesis.
    - Abdominal US may be conducted to look for renal and ureter abnormalities.
    - Echocardiography may be performed to evaluate the presence of any concomitant cardiac defects.
    - Skeletal radiographs should be obtained as directed by the physical examination findings or suspicion for syndromic involvement.

Expected Outcome/Prognosis

- The degree of pulmonary hypoplasia, the underlying cause, and other associated congenital abnormalities can influence outcome and prognosis.
- Severe pulmonary hypoplasia has a high mortality rate. In infants with CDH, pulmonary arterial hypertension is associated with poor outcomes.
- In infants with unilateral pulmonary hypoplasia, cardiac, skeletal, and neurological problems will influence survival.
- Survivors commonly experience chronic respiratory problems, including impaired lung function and recurrent pulmonary infections.
- Improved survival rates can be credited to new diagnostic and surgical techniques.

When to Refer

- Antenatal diagnosis
  - Prenatal parental counseling and planning should occur in a timely manner.
  - Fetal surgery may be an option.
  - Delivery of the neonate should occur in a tertiary care center, with neonatal and surgical teams available to assess and manage the newborn.
- Newborns with respiratory distress should be evaluated by the neonatal team.

When to Admit

- Admit pregnant women with fetuses suspected of having pulmonary hypoplasia or arrange for delivery at a tertiary care center with a fetal medicine team, neonatal intensive care unit, and surgical support services.
- Management of associated comorbidities and surgically correctable lesions may also require hospitalizations.

Prevention

- At this time, there are no strategies for preventing pulmonary hypoplasia.
- Fetal surgical intervention for congenital diaphragmatic hernia, such as fetoscopic endoluminal tracheal occlusion, remains experimental but may decrease the severity of pulmonary hypoplasia associated with CDH.

Resources for Families

- American Alliance for pPROM Support. aapprom.org
- Pulmonary Hypoplasia (Patient). Patient.info/doctor/pulmonary-hypoplasia

Clinical Pearls

- Anomalies that occur early in pregnancy are associated with more severe pulmonary hypoplasia.
- Prenatal diagnosis allows appropriate intervention and preparation for issues at delivery.
- Pulmonary hypoplasia is often associated with other anomalies.
- Long-term outcomes for mild pulmonary hypoplasia are excellent.

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Chapter 17

Pulmonary Sequestration

T. Bernard Kinane, MD

Introduction

- Pulmonary sequestration is a cystic mass that is composed of primitive, nonfunctional lung tissue.
- Pulmonary sequestrations are rare and represent 0.15%–6.0% of all congenital pulmonary malformations.
- Most cases occur sporadically.
- This malformation is separate from the tracheobronchial tree and receives its blood supply from a systemic artery rather than the pulmonary artery.
- Because it fails to connect with the tracheobronchial tree, it does not contribute to respiration.
- There are 2 types of pulmonary sequestration: intralobar and extralobar. Intralobar sequestration occurs within a normal lobe of the lung and accordingly does not have its own visceral pleura. An extralobar sequestration is outside the lung and has its own visceral pleura.
- Intralobar sequestration is the most prevalent of the 2 types and accounts for about 80% of all sequestrations.
- Male and female patients are equally affected by the intralobar type.
- The extralobar type has a male to female ratio of 4:1.
- Only the extralobar type is associated with other congenital anomalies, which occur in about 60% of cases. The anomalies include pulmonary malformations such as congenital pulmonary airway malformation (CPAM), diaphragmatic hernia, and lobar emphysema, as well congenital heart disease.

Pathophysiology

- A sequestration is derived from an accessory lung bud that develops from the primitive foregut. Its blood supply is derived from the aorta and the adjoining vessels.
- Early embryologic development of the accessory foregut bud results in the formation of this additional structure in parallel with the normal lung. This process leads to the formation of a sequestration within normal lung tissue, which results in the intrapulmonary variant. However, later development of the accessory lung bud leads to the formation of the accessory structure outside the normal lung, resulting in the extrapulmonary sequestration.

- The arterial source is systemic in both types of sequestration and is usually derived from the lower thoracic or upper abdominal aorta. On occasion, the celiac axis, the internal mammary artery, or the renal artery may be the source.
- On the other hand, the venous drainage of the intralobar sequestration usually occurs via the pulmonary veins to the left atrium, setting up a right to left shunt. Extralobar sequestrations usually drain via systemic veins, such as the vena cava and azygous systems.
- Intralobar sequestration is found in the left lower lobe in about 66% of cases, usually in the posterior basal segment of that lobe. The extralobar type can occur above or below the diaphragm, and nearly all appear on the left side.
- No communication with the tracheobronchial tree occurs.

Clinical Features

- Presentation of intralobar sequestration occurs later in childhood or during young adulthood. The most frequent presentation is pneumonia with fever and cough. Infection is thought to occur via the migration of bacteria through the pores of Kohn. Hemoptysis is seen in about 30% of cases. Occasionally it manifests as an incidental pulmonary mass in the left lower lobe.
- Presentation of extralobar sequestration usually occurs in infancy or early childhood as a thoracic or subdiaphragmatic or retroperitoneal mass. It is now regularly identified as a mass at prenatal ultrasonography (US). It infrequently gets infected because it has its own pleural sac. Many patients are asymptomatic. Others can present with respiratory symptoms or high-output cardiac failure from blood flow through the sequestration.
- Physical findings can include an area of dullness to percussion and decreased breath sounds over the lesion.

Differential Diagnosis

- Because extralobar sequestration appears mainly as a mass-like lesion at presentation, the differential includes CPAM and tumor, both benign and malignant.
- Because intralobar sequestration appears as reoccurring localized pneumonia at presentation, the differential includes immunodeficiencies, other infected malformations that include CPAM, and an obstructed bronchus from foreign body and bronchial tumor, such as carcinoid.

Diagnostic Considerations

- Imaging should be performed to delineate the systemic blood supply.
- Chest radiographic findings can indicate the diagnosis according to the characteristic location of a mass in the left lower lobe. Indeed, recurrent infections might lead to the formation of cysts with this structure, which make it hard to differentiate from CPAM (Figure 17-1).

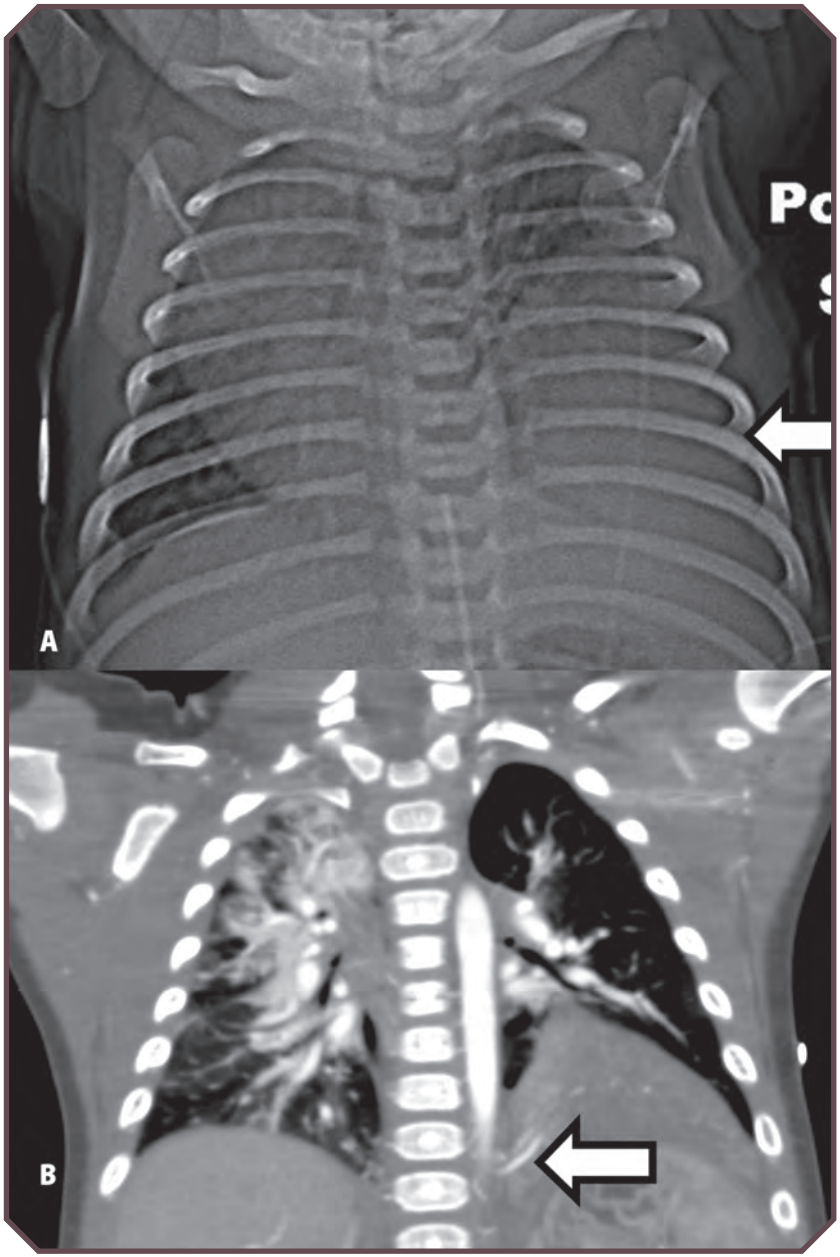

Figure 17-1. Extrapulmonary sequestration in a 5-month-old male infant. A. Frontal chest radiograph shows a left lung base opacity (arrow). B. Coronal reconstructed computed tomographic image obtained with contrast material confirms a density in the left lung base and demonstrates a vessel that extends from the aorta (arrow). These findings are diagnostic for sequestration.

- US and Doppler US can be used to identify an echogenic homogeneous mass with a feeding systemic artery. Such a mass can be detected at prenatal US. US is less useful in the postnatal period.
- Chest computed tomography (CT) is now the standard of reference and is used to establish the diagnosis correctly in 90% of cases. The characteristic features are a solid mass in the typical location, with a feeding systemic artery. Three-dimensional reconstruction often aids in the identification of the feeding artery.
- Contrast-enhanced magnetic resonance angiography can be used to establish the diagnosis but does not rival the sharper images that are provided by CT.

Management

- Usually, symptomatic sequestration is removed via video-assisted thoracoscopic surgery or thoracotomy. Resection of asymptomatic sequestration is not always indicated. If the risk of infection is high, as in intralobar sequestration, or if there is a risk of developing high-output heart failure, as in the case of large feeder vessels, resection should be considered. Identification of the feeding artery is critical for a successful surgery.
- Extralobar sequestrations can be removed in their entirety.
- Intralobar sequestrations may be removed via a wedge resection, segmentectomy, or lobectomy.
- The arterial embolization of the sequestration is increasingly used, but numbers are still low. It is less invasive than surgical resection. It is important that embolization be performed by providers experienced in identifying and avoiding embolization of arterial branches that feed other organs, including the spine.

Expected Outcomes/Prognosis

- Resection is curative. Long-term risks are infrequent and mainly relate to scar formation.

When to Refer

- All patients with prenatal lung masses should be referred to a pulmonary specialist.
- Patients with recurring localized pneumonia should be referred because there may be an underlying pulmonary malformation, such as a sequestration or a CPAM.
- All lung masses should be referred to a clinical team, which will include a pediatric pulmonologist, pediatric surgeon, cardiologist, pediatric radiologist, and general pediatrician.

When to Admit

- Hospital admission should be considered for evaluation and treatment of acute respiratory infections and surgery.

Prevention

- At this time, there are no options for prevention.

Resources for Families

- Pulmonary Sequestration (National Center for Advancing Translational Sciences). rarediseases.info.nih.gov/gard/4593/pulmonary-sequestration/resources/1

Clinical Pearls

- Consider pulmonary sequestration in patients with reoccurring left lower lobe pneumonia.
- Extralobar sequestration is the least prevalent type but is associated with other congenital anomalies.
- Identification of a feeder vessel is critical to establishing the diagnosis.

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Chapter 18

Overinflation and Congenital Lobar Emphysema

Kevin Kuriakose, MD, FAAP

Overinflation

Introduction/Etiology/Epidemiology

- Overinflation consists of distended air spaces; however, it is often reversible.
- The terms *overinflation* and *hyperinflation* have been used interchangeably in medical practice. Both terms refer to distended air spaces that appear as excessive inflation of the lung parenchyma at presentation.
- Potential etiologic origins for overinflation include
  - Intrinsic airway factors
    - Asthma and bronchiolitis
    - Cystic fibrosis
    - Aspiration of zinc stearate powder or other chemicals and irritants
    - Foreign bodies
    - Endobronchial tumors
    - Severe bronchomalacia
  - Extrinsic airway factors
    - Mediastinal tumors
    - Pulmonary vascular abnormalities
- Unilateral hyperlucent lung is a localized overinflation in 1 lung or lobe, which includes
  - Obstructive overinflation
  - Pulmonary venolobar syndrome (also known as *scimitar syndrome*)
  - Congenital lobar emphysema (CLE)

Pathophysiology

- Partial obstruction of the airway results in distention of air spaces distal to the obstruction.
- Key points that distinguish overinflation from other forms of hyperlucency of the lungs include
  - Hyperinflated normal alveoli
  - Alveoli or lung parenchyma communicating with the respiratory tree
  - Overinflation that is usually reversible once the underlying cause is addressed

Clinical Features

- Symptoms
  - Dyspnea
  - Shortness of breath or difficulty exhaling
  - Patients may present with no symptoms or with symptoms only on exertion
- Signs at physical examination
  - Increased respiratory rate
  - Prolonged expiratory phase
  - Hyperresonance on percussion
  - Retractions

Differential Diagnosis

- Pulmonary emphysema
- Congenital cystic adenomatoid malformation
- Pulmonary sequestration
- Pneumothorax

Diagnostic Considerations

- Chest radiography or thin-section computed tomography (CT) performed with or without contrast material may demonstrate
  - Localized hyperlucency on radiographs or localized hyperattenuation on CT images
    - Based on the size of the hyperlucency or hyperattenuation, images may show
      - ~ Mediastinal shift
      - ~ Flattening of the ipsilateral diaphragm
  - Pulmonary vascular markings
    - The presence or absence of markings can help distinguish the diagnosis among the differential diagnoses.
- Bronchoscopy can be used to visualize an abnormality of the airway that is causing partial obstruction, resulting in a check valve effect, where airflow is unidirectional.
- A ventilation-perfusion scan can be used to identify a perfusion defect.

Management

- Respiratory distress or clinically significant respiratory symptoms will require supportive care.
- Treat the underlying cause of the overinflation.
  - Clinically significant respiratory symptoms may require surgical intervention.
  - Caution must be taken when intubating and using mechanical ventilation or positive pressure.
  - Clinically significant signs and symptoms may require further evaluation and management prior to air travel.

Expected Outcomes/Prognosis

- Prognosis is typically good to excellent, because overinflation is often reversible.
- Factors that decrease prognosis are dependent on the underlying cause of overinflation and any sequelae.

When to Refer

- Refer the patient to a specialist for recurrent or persistent bilateral diffuse hyperinflation secondary to an illness (eg, bronchiolitis, asthma).
- Unilateral or localized overinflation with or without symptoms necessitates referral.
- Multidisciplinary teams may include the following pediatric subspecialists:
  - Pulmonologist
  - Ear, nose, and throat specialist and/or surgeon
  - Cardiologist
  - Infectious diseases specialist

When to Admit

- Respiratory symptoms that progressively worsen
- Respiratory distress or clinically significant respiratory symptoms that require increasing supportive care

Prevention

- Encourage vaccinations.
- Schedule monitoring and surveillance, including the use of subspecialty referral and monitoring studies as indicated.
- Promote family education, involving
  - Infection control measures
  - Reducing foreign-body risk from foods and/or objects
  - Genetic counseling if related to congenital malformations

Pulmonary Venolobar Syndrome (Scimitar Syndrome)

Introduction/Etiology/Epidemiology

- Pulmonary venolobar syndrome (or Scimitar syndrome) is an overinflation of the contralateral lung secondary to hypoplasia of the right lung due to partial anomalous pulmonary vein connection.
- The name originates from the shadow of the anomalous pulmonary vein that drains into the vena cava (typically the inferior vena cava at the level of the diaphragm), which resembles a curved Turkish sword known as a *scimitar*.
- It is a rare, sporadic process that occurs in 1 in 2,000 cases of congenital heart disease (CHD).

- Associated malformations (CHD, congenital cystic malformations, congenital diaphragmatic hernia, vertebral anomalies) increase the risk of chromosomal defects by 50%.

Pathophysiology

- The pathophysiology is unclear but appears to be caused by abnormal lung development during embryogenesis.

Clinical Features

- Scimitar syndrome is typically asymptomatic from birth to late childhood, even into adulthood.
- Symptoms may appear in late childhood into adulthood because of the development of pulmonary hypertension and/or the degree of lung hypoplasia.
- Symptoms may consist of
  - Recurrent respiratory tract infections
  - Dyspnea with exercise
  - Chest pain
  - Hemoptysis
  - Poor weight gain

Differential Diagnosis

- Aberrant pulmonary veins

Diagnostic Considerations

- Pulmonary venolobar syndrome may be identified during prenatal care with the use of fetal ultrasonography.
- Radiologic techniques (chest radiography, CT, magnetic resonance imaging, magnetic resonance angiography) demonstrate anomalous pulmonary vein draining to the vena cava and mediastinal shift due to pulmonary hypoplasia with contralateral lung hyperlucency.
- The scimitar sign is seen on chest radiographs and consists of a broad shadow of the anomalous pulmonary vein draining into the inferior vena cava, creating a silhouette of a curved Turkish sword (see Figure 18-1). This sign is pathognomonic, along with radiographic findings of ipsilateral mediastinal shift.

Management

- Management is usually conservative, with observation and monitoring conducted by a pulmonologist and a cardiologist.
- Surgical repair of the anomalous pulmonary venous connection by a CHD surgeon may be warranted if severe symptoms develop secondary to pulmonary hypertension.
- Lobectomies have been considered because of recurrent respiratory infections and the risk of developing bronchiectasis.

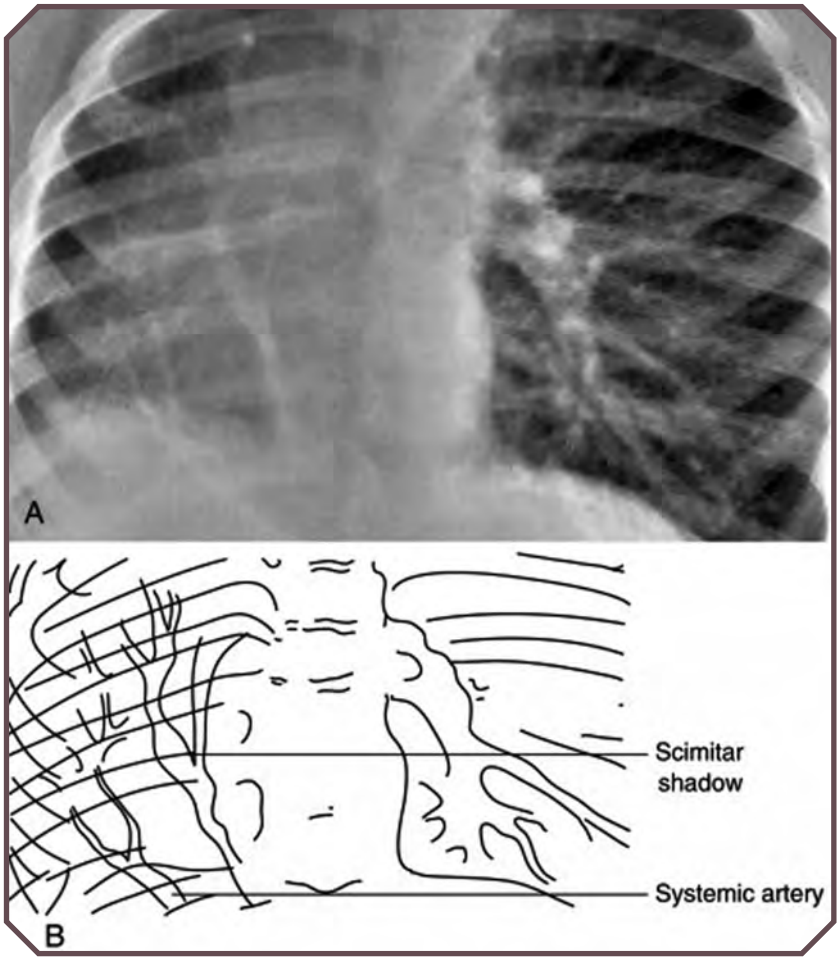

Figure 18-1. Scimitar syndrome. A. On the radiograph, note the hypoplastic right lung and scimitar-shaped shadow formed by pulmonary veins draining the sequestered segment and connecting to the inferior vena cava. B. On the diagram, note also the systemic artery coursing diagonally upward from the abdominal aorta to the sequestered lobe. From Beerman LB, Kreutzer J, Allada V. Cardiology. In: Zitelli BJ, McIntire S, Nowalk AJ, eds. *Zitelli and Davis' Atlas of Pediatric Physical Diagnosis.* 6th ed. Philadelphia, PA: Saunders; 2012:145–179.

Expected Outcomes/Prognosis

- The prognosis for asymptomatic patients is good to fair.
- Prognosis decreases with worsening symptoms due to pulmonary hypertension and/or comorbidities.

When to Refer

- For initial findings at radiography or other diagnostic testing in an asymptomatic child, refer the patient to a cardiologist and a pulmonologist.
- For worsening symptoms, in addition to a cardiologist and a pulmonologist, consider referral to a surgeon or cardiovascular surgeon.

Prevention

- Schedule monitoring and surveillance, including the use of diagnostic studies and consultation and follow-up with a cardiologist and a pulmonologist, to minimize complications and progression of the disease state.
- Genetic counseling is important, especially if other congenital malformations are present.

Congenital Lobar Emphysema

Introduction/Etiology/Epidemiology

- CLE is a rare congenital process that causes overinflation of a unilateral lung (typically a segment or lobe).
  - The term *emphysema* in the name is a misnomer. Emphysema is characterized by both overinflation and destruction of the alveoli, while CLE is characterized by overinflation with normal alveoli.
- The etiologic origin is not identified in 50% of cases.
- When identified, causes typically consist of
  - Bronchial cartilage defect
  - Bronchial obstruction
- Prevalence is approximately 1 in 20,000 to 1 in 30,000.

Pathophysiology

- An airway defect causes a check valve effect, where airflow is unidirectional, resulting in overinflation of alveoli in a particular lobe or segment.
- Airway defect appears to occur during embryogenesis of lung development in late saccular or alveolar stages.
- Histologically, 2 forms are noted.
  - The classic form (the more common variant) has a normal number of alveoli.
  - The polyalveolar form has an increased number of alveoli (but is otherwise histologically normal).

Clinical Features

- Symptoms
  - Cough
  - Dyspnea

- Signs at physical examination
  - Tachypnea
  - Retractions
  - Wheezing
  - Oxygen desaturations
- Typically, CLE is symptomatic during infancy, with most cases occurring in the first 2 months of life.
- Severe respiratory symptoms appear more commonly at earlier ages (infancy). Older children present with less severe to milder symptoms.
- Asymptomatic cases are uncommon and are historically diagnosed in adulthood.

Differential Diagnosis

- Pneumothorax
- Bullous emphysema
- Congenital cystic adenomatoid malformation

Diagnostic Considerations

- CLE may be seen during prenatal care as fluid-filled cystic lesions at fetal ultrasonography.
- Chest radiographic findings (Figure 18-2) include the following.
  - Hyperlucency can involve a lobe or a segment.
    - It most commonly occurs in the left upper lobe, followed by the right middle lobe and the right upper lobe.
  - Bronchovascular markings can be noted, which can be used to differentiate CLE from pneumothorax or other cystic lesions.
- Radiographic findings are more easily seen on thin-section CT scans than on chest radiographs (Figure 18-3).
- Ventilation-perfusion scan may be performed.
- Bronchoscopy is an option.

Management

- Severe respiratory symptoms will require surgical intervention, such as lobectomy or segmental lung resection.
- Asymptomatic children or those with mild symptoms should be observed and monitored.
- An algorithm for management is provided in Figure 18-4.

Expected Outcomes/Prognosis

- Prognosis is good with clinically significant improvement in signs and symptoms.
- Despite a favorable prognosis, persistent tachypnea and slow weight gain have been reported postoperatively.
- Information about long-term outcomes is limited.

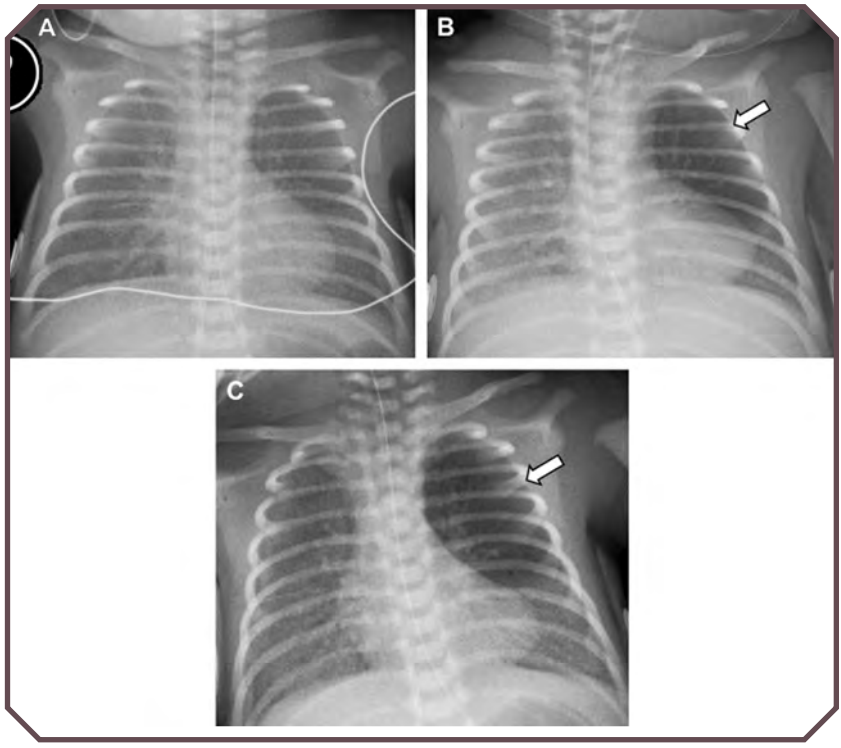

Figure 18-2. Congenital lobar emphysema in a female neonate with progressively worsening respiratory distress. A. Initial frontal chest radiograph obtained at birth is unremarkable. B. Frontal chest radiograph obtained 4 hours after birth demonstrates interval development of hyperlucency (arrow) in the left upper lobe. C. Frontal chest radiograph obtained 7 hours after birth shows increased hyperlucency (arrow) of the left upper lobe. From Lee EY, Dorkin H, Vargas SO. Congenital pulmonary malformations in pediatric patients: review and update on etiology, classification, and imaging findings. *Radiol Clin North Am.* 2011;49(5):921–948. Copyright 2011, with permission from Elsevier.

When to Refer

- Refer patients with severe respiratory symptoms to a surgeon.
- Refer patients with mild to no symptoms to a surgeon and/or a pulmonologist.

When to Admit

- Admit the patient for severe respiratory symptoms that require an increasing level of care or possible surgical intervention.

Prevention

No specific preventive measures are available at this time.

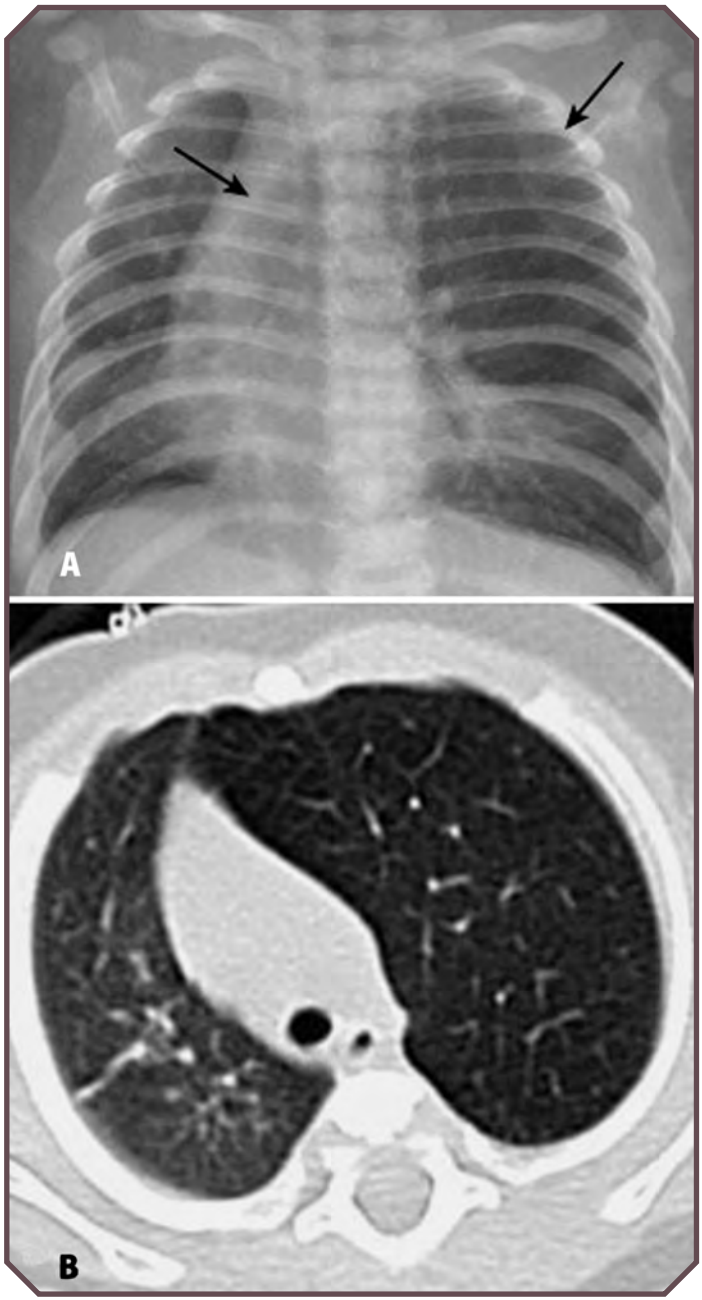

Figure 18-3. Congenital lobar emphysema. A. Frontal radiograph obtained in a 1-day-old neonate shows diffuse lucency and enlargement of the left upper lobe (arrows). B. Axial computed tomographic scan shows a hyperattenuating and enlarged left upper lobe with asymmetrical attenuation of vascular structures and increased space between the interstitial septa. From Donnelly LF. *Pediatric Imaging: The Fundamentals.* Philadelphia, PA: Saunders; 2009:26–61. Copyright 2009, with permission from Elsevier.

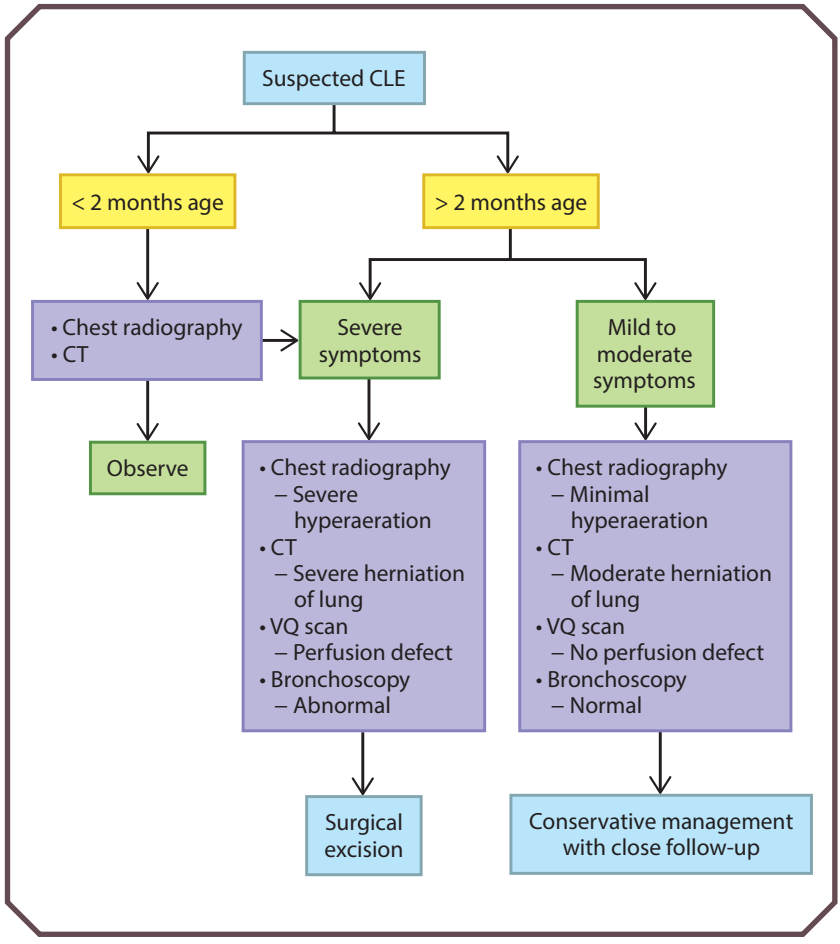

Figure 18-4. Algorithm for evaluation and treatment of congenital lobar emphysema (CLE). From Boas SR, Winnie GB. Emphysema and Overinflation. In: Kliegman RM, ed. *Nelson Textbook of Pediatrics.* 20th ed. Philadelphia, PA: Elsevier; 2016: 2050–2052. CT = computed tomography, VQ = ventilation-perfusion. Copyright 2016, with permission from Elsevier.

Resources for Families

- American Lung Association. www.lung.org
- Global Genes: Allies in Rare Disease. globalgenes.org
- National Organization for Rare Disorders. www.rarediseases.org
- Genetic and Rare Diseases Information Center (National Center for Advancing Translational Sciences). rarediseases.info.nih.gov

Chapter 19

Congenital Pulmonary Airway Malformation

Marianna M. Sockrider, MD, DrPH, FAAP

Introduction/Etiology/Epidemiology

- Congenital pulmonary airway malformation (CPAM), which refers to congenital malformations of the lung, was previously known as *congenital cystic adenomatoid malformations* or *CCAM*.
- CPAMs are characterized by adenomatoid proliferation of bronchioles that results in cysts rather than alveoli. These lesions are thought to result from abnormal branching of bronchioles during lung morphogenesis. Lesions usually communicate with the normal tracheobronchial tree, though the connection may be constricted or anomalous. Blood supply is usually pulmonary arterial in origin, although some cases have been described with systemic arteries.
- CPAM has been the most commonly diagnosed lung malformation in fetuses, accounting for 30%–40% of all congenital lung diseases. Incidence is estimated at 1 in 10,000 to 1 in 35,000.
- Cases are sporadic, with no familial predisposition or known association with chromosome abnormalities. No association with race or maternal age has been found. Type 3 CPAM is seen predominantly in male infants.

Pathophysiology

- CPAM is usually unilateral, affecting only 1 lobe of the lung.
- Stocker's classification has 5 types, based on cyst size and histopathologic findings, with proposed correspondence to insults at different levels of the airways.
  - — Type 0: Acinar dysplasia or dysgenesis is seen at the bronchial level and involves all lung lobes. This type is rare, incompatible with life, and associated with other abnormalities.
  - — Type 1: Single or multiloculated large cysts are variable in size, from 2 to 10 cm. They are seen at the bronchial and/or bronchiolar level, and this is the most common type (50%–70% prevalence) with the best prognosis. This type is localized, typically to part of 1 lobe (Figures 19-1, 19-2). There is a correlation with bronchoalveolar carcinoma.

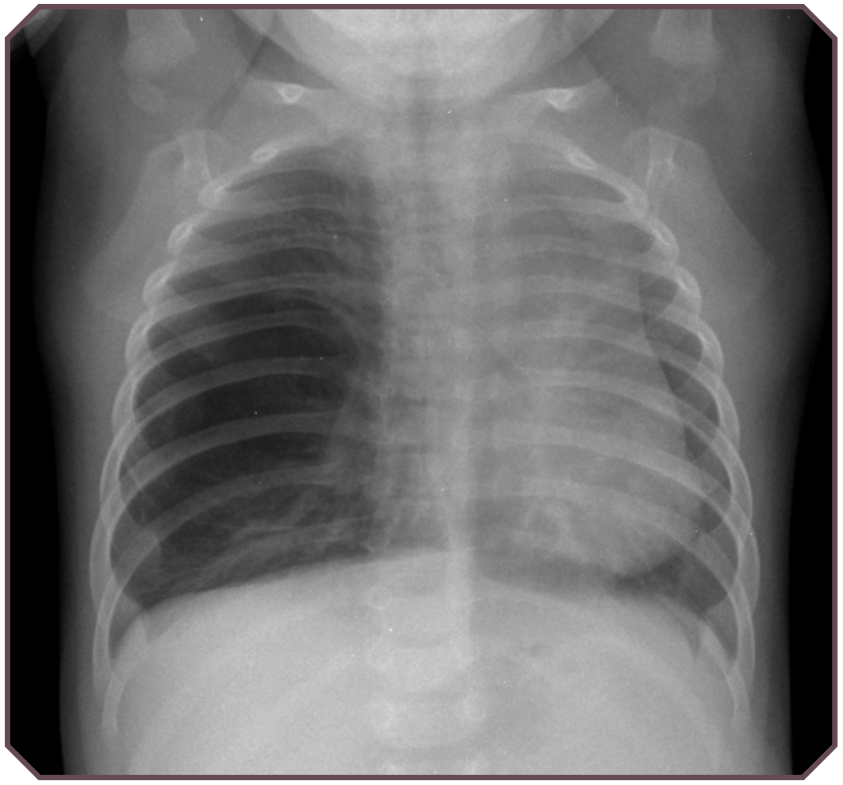

Figure 19-1. Type 1 congenital pulmonary airway malformation incidentally identified in a 3-month-old full-term male infant with a cough. Posteroanterior chest radiograph demonstrates hyperlucency of the right hemithorax, with right to left midline shift. Image courtesy of Robert Paul Guillerman, MD, Pediatric Radiology, Texas Children's Hospital.

- Type 2: Single or multiple small cysts from 0.5 to 2.0 cm occur at the bronchiolar level. This is the second most common type (15%–30% prevalence). Up to 60% of cases of type 2 CPAM occur with other associated anomalies.
- Type 3: This type has a microcystic appearance (<0.5 cm) histologically and occurs at the bronchiolar and/or alveolar duct level. It is uncommon, with 5%–10% prevalence. It involves the whole lobe, with compression of the adjacent lung. The cysts are so small that the mass may appear to be solid on images, with air spaces resembling late fetal lung and virtual absence of pulmonary arteries within the lesion histologically.
- Type 4: Multiloculated, large (≤10 cm), thin-walled peripheral cysts are seen with this type, which is uncommon (5%–15% prevalence) and has a correlation with pleuropulmonary blastoma.

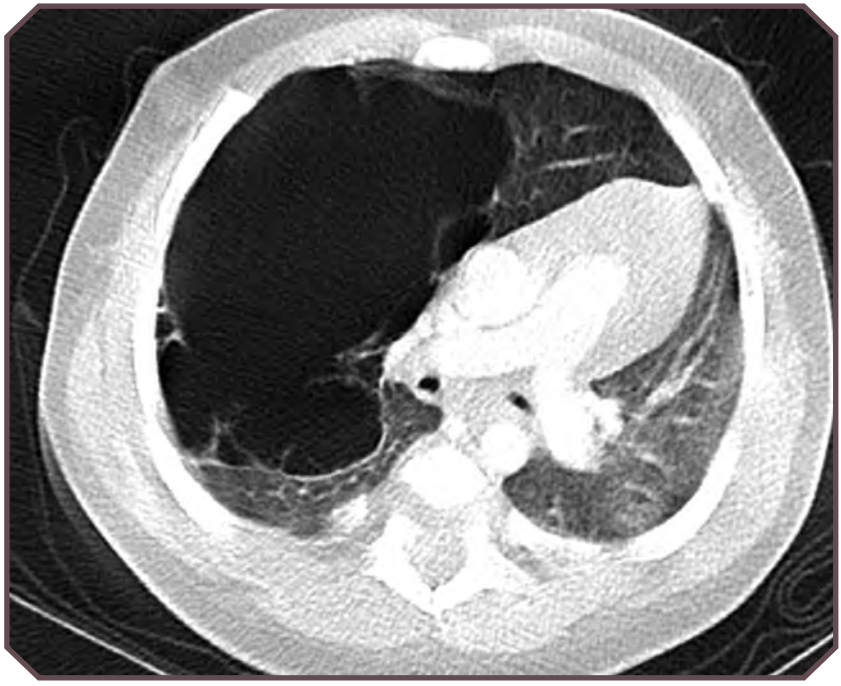

Figure 19-2. Type 1 congenital pulmonary airway malformation incidentally identified in a 3-month-old full-term male infant. Axial chest computed tomographic image shows a multicystic lesion with right to left midline shift in the right hemithorax. Image courtesy of Robert Paul Guillerman, MD, Pediatric Radiology, Texas Children's Hospital.

- Adzick proposes only 2 categories, with detection performed via antenatal screening: macrocystic (type 1, >5 mm) and microcystic (type 2, <5 mm).
- There may be other associated abnormalities of the bronchial tree. Large lesions can compress the adjacent lung, and large cysts can cause mediastinal shift in young infants. This shift may regress with increasing age.
- There is a rare risk of neoplastic and/or malignant transformation.

Clinical Features

- Almost all CPAMs can be detected in utero via ultrasonography (US) and may not be symptomatic after birth.
- Pregnancy may be complicated by hydramnios, pre-eclampsia, and premature birth.
- Up to 40% of patients develop hydrops fetalis, particularly with type 3 CPAM.
- Stillbirth can occur, particularly if associated with hydrops; however, survival to delivery is reported in >95% of cases.
- In <10% of cases, there may be a need for fetal intervention because of an enlarging mass or development of hydrops fetalis.

- CPAM can appear with progressive respiratory distress in the neonatal period or the first month after birth. The cysts become aerated and can progressively expand as the fetal lung fluid clears.
- Type 2 CPAM often appears with respiratory distress in the first month after birth.
- Between 50% and 65% of cases appear after the neonatal period. Children or adults can present with recurrent pulmonary infections. A few cases of spontaneous pneumothorax have been reported.

Differential Diagnosis

- In an infant, congenital diaphragmatic hernia (CDH) with herniated bowel in the thorax may have an appearance similar to a CPAM. The presence of peristalsis and the absence of an intra-abdominal stomach bubble at US suggest CDH. CDH and CPAM have been reported in the same patient.
- Bronchopulmonary sequestration may appear similar to a type 3 CPAM at US but may be intra-abdominal in location, has no connection to the tracheobronchial tree, and has a systemic rather than pulmonary arterial blood supply. "Hybrid" lesions with features of both CPAM and bronchopulmonary sequestration have been described.
- A bronchogenic cyst is typically single rather than multilocular, but a unilocular CPAM may appear similar. Both would typically be resected.
- A single large cyst may mimic lobar empyema; resection is indicated for both.
- Bronchiectasis from recurrent infection may have a cystic appearance. Cystic lesions in the area of a resolving pneumonia may represent postpneumonic pneumatoceles or abscesses. However, these should spontaneously resolve over time.
- Pleuropulmonary blastoma is a rare malignant tumor of infancy and early childhood that can mimic CPAM (see the Management section).

Diagnostic Considerations

- Prenatal US or magnetic resonance (MR) imaging
  - — Prenatal US is the primary imaging modality for evaluating the fetus. Close to 100% of CPAMs are detected at antenatal US by 20 weeks of gestation.
  - — When further evaluation of congenital lung lesions is necessary, prenatal MR imaging is the modality of choice, particularly when US findings are inconclusive.
  - — Serial US monitoring of congenital cystic lung lesions has demonstrated that approximately 15%–30% of these lesions decrease in size and may regress spontaneously. However, although the lesions may seem to disappear antenatally at US, some will still be present on postnatal CT images; therefore, follow-up is suggested, regardless of the prenatal US course.

- Chest radiography
  - — Chest radiography is only 60% sensitive in asymptomatic infants with lesions noted at prenatal US.
  - — Immediately after birth, the lesion may appear solid because of delayed clearing of fetal lung fluid from the cysts.
  - — Adjacent lung tissue may show atelectasis with mediastinal shift.
  - — In an asymptomatic older child, a lesion may be found incidentally on chest radiographs. (Figure 19-1 shows a radiograph of a type 1 CPAM.)
- Thin-section chest computed tomography (CT) is advised in asymptomatic infants with abnormal prenatal US findings to further define the abnormality. This may be performed without sedation in the first months after birth (the "feed and wrap" technique). (Figure 19-2 shows a CT image of a type 1 CPAM.)
- Chest MR imaging may be considered and has no radiation exposure but often requires sedation in young children.
- For a multicystic lesion in the left thorax, barium swallow could help distinguish CPAM from diaphragmatic hernia.

Management

- If symptomatic, surgical excision is recommended. Anecdotally, it has been reported that some infants who undergo elective resection are more lively afterward, suggesting they may not have been as well as was thought prior to resection.
- Large lesions are removed to prevent them from compressing adjacent lung growth, even in asymptomatic patients, but there is little evidence to support this concern.
- The incidence of pneumonia in infants with CPAM who are asymptomatic as neonates is estimated at 3%–5% and occurrs at a median age of 7 months. If infected, excision should follow appropriate antibiotic therapy. If infected once, a child is likely to have recurrent infection.
- Elective excision is controversial for asymptomatic patients, such as those whose CPAM is detected prenatally. Reasons cited to perform surgery include prevention of nonmalignant complications such as infection, allowing optimal lung growth of the remaining lung, and prevention of malignant transformation. Bronchoalveolar carcinoma, pleuropulmonary blastoma, and rhabdomyosarcoma are known to have an association with CPAM. However, there is limited evidence regarding the natural history, and some elect to monitor the condition medically. Performing follow-up chest radiography or CT also comes with risk associated with radiation exposure.
- Surgery is often performed in the first 3 to 6 months after birth because it is technically easier with a low risk of infection and need for respiratory support. Previous pneumonia is a risk factor for the need to convert video-assisted thoracic surgery to open thoracotomy.

- At surgical removal, as much normal lung should be conserved as possible. Often, surgery can be performed thoracoscopically.
- Prenatal interventions for large masses or CPAM with hydrops include thoracentesis, thoracoamniotic shunt placement, percutaneous laser ablation, and, rarely, open fetal surgery. Prerequisites for intervention include normal chromosomal analysis and absence of other obvious anomalies. Fluid may reaccumulate soon after thoracentesis. Experience with prenatal interventions is limited, and they are risky.

Associated Conditions

- Other associated anomalies are rare, except for type 2 CPAM (up to 60%).
- Associated genitourinary (including renal agenesis), gastrointestinal, cardiovascular, and pulmonary abnormalities may be present.
- Congenital diaphragmatic hernia and syringomyelia have been reported with CPAM.
- Screen for other abnormalities with echocardiography and US.

Expected Outcomes/Prognosis

- Type 0 CPAM is lethal.
- Surgery is usually curative for the other types, and the complication rate is very low.
- The risk of pulmonary hypoplasia is greatest for type 3 CPAM, and little is known about the degree of compensatory growth of new lung tissue after resection in infancy. Prognosis can depend on other associated conditions.

When to Refer

- Refer all patients suspected of having CPAM to a pediatric surgeon to discuss the need and timing of excision.
- Consider referral to a pediatric pulmonologist for patients with a history of recurrent lower respiratory infections and for monitoring of lung function, particularly for those at risk of limited lung function due to type 3 CPAM.

When to Admit

- If an infant has respiratory distress, admission and prompt CPAM removal are necessary.
- If a child has an acute infection, consider admission to administer intravenous antibiotics.

Clinical Pearls

- CPAM is the most common congenital lung malformation and is often detected prenatally.
- Perform contrast-enhanced chest CT to further delineate the lesion and plan for surgery.
- Consider the possibility of CPAM in an older child or adult who has recurrent lower respiratory infections, particularly in the same area.

Resources for Families

- Congenital Abnormalities (American Academy of Pediatrics). www.healthychildren.org/English/health-issues/conditions/developmental-disabilities/Pages/Congenital-Abnormalities.aspx
- Congenital Cystic Adenomatoid Malformation (Patient). patient.info/health/congenital-cystic-adenomatoid-malformation-leaflet

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Chapter 20

Bronchogenic Cysts

Marianna M. Sockrider, MD, DrPH, FAAP

Introduction/Etiology/Epidemiology

- Bronchogenic cysts are congenital malformations of the lung. They are a type of foregut duplication cyst derived from abnormal budding of the tracheal diverticulum before 16 weeks of gestation.
- A bronchogenic cyst is a closed sac typically made up of respiratory-type epithelium. It may have any of the elements normally present in the trachea and bronchi, including fibrous connective tissue, mucous glands, smooth muscle, and cartilage in the wall. There can be squamous metaplasia.
- Usually there is a single unilocular cyst filled with clear fluid or mucus. However, there can be multilocular and multiple cysts at times.
- It is the most common type of lung cyst in infancy, although it may not appear until adulthood.
- The exact incidence is not known, but it has been estimated that bronchogenic cysts make up 14%–22% of congenital lung cysts and 10% of mediastinal masses in children.
- Mediastinal cysts occur equally in male and female patients; intrapulmonary cysts may be more common in male patients.

Pathophysiology

- The most common location is in the mediastinum. About half are located within about 3 cm of the carina, most often on the right side (Figure 20-1).
- There are 5 groups based on location:
  - Paratracheal cysts
  - Carinal cysts
  - Paraesophageal cysts, which may communicate with the esophagus
  - Hilar cysts, which come off the main or lobar bronchi or can migrate into the lung parenchyma
  - Miscellaneous cysts, which are rare, having migrated during embryonic development to unusual sites such as abdominal, cervical, retroperitoneal, and subcutaneous locations
- Mediastinal cysts may communicate with the tracheobronchial tree.
- A few patients have had a systemic blood supply.
- Bronchogenic cysts can progressively enlarge in utero with advancing gestation and over time after birth.

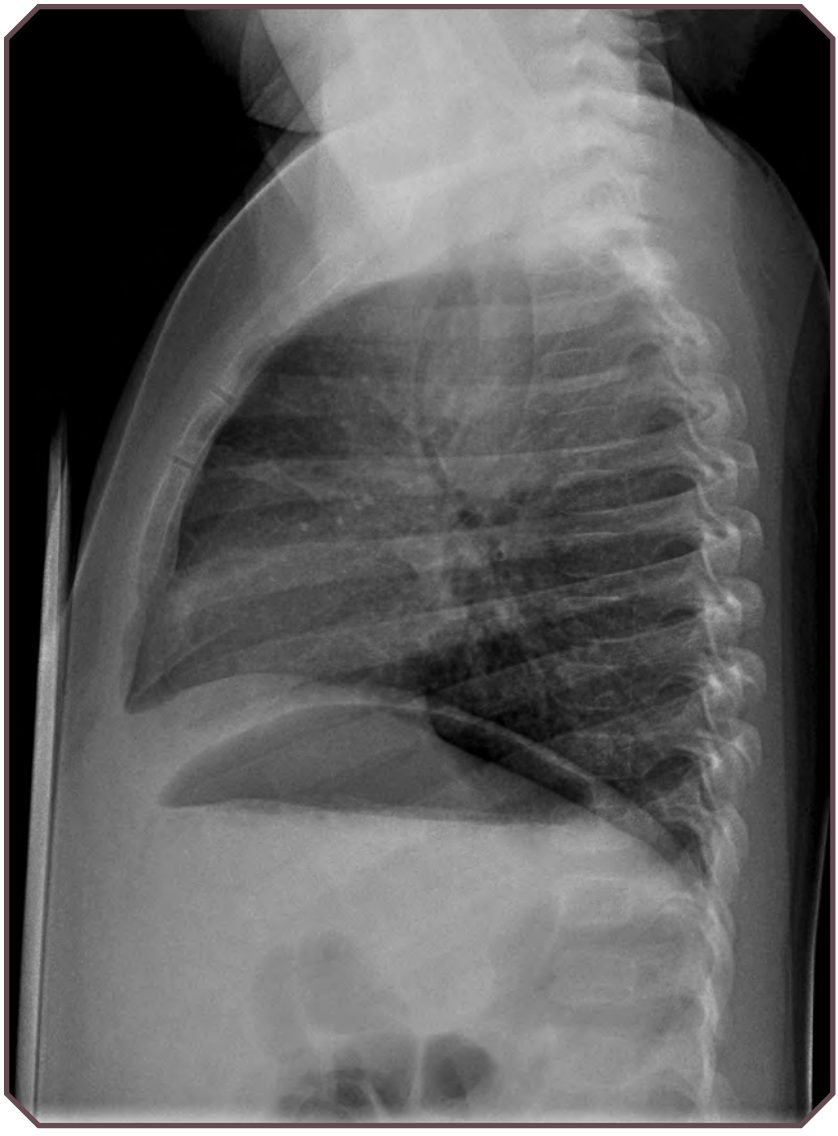

Figure 20-1. Lateral chest radiograph of a 17-month-old girl with bronchogenic cyst shows anterior bowing and narrowing of the trachea by a fluid-filled mass of the middle mediastinum centered at the level of the trachea and the aortic arch, above the carina. Image courtesy of Robert Paul Guillerman, MD, Pediatric Radiology, Texas Children's Hospital.

- Bronchogenic cysts can cause symptoms due to mass effect, direct pressure on an airway that leads to air trapping, or secondary infection.
  - Compression of the bronchus or esophagus may occur even with a small cyst (1.5–3.0 cm).

- A large cyst may compress normal lung parenchyma, resulting in atelectasis, recurrent infection, and mediastinal shift.
- Compression with a large cyst in utero may result in pulmonary hypoplasia of the adjacent lung.

Clinical Features

Clinical manifestations vary with location and size.

- Up to 20% of bronchogenic cysts remain asymptomatic and may only be detected as an isolated, incidental finding on a chest radiograph—typically appearing as a mediastinal mass.
- Most symptomatic cysts appear in infancy or early childhood; however, symptoms can develop at any age.
- An infant can present with acute respiratory distress because of airway compression. Symptoms can be worse with feeding or crying. The clinical picture may be similar to that of congenital lobar emphysema, with progressive overinflation of the obstructed lung or lobe.
- Bronchogenic cysts are prone to infection. Fever, chest pain, and productive cough are the most common presenting symptoms.
- Rarely, a cyst ruptures, leading to pneumothorax.

Differential Diagnosis

The differential diagnosis of a cyst or cysts depends primarily on findings at chest radiography or computed tomography (CT).

- Clinically, is a congenital lesion or acquired cyst suspected? This can be a difficult question to answer in the context of an acute infection, but cysts will persist over time.
- Is the cyst (or cysts) located in the lung parenchyma or the mediastinum?
  - Bronchogenic cysts are most often located in the middle mediastinum.
  - The other type of congenital cysts most often found in the mediastinum are enterogenous cysts (either esophageal or gastroenteric duplication cysts). They are also usually single embryologically formed foregut cysts. An esophageal cyst is intramural in the esophagus and is the more common of the two. A gastroenteric duplication cyst does not connect to the esophagus and usually occurs as a posterior mediastinal mass in a paravertebral location, often in the region of the sixth to the eighth vertebrae. These cysts are more likely to be associated vertebral anomalies than bronchogenic cysts.
- Does the cyst appear to be air filled, fluid filled, or air and fluid filled?
  - Bronchogenic cysts are usually fluid filled.
  - When appearing in association with acute pneumonia, a bronchogenic cyst with an air-fluid level is difficult to distinguish from a lung abscess.

  - An air-filled cyst has the appearance of a pneumatocele. Persistence of the lesion on follow-up radiographs is suggestive of a bronchogenic cyst.
- Is there a single cyst, or are there multiple cysts?
  - Bronchogenic cysts are typically single.
  - If there are multiple cystic lesions of the lung, consider a congenital pulmonary airway malformation. Pulmonary sequestration can have a presentation similar to that of an intralobar multicystic mass, usually in a posterior basilar location. It usually appears in an older child or adult.
- Does it appear to have a smooth or irregular contour with a thick or thin wall?
  - Bronchogenic cysts usually have a smooth appearance.
  - Bronchogenic cysts often have a thicker wall than that of a congenital pulmonary airway malformation or pneumatoceles.

Diagnostic Considerations

- Prenatal imaging
  - Prenatal ultrasonography (US) is the primary imaging modality for evaluating the fetus. It is safe, easily accessible, and inexpensive. Most lung lesions can be detected at routine 18- to 20-week US.
  - Prenatal magnetic resonance (MR) imaging is increasingly being used in the further evaluation of fetal lung lesions and has been shown to be particularly useful when US findings are inconclusive.
- Chest radiographs
  - A bronchogenic cyst usually appears as a single, smooth-bordered, spherical mass on chest radiographs (Figure 20-1). It has a uniform tissue density similar to that of the cardiac shadow. Calcification is unusual.
  - However, a cyst may not be seen on chest radiographs, with only signs of airway compression with hyperinflation of a lobe or lung evident.
- Chest CT will demonstrate the cyst and anatomy more fully (Figures 20-2, 20-3).
- MR imaging can demonstrate a bronchogenic cyst and demonstrate anomalous systemic arteries.
- Flexible bronchoscopy may show extrinsic compression of the airway.

Management

- The preferred treatment is cyst excision. Excision is indicated in all symptomatic cases. Elective excision is advised for asymptomatic patients as well, because of the high likelihood of future symptoms and the potential for serious illness from airway obstruction, infection, or malignancy. Often, surgery can be performed thoracoscopically, and lobectomy is usually not required.

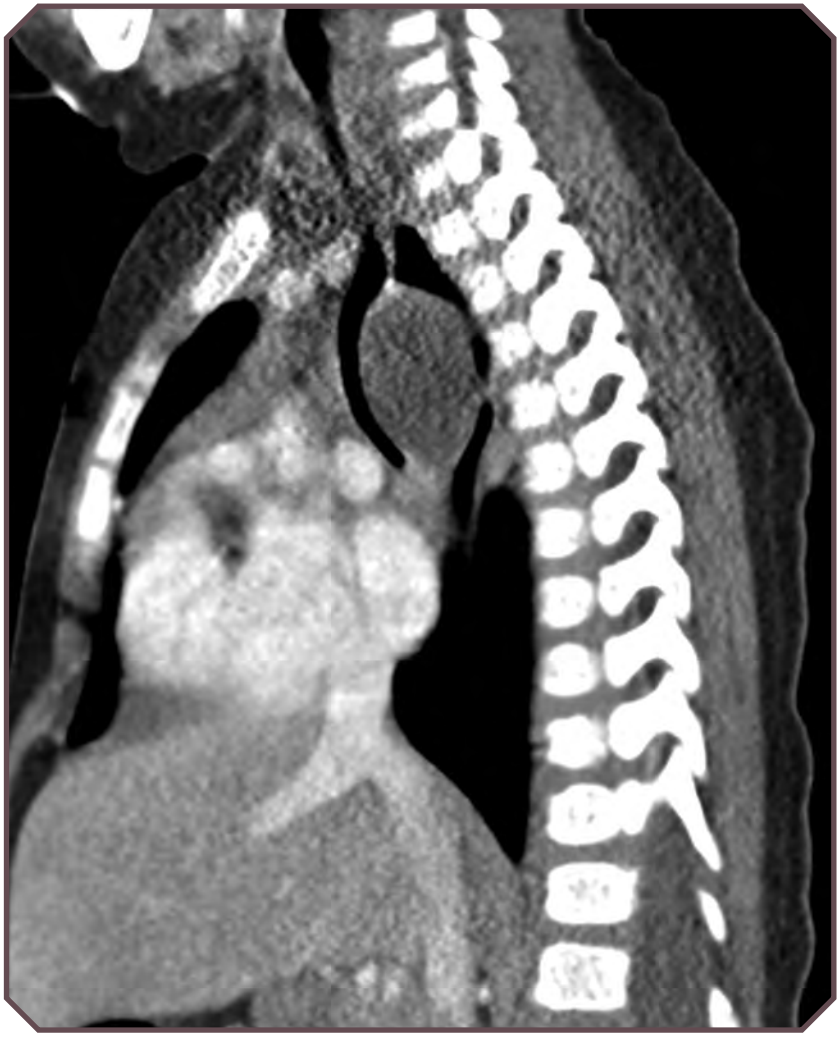

Figure 20-2. Sagittal contrast-enhanced computed tomographic image obtained in a 17-month-old girl with a bronchogenic cyst shows anterior bowing and narrowing of the trachea by a fluid-filled mass of the middle mediastinum, centered at the level of the trachea and aortic arch above the carina. Image courtesy of Robert Paul Guillerman, MD, Pediatric Radiology, Texas Children's Hospital.

- If infected, excision should be performed after appropriate antibiotic therapy.
- Successful prenatal percutaneous aspiration has been reported for a large cyst to reduce lung compression.

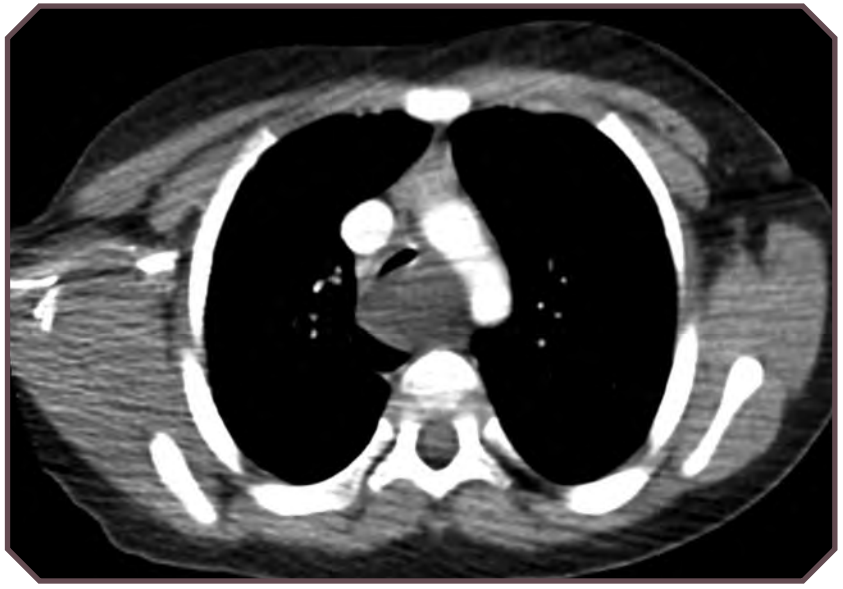

Figure 20-3. Axial contrast-enhanced computed tomographic image obtained in a 17-month-old girl with a bronchogenic cyst shows a fluid-filled mass of the middle mediastinum centered at the level of the trachea and aortic arch above the carina, with right posterolateral displacement of the esophagus by the cyst. Image courtesy of Robert Paul Guillerman, MD, Pediatric Radiology, Texas Children's Hospital.

Treating Associated Conditions

- There can be associated vertebral anomalies, although these are more typical with an esophageal or gastroenteric duplication cyst.
- Identification of an adjacent vertebral anomaly with a mediastinal mass should prompt MR imaging for neuroenteric cyst with intraspinal involvement.
- Patients with vertebral anomalies should be monitored for the development of scoliosis.

Expected Outcomes/Prognosis

- Surgery is usually curative, and the complication rate is low.
- Infants with marked emphysema of a lung secondary to bronchogenic cyst exhibit gradual resolution of the emphysema postoperatively. If it was a large cyst in utero, there can be residual pulmonary hypoplasia. An area of bronchomalacia can contribute to continued symptoms, which often resolve over several months.
- Untreated, a cyst can become infected, which could complicate future resection if normal tissue planes are obliterated with inflammation and scarring.

When to Refer

- Refer all patients suspected of having a bronchogenic cyst to a pediatric surgeon to discuss the need and timing of excision.
- Consider referral to a pediatric pulmonologist for patients with a history of recurrent lower respiratory infections and for monitoring of lung function, particularly for those at risk of limited lung function due to large cyst in utero and pulmonary hypoplasia.

When to Admit

- If an infant has respiratory distress, hospital admission and prompt removal of the cyst are necessary. If a child has an acute infection, consider hospital admission to administer intravenous antibiotics.

Resources for Families

- Congenital Abnormalities (American Academy of Pediatrics). www.healthychildren.org/English/health-issues/conditions/developmental-disabilities/Pages/Congenital-Abnormalities.aspx

Clinical Pearls

- Bronchgenic cysts are the most common type of congenital lung cyst and may be detected prenatally but can be found at any age.
- Perform contrast-enhanced chest CT to further delineate the lesion and plan for surgery.
- Consider the possibility of bronchogenic cyst in an older child or adult who has an acute lower respiratory infection and chest radiographic findings suggestive of a cyst or abscess.

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Chapter 21

Pulmonary Arteriovenous Malformations

Matthew F. Abts, MD, and Susanna A. McColley, MD, FAAP, FCCP

Introduction/Etiology/Epidemiology

Definition

Pulmonary arteriovenous malformations (PAVMs) are abnormal fistulous connections between pulmonary arteries and veins that bypass the alveolar-capillary network and prevent the exchange of oxygen.

Etiology/Epidemiology

- PAVMs have an incidence rate of 2 to 3 per 100,000 people, with a female-to-male ratio of 1.5 to 1.0.
- Congenital (>80%): May be idiopathic or associated with hereditary hemorrhagic telangiectasia (HHT), an autosomal dominant disorder characterized by vascular shunts in multiple organ systems
- Acquired (<20%): May be due to infection, chest trauma, cardiac surgery, hepatic cirrhosis, Fanconi anemia, malignancy, and/or pregnancy

Pathophysiology

Underlying Pathogenesis

- Possibly due to incomplete resorption of vascular septae during fetal capillary development and the formation of cavernous, thin-walled vascular beds
- HHT-associated PAVMs due to mutations in the endoglin *(ENG)* gene, activin A receptor type II kinase 1 *(ALK1/ACVRL1)* gene, or *MADH4* gene

Anatomic Characteristics

- Defect commonly occurs at the arteriolar level but may be more proximal.
- HHT-associated PAVMs are usually multiple, involving the lower lobes.
- Idiopathic PAVMs are usually isolated or single lesions with no lobe preference.
- Most PAVMs are peripheral and frequently involve the pleura.

- There are multiple subclassifications:
  - Simple (80%): Aneurysmal fistulous sac with a single afferent artery and 1 or more draining veins
  - Complex (20%): Multilobed fistulous sac with multiple feeding arteries and draining vessels
  - Diffuse (rare): May involve whole lung segments or entire lobe(s)
  - Telangiectatic: Subtle, multiple, and associated with HHT

Physiology

- Right to left intrapulmonary shunting and systemic hypoxemia
- Deoxygenated pulmonary arterial blood from the right side of the heart flowing through 1 or more fistulous vascular conduits (PAVMs) and directly into the pulmonary venous circulation, thereby completely bypassing the alveolar-capillary network

Natural History

- Time, hemodynamic stress, and hormonal changes as seen during puberty and pregnancy may cause progressive enlargement and wall necrosis or erosion of PAVMs.

Clinical Features

- Half of cases are asymptomatic and may not appear until early adulthood.
- Symptoms are more common when lesions are large in size and/or number.
- Symptoms and signs usually do not appear until right-to-left shunt accounts for >20% of systemic cardiac output.

Signs and symptoms include

- Dyspnea
- Chest pain
- Cough
- Cyanosis
- Clubbing
- Hemoptysis
- Thoracic bruit or thrill
- Hypoxemia that *does not* improve with administration of supplemental oxygen
- Platypnea: Dyspnea in the upright position that is relieved with recumbence
- Orthodeoxia: Decrease in oxyhemoglobin saturation ≥2% in the upright position

Differential Diagnosis

- Hepatopulmonary syndrome
  - Seen in the context of chronic liver disease and portal hypertension
  - Intrapulmonary capillary and/or venous dilations with right-to-left shunting and clinical manifestations that overlap with PAVMs
- Radiographically, PAVMs may be confused with
  - Pulmonary artery aneurysmal disease
  - Pulmonary sequestration
  - Congenital pulmonary airway malformation
  - Bronchogenic cyst
  - Bronchocele
  - Infection or pneumonia
  - Vascular tumors

Diagnostic Considerations

Chest Radiography

- PAVMs are well-circumscribed, round areas of soft-tissue density (usually 1–2 cm in diameter) with accompanying linear extensions that represent afferent or efferent vessels.
- Small or complex PAVMs may be less well defined.
- See Figure 21-1.

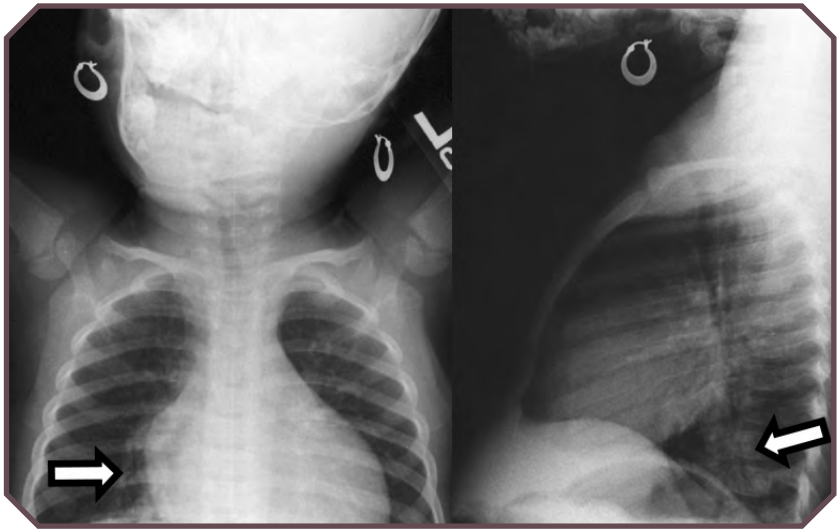

Figure 21-1: Plain frontal (left) and lateral (right) radiographs obtained in a 2-year-old girl with profound hypoxemia and suspected pulmonary arteriovenous malformation. Note the focal consolidation in the right lung base (arrows) and poor visualization of the right hemidiaphragm on the lateral projection.

Contrast-Enhanced Echocardiography (aka "Bubble Study")

- The preferred initial screening test for those with suspected PAVM, this modality is useful in diagnosing hepatopulmonary syndrome.
- It is a noninvasive and highly sensitive test that confirms the presence of right-to-left shunting (sensitivity of 100% and negative predictive value of 100% for PAVMs).
- Imaging is performed by injecting agitated saline ("microbubbles") into the peripheral venous system and observing its passage through the cardiopulmonary cycle via 2-dimensional echocardiography.
- Right-to-left shunting is confirmed by the presence of unfiltered microbubbles within the left atrium. If present, the quantity of microbubbles (grading) present in the left atrium over time (timing) is helpful in predicting the location and size of the suspected lesion.
- See Figure 21-2.

Computed Tomography

- Contrast-enhanced computed tomography (CT) is the preferred modality for diagnosis and is more sensitive than conventional angiography (98% vs 60%, respectively).
- A PAVM appears as a well-defined, uniform, round or oval area of high attenuation, with or without multilobulation.
- Feeding arteries and draining veins blend seamlessly with each lesion and are generally larger than neighboring vessels.

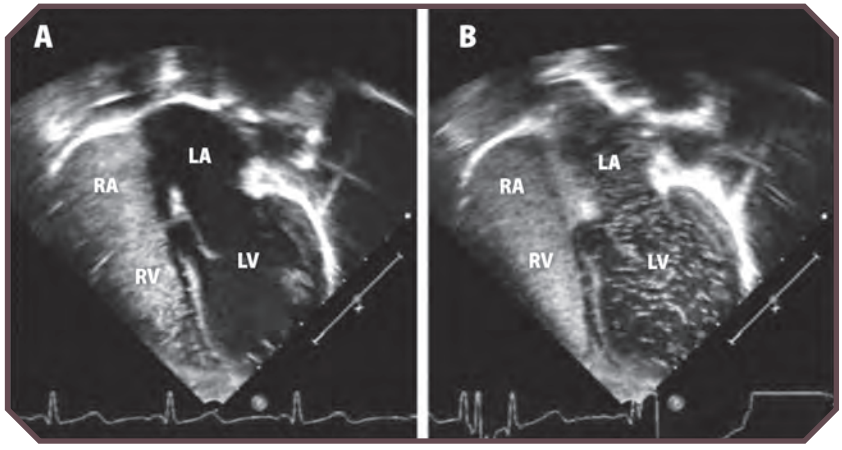

Figure 21-2. Contrast-enhanced echocardiography. An apical 4-window view was obtained after peripheral venous injection of agitated saline. A. Agitated saline is noticeable in the right atrium (RA) and right ventricle (RV). Note the absence of bubbles on the left side of the heart. B. After 3–4 cardiac cycles, agitated saline is now visible in the left atrium (LA) and left ventricle (LV). Findings are suggestive of intrapulmonary shunting. Images courtesy of Michael R. Carr, MD.

- Associated vessels tend to be larger than neighboring vessels, and draining veins may be slightly larger than feeding arteries by 1–2 mm.
- See Figure 21-3.

Contrast-Enhanced Pulmonary Angiography

- The standard of reference for defining anatomy and architecture of suspected PAVM
- Should be performed for the purpose of therapeutic embolization or surgical planning
- Visualized as 1 or more fistulous sacs with dilated feeding and/or draining arteries and veins
- Blood flow through the lesion brisk and dependent on size
- See Figure 21-4

Other Helpful Diagnostic Tests

- Pulmonary shunt fraction
- Arterial blood gas analysis
- Complete blood count to look for anemia and/or polycythemia
- Complete metabolic panel to look for evidence of liver and/or kidney disease

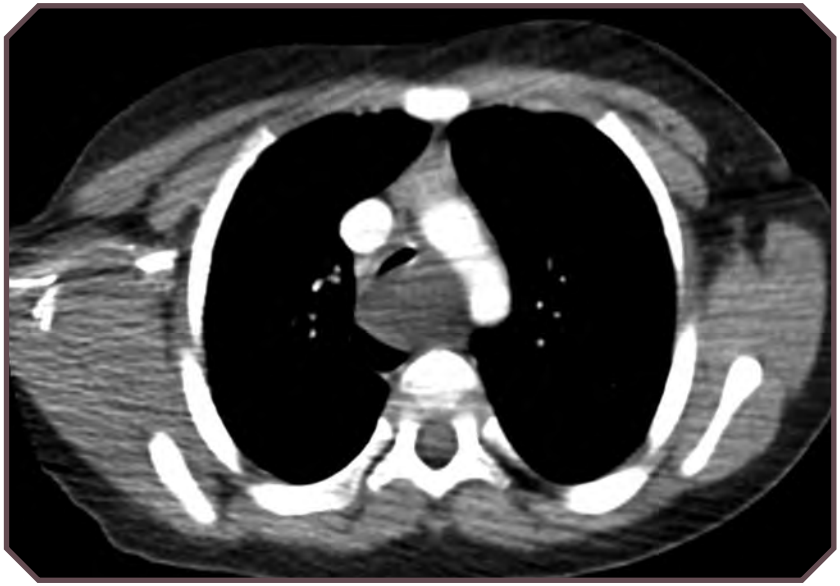

Figure 21-3. Axial contrast-enhanced computed tomographic image obtained in a 2-year-old girl with profound hypoxemia and a suspected pulmonary arteriovenous malformation that is represented by a multilobular vascular mass in the right lower lobe.

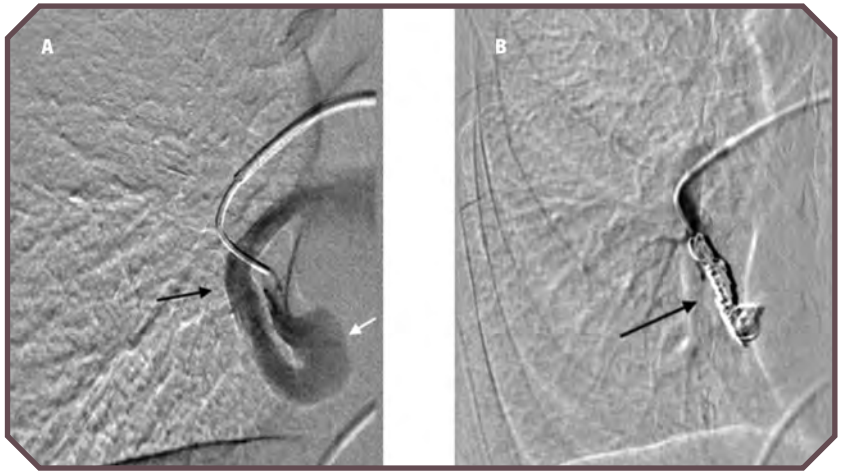

Figure 21-4. Selective catheter angiography. A. Simple-type pulmonary arteriovenous malformation with an aneurysmal sac (white arrow) shunting into pulmonary venous drainage (black arrow). B. Selective embolization of the feeding pulmonary artery with multiple 8- and 10-mm platinum coils (arrow); there is cessation of flow through the shunt. (Images courtesy Karim Valji, MD, and Giri Shivaram, MD.)

Management

Not all PAVMs require intervention, particularly in the asymptomatic child. The decision to pursue therapy should be based on individual patient characteristics, the size and number of vascular lesions, and the relative risks and/or benefits of each type of procedure.

Embolotherapy

- Invasive angiographic occlusion of feeding arteries via catheter-directed placement of intravascular coils or plugs (Figure 21-4)
- Usually performed in those with afferent artery size of ≥2 mm
- Should result in immediate and long-term improvements regarding symptoms, radiographic findings, and oxygenation

Surgical Intervention

- Reserved for those with lesions refractory to embolotherapy and those with life-threatening complications where embolotherapy is not an option
- Vascular ligation, local resection, lobectomy, pneumonectomy
- Lung transplantation
- For hepatopulmonary syndrome, liver transplant

Adjunctive Therapies

- There is no approved pharmacological therapy for PAVMs at this time.
- Estrogens, antifibrinolytic agents, and angiogenesis inhibitors are emerging as possible therapies for HHT-related extrapulmonary vascular lesions.

Treating Associated Conditions

- If HHT is suspected, international HHT guidelines suggest referral to a center experienced in caring for patients with this relatively rare condition.
- Iron supplementation may be indicated if iron-deficiency anemia is present.
- Avoid air emboli during intravenous infusions.
- Antibiotic prophylaxis may be indicated for nonsterile surgeries (eg, dental work).
- The patient should avoid scuba diving because of the risk of air emboli.

Expected Outcomes/Prognosis

Complications

- Reactive polycythemia due to chronic hypoxemia
- Iron deficiency anemia
- Pulmonary hemorrhage due to ruptured PAVM
- Hemothorax due to ruptured PAVM
- Paradoxical emboli
- Migraine headaches
- Cerebrovascular or transient ischemic attacks
- Brain abscesses and/or endocarditis
- Pulmonary hypertension
- High-output cardiac failure (usually only seen in HHT)

Short-term Complications after Embolization

- Pleuritic chest pain (the most common complication; may respond to short-term corticosteroids)
- Transient ischemic attacks, stroke
- Dislodgement and migration of embolic material
- Arterial perforation

Long-term Complications after Embolization

- Growth of pulmonary or systemic collateral vessels
- Worsening pulmonary hypertension
- Chronic pleurisy

Prognosis

- PAVMs do not resolve spontaneously.
- Prognosis is dependent on the severity of lesion(s) and presence of comorbidities.
- Prognosis is worse in high-risk individuals (adolescents, pregnant women).
- Embolotherapy carries a success rate as high as 98%.

When to Refer

- Children with unexplained hypoxemia should be referred to an experienced pulmonologist for thorough evaluation.
- Any suspicion for underlying HHT necessitates referral to a medical center with staff experienced in caring for patients with this relatively rare condition.

When to Admit

- Persistent hypoxemia, dyspnea, and/or hemoptysis
- Acute neurological or mental status changes in the setting of known PAVM

Resources for Families

- HHT Foundation International. www.curehht.org

Clinical Pearls

- PAVMs result in right to left intrapulmonary shunting and systemic hypoxemia.
- PAVMs should be suspected in the setting of unexplained hypoxemia that is unresponsive to supplemental oxygen.
- Contrast-enhanced echocardiography is a highly sensitive and noninvasive screening tool.
- Contrast-enhanced CT is the diagnostic test of choice for suspected PAVMs.
- Angiography with embolotherapy is the mainstay of treatment.

Section 3. Structural Abnormalities of the Chest Wall

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Chapter 22

Chest Wall Deformities: Thoracic Insufficiency Syndrome

Nicholas L. Friedman DO, FAAP, and Oscar Henry Mayer, MD

Introduction

- Thoracic insufficiency syndrome (TIS) is the inability of the thorax to support normal respiration or lung growth.
- TIS is a broad categorization of chest wall and spinal deformities, all of which require a novel approach for both assessment and treatment.
- Progressive worsening of the chest wall and spine deformity can lead to respiratory insufficiency, as patients are not able to compensate fully for abnormal respiratory mechanics and restrictive respiratory disease by increasing their respiratory rate.

Etiology

- In TIS, there is a 3-dimensional deformity of the thorax that reduces the volume available for the lungs.
- These volume depletion deformities can be categorized as unilateral or bilateral and classified in 1 of the 4 categories discussed in the Differential Diagnosis section.

Pathophysiology

- The thorax includes the spine, ribs, and sternum and functions by increasing its cross-sectional area during inspiration.
- Thoracic expansion in inspiration occurs through both contraction of the diaphragm and upward and outward chest wall motion.
- Limitation of the thorax to fully expand during inspiration and/or limitation in the resting lung volume (functional residual capacity) may cause progressive loss of lung volume and an inability to support normal respiration.
- Alveolar development and lung growth primarily occur in the first 2–3 years of life; however, they occur throughout childhood and adolescence.
- Symmetrical growth of the thoracic cage must occur simultaneously to allow for normal lung growth.

- Complex scoliosis with spinal rotation and lordosis into the convex hemithorax can create an asymmetrical chest that further restricts lung volume and worsens respiratory mechanics.
- Caudal displacement of the ribs, as is seen in neuromuscular disease, can cause a narrow superior thorax and broad inferior thorax, shaped like a Christmas tree. This is known as the "collapsing parasol deformity," and it restricts lung volumes and worsens respiratory mechanics.

Differential Diagnosis

Type I: Absent Ribs and Presence of Scoliosis

- Congenital rib absence
- Iatrogenic after chest wall resection (complication or deliberate alteration)

Type II: Fused Ribs and Scoliosis

- VATER (vertebral defects, imperforate anus, tracheoesophageal fistula, radial and renal dysplasia) and/or VACTERL (vertebral, anal, cardiac, tracheal, esophageal, renal, and limb) associations
- Chest wall scarring secondary to radiation treatment

Type IIIa: Thoracic Foreshortening

- Jarcho-Levin syndrome (spondylothoracic dysplasia or spondylocostal dysostosis)
- Severe thoracic kyphosis
- Early spine fusion

Type IIIb: Thoracic Narrowing

- Jeune syndrome (asphyxiating thoracic dystrophy)
- Ellis–van Creveld syndrome

Type IV: Congenital and Neuromuscular Scoliosis

- Congenital or infantile scoliosis
- Spinal muscular atrophy
- Spina bifida
- Spinal cord neoplasms
- Static encephalopathy

Diagnostic Considerations

History

- Hypoplastic thorax at prenatal ultrasonography
- Early onset of clinical scoliosis (<3 years of age)
- Truncal upright instability, with abnormal chest wall contour
- Chest wall deformity (rib hump and shoulder asymmetry)

- Gross motor abnormalities secondary to postural instability
- Exertional intolerance due to an inadequate ability to maintain minute ventilation

Physical Examination

- The physical examination in patients with suspected TIS should include comprehensive musculoskeletal and respiratory evaluations.

Musculoskeletal Evaluation

- Palpate the vertebrae and ribs to assess the spinal alignment in the upright position.
- Palpate the ribs to assess whether there is any rib absence or fusion.
- Evaluate the patient for rib hump by having the patient bend forward from a standing position.

Respiratory Evaluation

- Observation of the respiratory cycle is key in the evaluation of TIS. When observing the patient's breathing, pay close attention to the following:
  - Symmetrical thoracic rise and fall, including assessment for unilateral ribcage invagination, as can be seen in flail chest syndrome
  - Work of breathing, including respiratory rate (which may be high to compensate for respiratory insufficiency), accessory muscle usage with inspiration (retractions in the intercostal, subcostal, and suprasternal spaces), and nasal flaring
  - Thoracoabdominal asynchrony, as seen with a highly compliant or poorly compliant chest wall that moves out of phase with diaphragmatic contraction, with the degree of thoracoabdominal asynchrony directly related to the degree of chest wall deformity
- Auscultation to assess for symmetry of aeration throughout all lung fields
- Measurement of pulse oximetry and end-tidal carbon dioxide
- Because children with TIS may develop pulmonary hypertension secondary to their respiratory insufficiency, one should evaluate whether there are any signs of right-sided heart strain, such as hepatomegaly, jugular venous distention, and a subxiphoid impulse, if concerned for worsening cardiac function. Point of maximal impulse, if subxiphoid, may be indicative of right-sided heart strain.

Laboratory Tests

- Arterial blood gas analysis should be performed if there is concern for acute respiratory failure.
- Increased serum bicarbonate level can be used as an indirect marker for chronic hypoventilation.
- Brain-type natriuretic peptide can be used to assess the patient for progressive heart strain or failure.
- One may want to involve a geneticist to evaluate the need for genetic testing to look for an underlying etiologic origin.

Imaging

Radiography

- Standing or upright anteroposterior and lateral chest and spinal radiographs may be obtained to assess the severity of scoliosis in both the sagittal and coronal planes.
- Radiographs obtained with the patient in the lateral bending position are necessary to establish the flexibility of the scoliosis curve.
- The kyphosis angle can be measured on a lateral spinal radiograph, from T4 to T12. The kyphosis angle does not correlate well with the degree of respiratory function.

Computed Tomography

- Unenhanced chest computed tomography (CT) may be performed with 5-mm sections acquired with minimal radiation settings, with spinal and chest wall reconstruction conducted to assess thoracic anatomy 3-dimensionally.
- Chest CT may also be used to assess the presence of any right-to-left asymmetry and rotation of the sternum to look for a rotational defect.

Magnetic Resonance Imaging

- Magnetic resonance (MR) imaging of the spine and spinal cord may be performed to assess the patient for the presence of any spinal cord abnormalities, such as syrinx, tethered cord, and Chiari malformation.
- Dynamic MR imaging may be performed to assess the motion of the chest wall, diaphragm, and abdomen.

Pulmonary Function Testing

- Use arm span as a surrogate for vertical height, and do this consistently.
- Forced spirometry
  - Forced vital capacity (FVC)
  - Forced expiratory volume in 1 second (FEV_1)
  - Ratio of FEV_1 to FVC
  - Forced expiratory flow between 25% and 75% of vital capacity
- Static lung volume measurements
  - Total lung capacity (TLC)
  - Functional residual capacity
  - Residual volume
  - Ratio of residual volume to TLC
- Measures of respiratory muscle strength with maximal inspiratory pressure and maximal expiratory pressure
- Overnight polysomnography to assess for nocturnal hypoventilation

Cardiac Testing

- Echocardiography may be performed if there is concern for pulmonary hypertension and/or cor pulmonale.

Management

Nonsurgical

- Physical and occupational therapy to maximize thoracic range of motion
- Bracing and halo-gravity traction as temporizing measures that may improve but not correct scoliosis
- Treatment of progressive respiratory failure and optimization of respiratory status preoperatively
- Nutritional assessment and support as needed to improve wound healing and recovery
- Optimization of airway clearance preoperatively to promote postoperative recovery (ie, manual percussion and mechanical insufflation-exsufflation)

Surgical

- The goal of surgical management is to stabilize and reconstruct the chest wall and spine to support thoracic function and lung growth.
- Vertical expandable titanium rib (VEPTR) expansion thoracoplasty is typically the initial surgical procedure performed in TIS and is unique in that it provides both spine and chest wall support and allows for thoracic and lung growth. VEPTR placement can be performed as early as 4–6 months of age, and VEPTR devices can be expanded in a simple day surgical procedure every 4–8 months in accordance with patient growth until skeletal maturity is achieved. Complications of VEPTR placement include
  - Wound infection or skin breakdown over the VEPTR
  - Occasional device breakage and rare dislodgement
  - Occasional and transient neurological complications related to the surgery
- Magnetic expansion control (MAGEC; NuVasive, San Diego, Calif) rods allow for nonsurgical expansion; however, they are often placed medially, and in that orientation, they provide spinal support but do not provide support to the chest wall.
- Unlike VEPTR and MAGEC rods, growing rods are not approved by the Food and Drug Administration. They are favored by some surgeons for more medial support of the spine and, like VEPTR, require surgical expansion.

Expected Outcomes/Prognosis

- Prognosis is dependent on the underlying etiologic cause of the TIS, any comorbid conditions, and the degree of respiratory insufficiency. The ultimate goal is to stop progress of the underlying condition.
- Ideally, VEPTR insertion should occur as early in life as possible to preserve lung growth and development when it is most rapid. VEPTR placement generally attenuates the rate of decline of vital capacity and has been shown by some to preserve lung volume.

- Occasionally there will be an increase in vital capacity but not a resolution of the underlying restrictive respiratory disease.
- Children experience improved quality of life and level of activity after VEPTR insertion.
- Longitudinally, patients may be liberated from ventilatory support.
- There are not high-quality long-term outcome studies that demonstrate the effectiveness of MAGEC rods, but the attraction of nonsurgical expansion is compelling.
- There are strong longitudinal data that demonstrate marked spinal growth in patients who had growing rods placed, but there have not been enough pulmonary function data to reach a conclusion about effect on lung volumes.

When to Refer

- All children suspected of having thoracic hypoplasia, chest wall constriction, severe scoliosis, or the potential to develop hypotonic neurogenic scoliosis (spinal muscular atrophy) should be referred to a pediatric pulmonologist and pediatric orthopedic surgeon who specialize in the management of TIS.
- Referral should occur at as early an age as possible to plan for potential surgical interventions to maximize lung growth.

When to Admit

- Children should be admitted for any signs of worsening respiratory insufficiency or respiratory failure.
- Preoperative admission should be considered to maximize respiratory status in advance of surgery.
- With the substantial tissue disruption that is part of the thoracotomy and chest wall reconstruction, postoperative care can be challenging and will require intensive care.

Resources for Families

- Thoracic Insufficiency Syndrome (Children's Hospital of Philadelphia). www.chop.edu/conditions-diseases/thoracic-insufficiency-syndrome/about#.VmmdUE_lvcs
- Thoracic Insufficiency Syndrome (Scoliosis Research Society). www.srs.org/patients-and-families/conditions-and-treatments/parents/scoliosis/early-onset-scoliosis/thoracic-insufficiency-syndrome

Chapter 23

Pectus Deformities: Pectus Excavatum and Pectus Carinatum

Georgia Koltsida, MD, and Oscar Henry Mayer, MD

Introduction/Etiology/Epidemiology

- Pectus deformities are the most common congenital skeletal deformities.
- The incidence rate of pectus excavatum is approximately 1 in 400 live births, whereas pectus carinatum is less frequent.
- Male patients are affected 5 times more often than female patients, while patients of African American and Hispanic descent rarely have pectus deformities.
- The exact pathogenesis of pectus deformities is unknown. No clear genetic link has been found, but there are collagen defects that can lead to abnormal costochondral growth.
- Pectus deformities may occur in isolation or in association with syndromes such as Marfan, Noonan, and Turner syndromes.
- Mechanical factors have also been proposed.

Pathophysiology

- The sternum consists of 3 parts:
  - The manubrium, the widest portion, which is attached to the clavicles and the first 2 pairs of ribs
  - The body, the longest segment, which is connected to the remaining ribs
  - The xiphoid process, which is small and triangular
- The sternum protects the heart, trachea, and thymus and provides attachment for the costal cartilage.
- The joints between the sternum and the costal cartilage of the ribs flex to allow the ribs to rotate upward and anteriorly during inspiration and increase the cross-sectional area of the thorax.
- Pectus excavatum and pectus carinatum can decrease the thoracic volume and impair the growth or expansion of the lungs. However, in a few patients with pectus deformities, obstructive and restrictive lung disease occurs.

- Pectus deformities may also affect the cardiovascular system, because the depression of the sternum can displace or compress the heart and affect contractility or cause dysrhythmias.

Clinical Features

- Pectus excavatum ("funnel chest") is the posterior depression of the sternum and adjacent costal cartilage. It is characterized by the substantial depth and length of the depression, the symmetry between the right and left hemithorax, and the presence of associated sternal rotation.
- Pectus carinatum ("pigeon chest") is the protrusion of the sternum and adjacent ribs. Two general variants exist.
  - The chondrogladiolar variant consists of anterior protrusion of the body of the sternum, with symmetrical protrusion of the lower costal cartilages.
  - In the costomanubrial variant, the manubrium protrudes and can be either symmetrical or asymmetrical.

Diagnostic Considerations

History

- Birth history: Congenital pectus deformities can appear at birth, but most are recognized during early childhood, becoming more prominent and likely symptomatic during periods of rapid growth.
- The history may include lung hypoplasia or agenesis, congenital diaphragmatic hernia, upper airway obstruction (subglottic stenosis, laryngomalacia), and congenital heart defects.
- Medical history: Screen for features of associated conditions, such as lens dislocation, cardiovascular disorders, joint laxity and fractures, and decreased bone mineral density.
- Family history: Family members may have pectus deformities or connective tissue disorder.
- History of present illness: Evaluate onset and progression of pectus deformity, skeletal growth and puberty, concomitant skeletal abnormalities (eg, scoliosis), presence of cardiac dysrhythmias, poor body image, and impaired psychosocial function.

Symptoms to Look for

- Exercise intolerance
- Progressive loss of endurance
- Chest pain and/or tightness, with or without activity
- Progressive fatigue, easy fatigability
- Palpitations, tachycardia
- Exercise-induced wheezing
- Fainting and/or dizziness

Physical Examination

- Dysmorphic features, Marfanoid body habitus (long extremities and fingers)
- Scoliosis and skeletal deformities
- Characteristic posture with forward pulling and tilting of the shoulders, protuberant abdomen
- Increased or decreased anteroposterior chest diameter

Studies and Imaging

- Perform pulmonary function testing, including spirometry and plethysmography, to evaluate obstructive or restrictive lung disease.
- Maximal inspiratory and expiratory pressures can be obtained to evaluate respiratory muscle strength.
- Conduct cardiopulmonary exercise testing to assess exercise tolerance.
- Nonenhanced computed tomography (CT) of the chest can be used to assess the deformity of the bony and cartilaginous skeleton, as well as cardiac compression or cardiac displacement. The Haller index is defined at the point of greatest sternal depression as the ratio of the inner width of the chest, divided by the distance between the posterior surface of the sternum and the anterior surface of the spine. In healthy people, the Haller index is <2.5, whereas an index >3.25 is considered severe enough to require surgical correction.
- Magnetic resonance imaging can be used instead of CT, but bony details are better assessed with CT.
- Perform electrocardiography for evaluation of any dysrhythmias.
- Echocardiography may be warranted. A depressed sternum may compress the right atrium and right ventricle, interfering with diastolic filling of these structures. Evaluation of the aortic root and mitral valve is also critical in patients suspected or confirmed to have Marfan syndrome.
- Genetic evaluation may be performed to exclude an underlying syndrome or connective tissue disorder.

Management

- Nonsurgical
  - Bracing offers good results and can effectively be used to treat pectus carinatum but not pectus excavatum.
- Surgical
  - For pectus excavatum, the most popular approaches are the minimally invasive Nuss procedure and the modified Ravitch procedure.
    - The Nuss procedure involves insertion of a metal bar, bent and fitted to the desired contour of the rib cage. After it is inserted, it is rotated and will push the sternum anteriorly. The bar is typically kept in place for about 2 years.

  - The modified Ravitch procedure involves modifying the costochondral cartilage, repositioning the sternum in a normal position, and providing support behind the sternum by using metal bars that are kept in place for 6 months to 2 years.
  - Repair from either procedure can be accomplished successfully with minimal complications and good pain control. Surgery is recommended during late adolescence to allow the patients to complete their growth and have a lower chance of recurrence.
  - Custom-made silicone implants can be used only to improve aesthetic outcome.
- For pectus carinatum, the standard surgical approach is similar to the modified Ravitch procedure.

Expected Outcomes/Prognosis

- Pectus deformities usually become more apparent and symptomatic during pubertal growth spurt.
- Surgical correction when indicated is associated with encouraging outcomes. The most substantial complication is pectus bar displacement in about 2% of cases. Therefore, it makes sense to repair the pectus defect in middle to late adolescence and near the end of growth but while the bones are still more flexible and responsive to remolding of the chest than in adulthood.

When to Refer

- Progression of the deformity
- Body image concern because of the pectus abnormality
- Concern about respiratory or cardiac limitation

Resources for Families

- The Pectus Excavatum Foundation. www.thepectusexcavatumfoundation.org
- Pectus Awareness and Support Foundation. www.pectus.com/learn/pe

Clinical Pearls

- Pectus excavatum is a posterior depression, and pectus carinatum is the protrusion of the sternum and adjacent ribs.
- Pectus deformities can occur in isolation or as manifestations of syndromes such as Marfan syndrome.
- These conditions are usually asymptomatic but can cause exercise intolerance and chest pain, especially in adolescence.
- Treatment is indicated for symptomatic patients and where substantial aesthetic concerns exist. Treatment includes external bracing or, rarely, in more severe cases, surgical correction.
- Nonsurgical bracing is effective in treating pectus carinatum but has not been successful in treating pectus excavatum.

Chapter 24

Spinal Deformities: Idiopathic Scoliosis and Kyphoscoliosis

Julian Allen, MD, FAAP

Introduction

- Scoliosis is a structural lateral and rotational deformity of the spine (Figure 24-1).
- Hyperkyphosis is an excessive degree of the normal thoracic antero-posterior curvature.
- Surgical correction is indicated for risk of progression through adulthood or pain in the case of severe kyphosis.

Etiology/Epidemiology

- Idiopathic scoliosis (IS) occurs in 1%–3% of adolescents and is usually defined by a Cobb angle >10°.
- The incidence of scoliosis in children with cerebral palsy is generally accepted to be about 20%–25%.
- The etiologic origin of IS is unclear. A genetic component is suggested by 75% concordance for the condition in monozygotic twins and 33% concordance in dizygotic twins. Family pedigrees suggest autosomal dominant inheritance, with incomplete penetrance.
- Multiple gene candidates related to collagen, fibrillin, and heparin N-sulfotransferase, vitamin D, and estrogen) are implicated in but not definitively known to cause IS.
- An imbalance of paravertebral muscles has been proposed and is also seen in the association of neuromuscular disease and scoliosis.
- Isolated hyperkyphosis can also be familial, such as in Scheuermann kyphosis, usually beginning during the adolescent growth spurt.
- Regarding epidemiology, juvenile IS starts in and progresses through adolescence; progression slows markedly or stops when growth stops. Adolescent patients with IS generally fare better than those with early-onset scoliosis, but lung function is still compromised as the severity of the curve increases (Figure 24-2). Curves >50° are associated with reduced vital capacity and dyspnea.

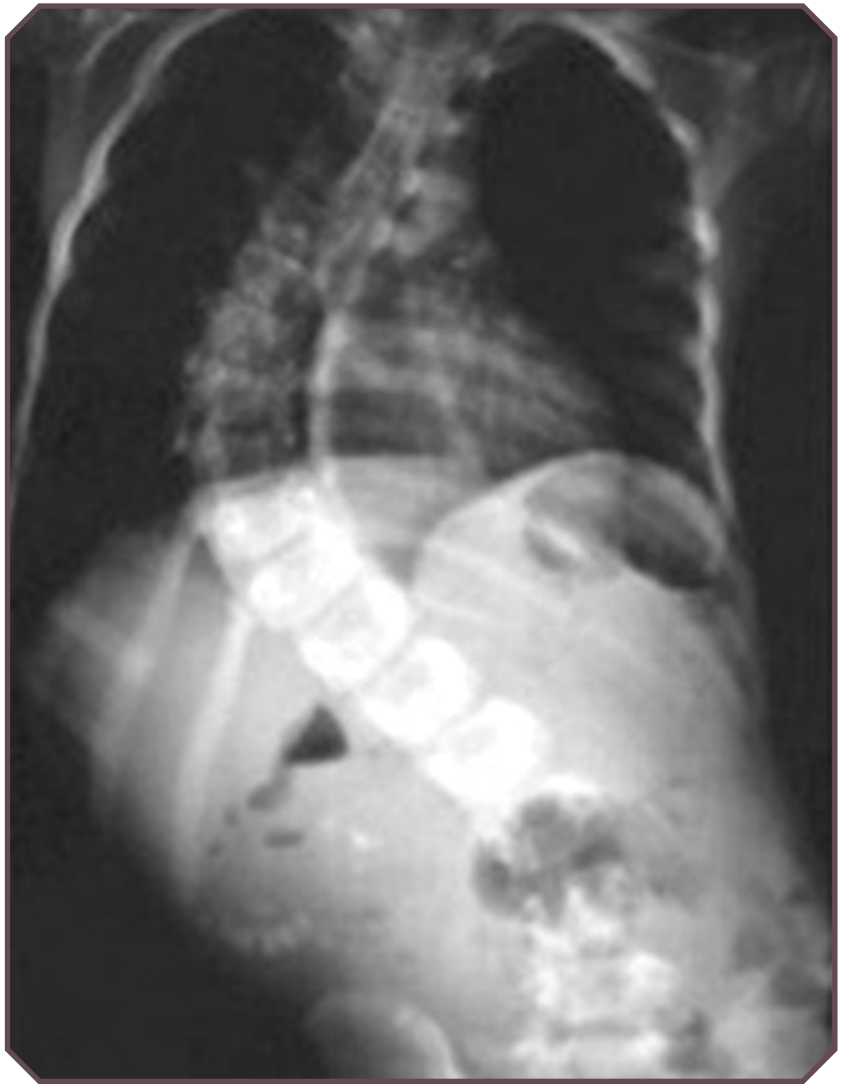

Figure 24-1. Posteroanterior radiograph shows the mid-lower thoracic curvature of scoliosis. From Dede O, Demirkiran G, Yazici M. Update on the 'growing spine surgery' for young children with scoliosis. *Curr Opin Pediatr*. 2014; 26(1):57–63. http://journals.lww.com/co-pediatrics/Abstract/2014/02000/2014_Update_on_the__growing_spine_surgery__for.10.aspx

- Early-onset scoliosis, which occurs before the age of 8 years, accounts for only 4% of all IS cases.
- Isolated hyperkyphosis is rarely associated with cardiorespiratory sequelae but can be associated with obstructive lung diseases, such as cystic fibrosis, which leads to air trapping. Hypokyphosis can be associated with a tendency toward recurrent pneumothoraces ("straight back syndrome").

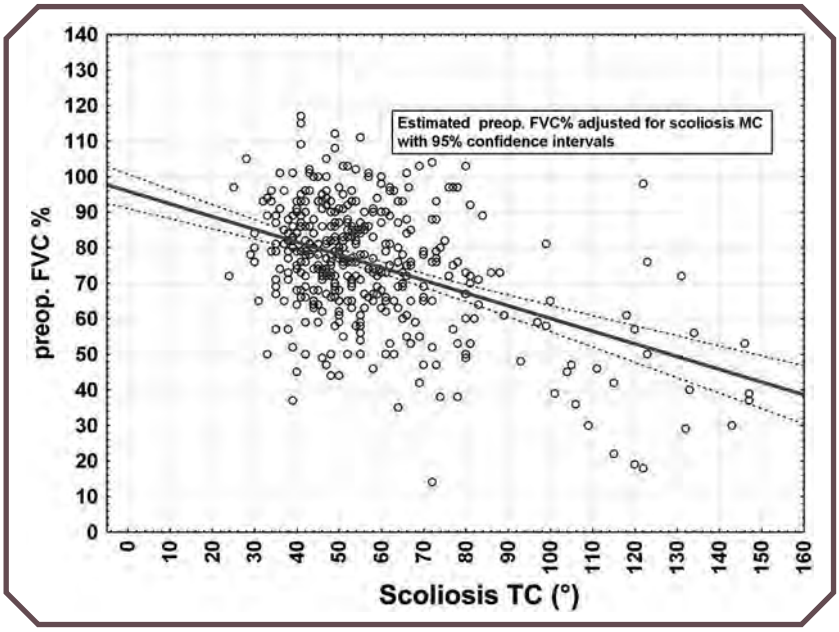

Figure 24-2. Forced vital capacity (FVC) as a function of scoliosis curve in degrees. MC = major curve, TC = thoracic curve. From Dreimann M, Hoffmann M, Kossow K, Hitzl W, Meier O, Koller H. Scoliosis and chest cage deformity measures predicting impairments in pulmonary function. *Spine.* 2014;39:2024–2033. http://journals.lww.com/spinejournal/Abstract/2014/11150/Scoliosis_and_Chest_Cage_Deformity_Measures.8.aspx

Pathophysiology

- The scoliotic chest wall, and to a lesser extent the lungs, are less compliant (stiffer) than normal (compare the normal respiratory system pressure-volume black curve with the severe respiratory system scoliosis red curve in Figure 24-3), which can lead to smaller lung volumes.
- Diaphragmatic function and strength may be diminished in scoliosis, probably as a result of a diminished area of apposition of the diaphragm to the inner chest wall. Flattening of the diaphragm due to the torsion on its fibers may make it less efficient. Patients with scoliosis have diminished maximal inspiratory (but not expiratory) pressures.
- Mild degrees of kyphoscoliosis do not usually lead to respiratory impairment. Lung restriction usually begins with scoliotic curves of ≥40°.

Clinical Features

- Pulmonary function tests (PFTs) in IS
  - The typical pattern of lung function abnormality is respiratory system restriction. There is some evidence that scoliosis can also lead to a subtle obstructive defect or unevenness of gas mixing (ventilation).

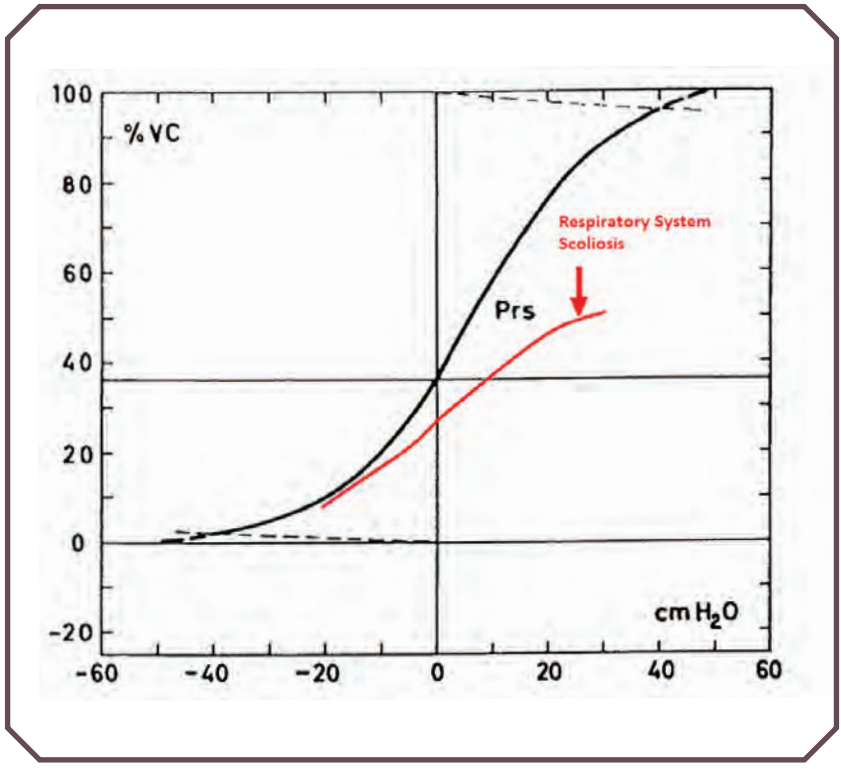

Figure 24-3. Pressure-volume curve of the respiratory system for normally developed subjects (black line) and subjects with severe scoliosis (red line). Respiratory system volume as a percentage of vital capacity *(VC)* on the y-axis is plotted against trans–respiratory system pressure *(Prs)* on the x-axis. The respiratory system compliance is the slope of the curves and is much lower than normal in the subjects with scoliosis. The data for normally developed subjects are from Rahn H, Otis AB, Chadwick LE and Fenn WO. Pressure-volume diagram of the thorax and lung. *Amer J Physiol.* 1946;146:161–178. The data for patients with scoliosis are adapted from Ting EY, Lyons HA. The relation of pressure and volume of the total respiratory system and its components in kyphoscoliosis. *Am Rev Respir Dis.* 1964;89:379–386.

— In general, lung volumes correlate inversely with the Cobb angle (Figure 24-2). This is probably a function of chest wall stiffness rather than respiratory muscle weakness, since *(a)* there is no correlation between lung volumes and measures of respiratory muscle strength and *(b)* there is positive correlation between chest wall compliance and lung volumes.
— One difficulty in interpreting PFT results in children with IS is the choice of the predicted value used when calculating the child's percentage of predicted value. The predicted value of PFTs in normally developing children is most closely predicted by using standing

height. In children with scoliosis, predicted value can be determined by using standing height, sitting height × 2 (in children >7 years old), or arm span (equal to height in normally developing children). The percentage predicted value in children with scoliosis will thus depend on the height value used. The percentage predicted value is greatest if actual height is used and is lowest if arm span is used.

- In severe disease with vertebral rotation, compression of central airways by anterior vertebral bodies described but extremely rare
- Exercise tolerance
  - Children with IS have decreased maximal exercise capacity.
  - As with PFTs, exercise limitation seems to be related to the degree of curvature.
  - The 6-minute walk test result can also be diminished.
- Respiratory failure
  - Respiratory failure is common in severe congenital scoliosis but rare in adolescent IS, at least during childhood and adolescence.
  - When it does occur, it tends to occur perioperatively and in subjects with the most severe curves.
  - Severe unrepaired scoliosis and kyphoscoliosis can cause both ventilatory defect leading to CO_2 retention and ventilation-perfusion mismatch in compressed segments of lung, leading to hypoxemia.
  - Isolated kyphosis rarely leads to respiratory impairment.
- Increased risk for atelectasis and/or pneumonia, especially in children with chronic comorbidities

Differential Diagnosis

The major differential is distinguishing idiopathic spinal deformity from other forms:

- Congenital, such as hemivertebrae
- Syndromic, with (eg, Jarcho-Levin and Jeune syndromes) or without (eg, VATER [vertebral defects, imperforate anus, tracheoesophageal fistula, radial and renal dysplasia], neurofibromatosis) thoracic insufficiency syndrome
- Neuromuscular, such as muscular dystrophy and spinal muscular atrophies

Diagnostic Considerations

- The normal spine has an anteroposterior curvature between 20° and 40° and a lateral curve of <10°. Hypokyphosis is a curvature <10°, and hyperkyphosis is a curve >40°.
- Physical examination
  - Most scoliosis curves will be easily demonstrated at physical examination, except for the most mild cases.

  - While standing behind the patient, have him or her perform the forward-bending test to look for thoracic asymmetry. This can be conducted with or without the use of a scoliometer, which is now available and validated as a smart phone app, to help discern more mild curves (Figure 24-4).
  - Hyperkyphosis can be observed by standing at the patient's side during forward bending.
- PFTs can help indicate the severity of lung function involvement, as well as indicate whether surgery carries increased intra- and postoperative risk, while recognizing that only severe curves generally affect lung function.
- Radiologic studies include spine series with measurement of the Cobb angle (Figure 24-1) and flexibility studies.
- Computed tomography and unenhanced static or dynamic magnetic resonance imaging of the entire spine are becoming commonplace and can help better assess the rotational component.

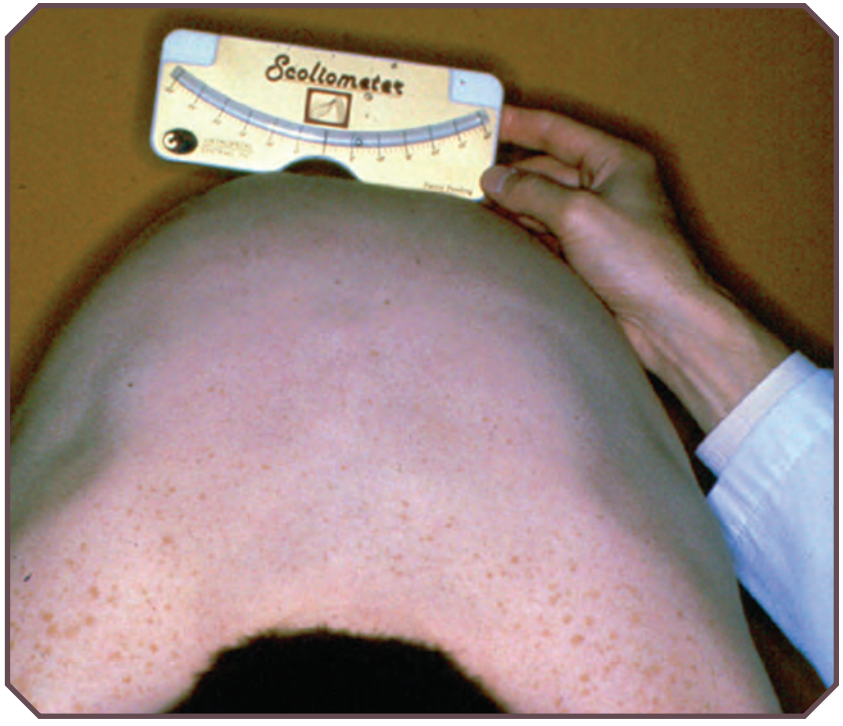

Figure 24-4. Forward bending performed with the use of a scoliometer. From Weinstein SL, Dolan LA, Cheng JCY, Danielsson A, Morcuende JA. Adolescent idiopathic scoliosis. *Lancet.* 2008;371:1527–1537. Copyright 2008, with permission from Elsevier.

Management

- Nonsurgical approaches may be warranted.
  - Watchful waiting is usually advised for curves <25°.
  - Physical therapy is sometimes used to prevent progression of such curves, but there is no evidence that it circumvents the need for surgery. It is commonly used in Europe (eg, the Schroth method).
  - Bracing may be effective.
- In adolescents with curves between 20° and 45°, bracing can be used to prevent progression of the curve to 50°. In the Bracing in Adolescent Idiopathic Scoliosis Trial, or BRAIST, a randomized cohort arm had a success rate of 75% in the brace group and 42% in the observation group.
- A positive association between hours of brace wear and the rate of treatment success was found; patients who wore the brace for >12.9 hours daily had success rates of 90%–93% versus 41% in patients who wore the brace for 0–6 hours daily.
  - Early casting may be performed for infantile forms of scoliosis.
    - Young children with milder curves demonstrate a higher rate of improvement with early casting.
    - Casts that derotate rather than just straighten the spine demonstrate a higher success rate.
- Scoliosis surgery may be indicated in some cases.
  - Usually reserved for curves >45°
  - Spinal fusion
    - In adolescent IS, spinal fusion should be reserved for patients who have already undergone substantial spinal growth but not delayed until growth is nearly completed.
    - Since curves in adolescence progress until growth ceases, the timing of spinal curve repair also needs to have the current Cobb angle taken into account, as well as the rate of progression and projected severity of curvature.
  - Growing rods
    - With growing rods, the spine will continue to grow, even if fused at an earlier age, while controlling the scoliotic deformity, allowing for more prompt intervention (Figure 24-5).
    - New magnetically controlled growing rods are available and recently approved by the Food and Drug Administration for the treatment of early-onset scoliosis. They prevent the need for repeated surgical lengthening procedures and can be placed as an outpatient procedure in the office.
- Management of respiratory failure
  - Patients with severe unrepaired kyphoscoliosis and respiratory failure are often successfully treated with nocturnal noninvasive ventilation.

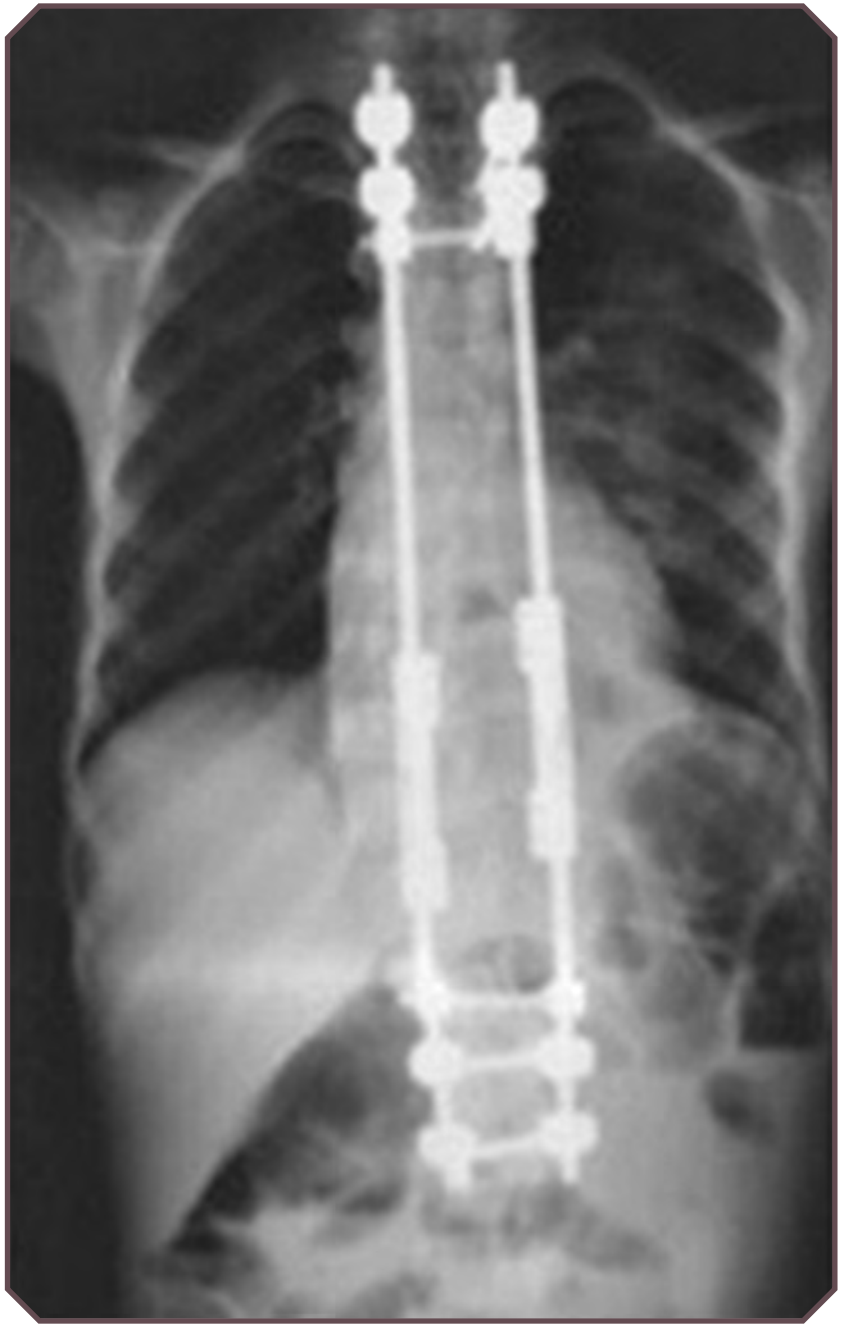

Figure 24-5. Frontal radiograph demonstrates implanted growing rods. Lengthening is achieved by distraction through the telescopic connectors. From Dede O, Demirkiran G, Yazici M. Update on the 'growing spine surgery' for young children with scoliosis. *Curr Opin Pediatr.* 2014;26(1):57–63. http://journals.lww.com/co-pediatrics/Abstract/2014/02000/2014_Update_on_the__growing_spine_surgery__for.10.aspx

— Nocturnal noninvasive ventilation can reduce nocturnal and daytime CO_2 retention, probably by increasing the thoracic cage flexibility and strength and resetting respiratory drive.

Expected Outcomes/Prognosis

- IS can progress throughout duration of growth and then generally remains static.
- The risk of progression is related to both degree of the curve at initial discovery and the amount of time left for growth. A curve of >40° discovered at age 12 has a nearly 100% chance of progression, while a curve of <30° discovered at age 16 has only a 10% chance of progression.
- The main reason for spinal fusion is to prevent this progression to avoid the natural history reported in untreated patients with large curves who have increased pain and disability.
- Long-term outcomes of scoliosis surgery on lung function vary with surgery performed, as well as the severity of the curve. The extent of actual correction of the spinal deformity varies markedly and appears to be related to the flexibility of the child's spine.
- Difficulties in interpreting the effects of surgery on lung function arise from whether absolute or percentage predicted values are used. Several studies have shown improvement in the former but not the latter. Furthermore, for percentage predicted value interpretation, it must be taken into account whether standing height or arm span is used.
- Poor preoperative lung function need not be prohibitive. Experienced multidisciplinary teams that include pulmonologists, nutritionists, and anesthesiologists report positive outcomes of surgical treatment for pediatric patients with forced vital capacity <40%. Such severe cases may require pre- or postoperative noninvasive ventilation, or both.
- Early-onset scoliosis, such as infantile and juvenile onset before the age of 8 years, has worse outcomes. Up to 40% of such patients die of respiratory failure if untreated, with a mean age of 54 years at death, although death in adolescence has been reported.
- In infantile and early-onset IS, spinal fusion does not improve outcomes; because it can create thoracic insufficiency syndrome, it is not a good option in the young child. The rate of vertebral growth after spinal fusion is reduced by approximately half, and in adulthood, these patients have permanently shortened spines. Vital capacity <50% is seen in 40%–60% of subjects who undergo early fusion. Growth-friendly instrumentation (ie, vertical expandable titanium rib, growing rods, magnetically controlled growing rods) are indicated for the surgical treatment of early-onset scoliosis and may change these outcomes. Long-term studies of lung function are pending.

When to Refer

- Prompt referral to an orthopedic surgeon is necessary when a spinal curve is first noticed, so that curve quantitation and progression can be assessed and followed up.

Prevention

- There is little evidence that scoliosis can be prevented, although exercise programs have been undertaken to do so. Rotational exercises may be of temporizing value, and only in mild cases.

Resources for Families

- Patients and Families (Scoliosis Research Society). www.srs.org/patients-and-families
- What Is Scoliosis? (U.S. Department of Health and Human Services). www.niams.nih.gov/Health_Info/Scoliosis/scoliosis_ff.pdf

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Part III. Asthma and Related Conditions

Associate Editor: James W. Stout, MD, MPH, FAAP

Chapter 25

Diagnosis of Asthma

Jonathan Cogen, MD, MPH

Introduction

- Asthma can be difficult to diagnose in children, particularly in those <5 years of age (see Chapter 43, Recurrent Wheezing in Infants, Toddlers, and Preschoolers).
- Many infants and toddlers wheeze during viral respiratory illnesses but do not go on to have asthma when they are older.
- The Asthma Predictive Index (API) was created to help forecast which children are more likely to have asthma later in life, which removes some ambiguity with this prognostic challenge.
- The API includes frequent wheezing during the first 3 years of life and either 1 major risk factor (parent history of asthma or child diagnosis of eczema) or 2 of 3 minor risk factors (blood eosinophilia, wheezing without colds, and allergic rhinitis).
- Children with a positive API were 4.3–9.8 times more likely to have active asthma between ages 6 and 13 than children with a negative API; children without API risk factors had a negative predictive value of 94% for the development of asthma at age 6.
- Misdiagnosis of asthma as pneumonia or bronchitis can lead to ineffective and unnecessary use of antibiotics.
- Overdiagnosis of asthma can result in unnecessary use of inhaled medications and oral steroids, as well as familial anxiety.

Clinical Features

- Typical signs and symptoms include
  - Polyphonic wheezes, predominantly on expiration
  - Recurrent and/or chronic cough
  - Chest tightness
  - Shortness of breath
- Specific triggers include
  - Colds and viral illnesses
  - Exercise
  - Exposure to cold air
  - Cough after laughing or crying
  - Allergens, including pets, mold, dust mites, and additional environmental exposures

  - Pollution (indoor or outdoor)
  - Passive exposure to smoke
- Additional allergic comorbidities (dust mites, pollen, trees, grasses, etc) occur in most children with asthma
- Cough is typically worse at night
- Parental or patient report of wheeze correlates poorly with physician-diagnosed wheeze; thus, any diagnosis of wheezing should be confirmed by a medical provider.
- Additional physical examination findings include an increased chest anterior-posterior diameter, an expiratory abdominal push, and a prolonged expiratory phase on respiration.

Differential Diagnosis

- Alternative diagnoses (Table 25-1) should be considered when
  - A patient is nonresponsive to standard asthma therapy (β_2-agonists or inhaled or oral corticosteroids)
    OR
  - Certain red flags are present, including digital clubbing, stridor, fixed monophonic wheeze at examination, cyanosis, or cardiac findings, including a cardiac murmur or asymmetrical peripheral pulses
- Differential diagnosis includes
  - Recurrent aspiration or dysphagia
  - Vocal cord dysfunction
  - Tracheal and/or bronchial malacia
  - Cystic fibrosis
  - Primary ciliary dyskinesia
- Although rare, providers should consider a pediatric pulmonary referral if a fixed airway obstruction is suspected, such as a vascular ring or sling, right-sided aortic arch, or endobronchial mass, if symptoms persist despite asthma therapy.
- Once asthma is diagnosed, the patient should be reassessed 4–6 weeks after therapy initiation to ensure symptom improvement.

Diagnostic Considerations

Pulmonary Function Testing (Spirometry)

- Pulmonary function testing can be used to support a diagnosis of asthma (Figure 25-1); most children with asthma, however, will have normal lung function.
- Spirometry is used to measure how much air the patient breathes in and out and how fast the air is exhaled.
  - Spirometry can typically be performed in developmentally appropriate children by 5 years of age.
- Spirometric findings of obstructive lung disease include the ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) in the <5th percentile when compared to predicted values.

Table 25-1. Differential Diagnosis of Asthma

Diagnosis	Age at Diagnosis[a]	Runny Nose	Sputum	Other Diagnostic Findings
Asthma	Variable; typically >2 y	Not a primary feature	Rare	Wheeze, chest tightness, shortness of breath
Cystic fibrosis	<1 y	Not a primary feature	Frequent	Clubbing, failure to thrive, pancreatic insufficiency
Gastroesophageal reflux disease	<1 y	Not a primary feature	Frequent	Emesis, back-arching, cough
Aspiration and/or dysphagia	<2 y	Not a primary feature	Rare	Coughing, faster breathing with eating and drinking
Primary ciliary dyskinesia	<1 y	Uniformly present	Rare	Neonatal respiratory distress common, recurrent sinopulmonary infections
Tracheal and/or bronchial malacia	<1 y	Not a primary feature	Absent	Monophonic expiratory wheeze
Habit cough	>8 y	Unrelated	Absent	Absent when asleep
Postnasal drip	<1 y	Very common	Rare	Absence of wheezes
Foreign body	>4 y	Unrelated	Occasional	Unilateral physical examination findings
Vocal cord dysfunction	>8 y	Unrelated	Rare	Inspiratory stridor when symptomatic

Adapted from Rosenthal M. Differential diagnosis of asthma. *Paediatr Respir Rev.* 2002;3:148–153. Copyright 2002, with permission from Elsevier.

- More typically, a FEV_1/FVC ratio of <80% is used to denote an obstructive process consistent with asthma in children.
- A change in absolute value of percentage predicted FEV_1 of ≥12% within 15 minutes after bronchodilator administration is considered a positive response and supports the diagnosis of asthma; a percentage predicted FEV_1 change of <8% is considered a negative response.
- Once a diagnosis of asthma is established, the severity of lung function impairment is largely based on percentage predicted FEV_1, as follows:
  - Mild persistent (≥80%)
  - Moderate persistent (60%–79%)
  - Severe persistent (<60%)
- Consistent percentage predicted FEV_1 values <60% typically warrant subspecialty consultation.
- A concomitant decrease in FEV_1 and FVC is most commonly caused by poor patient effort but may rarely reflect airflow obstruction that can be better assessed with body plethysmography (Figure 25-1).

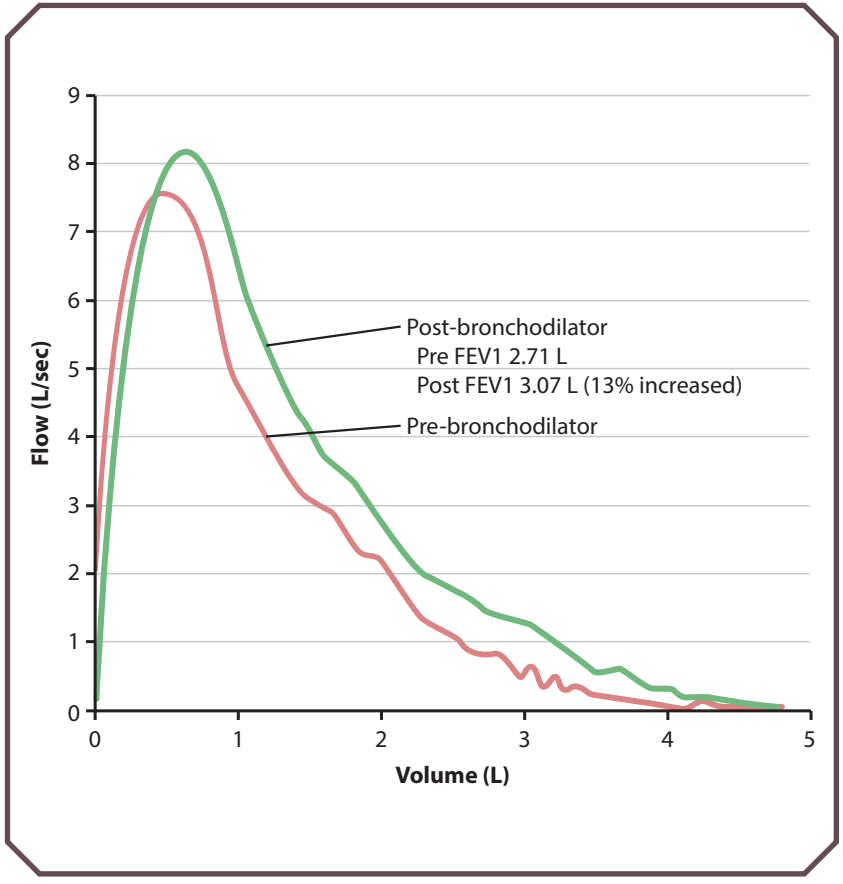

Figure 25-1. Example of an obstructive pattern at pulmonary function testing and a positive bronchodilator response consistent with obstructive lung disease (asthma). FEV1 = forced expiratory volume in 1 second. From National Heart, Lung, and Blood Institute. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma.* U.S. Department of Health and Human Services; 2007.

- A normal ratio of FEV_1 to vital capacity, coupled with a percentage predicted vital capacity <80%, could be consistent with a restrictive pulmonary defect; subspecialty consultation (along with additional lung function testing, including body plethysmography) should be sought.
- Spirometry values should be assessed over time as a marker of improvement and adherence to therapy.

Pulmonary Function Testing (Body Plethysmography, Airway Hyperresponsiveness Testing) and Fractional Exhalation of Nitric Oxide

- Additional testing available in pediatric pulmonary or allergy subspecialty clinics includes
  - Body plethysmography
  - Airway hyperresponsiveness
  - Bronchodilator or methacholine challenge testing
  - Fractional exhalation of nitric oxide (FENO)
- Body plethysmography can also be used to assess the presence of an obstructive defect; a residual volume to total lung capacity ratio of >25% to 30% predicted is suggestive of air trapping and is consistent with an obstructive defect.
- FENO can be used to determine the likelihood of eosinophilic inflammation and steroid responsiveness in individuals with asthma.
- A low FENO (<20 parts per billion [ppb] in children) indicates that a patient might be less likely to respond to corticosteroids, while a high FENO (>35 ppb in children) is predictive of corticosteroid responsiveness.

Resources for Families

- How Is Asthma Diagnosed? (American Lung Association). www.lung.org/lung-health-and-diseases/lung-disease-lookup/asthma/diagnosing-treating-asthma/how-is-asthma-diagnosed.html
- Asthma Basics (KidsHealth). kidshealth.org/en/parents/asthma-basics.html

Clinical Pearls

- Asthma is a clinical diagnosis established by obtaining a thorough history and performing physical examination and spirometry testing.
- Assessment for reversibility with bronchodilator testing can aid in the diagnosis of asthma (see Chapter 4, Office Pulmonary Function Testing).
- An increase in the absolute value of percentage predicted FEV_1 of ≥12% after bronchodilator administration is consistent with airway reversibility. With training, this evaluation for reversibility can be accomplished in a primary care office.
- In a subspecialist's office, more complete pulmonary function testing and FENO can be used in support of a diagnosis of asthma.
- Be sure to rule out other certain diagnoses (eg, cystic fibrosis) if red flags—including digital clubbing or stridor—are present.

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Chapter 26

Tobacco Smoke Exposure and Children

Harold J. Farber, MD, MSPH, FAAP, and
Marianna M. Sockrider, MD, DrPH, FAAP

Introduction

- Children can be harmed from tobacco smoke by direct inhalation of exhaled and sidestream smoke (secondhand smoke) and from the dermal absorption, ingestion, and inhalation of smoke that has been absorbed into surfaces (thirdhand smoke).
- Children can be exposed to tobacco smoke from many sources, including active use and involuntary exposure, both inside and outside of the home.
- There is no safe level of tobacco smoke exposure.
- In the United States, the largest source of a child's exposure to tobacco smoke is often the mother and other caregivers.

Adverse Effects

In Utero Tobacco Smoke Exposure

- Harms lung growth and development
  - — Reduces airway size and lung function
  - — Increases risk for wheezing as an infant and young child
  - — Increases risk for more severe asthma as an older child
- Harms brain development
  - — Increases risk for learning disabilities and attention-deficit disorder and attention-deficit/hyperactivity disorder
  - — Increases risk for sudden infant death syndrome
- Increases risk for adverse outcomes of pregnancy
  - — Stillbirth
  - — Lower birth weight
  - — Premature birth
  - — Placental abruption
- Is associated with other health problems
  - — Increased risk for orofacial clefts
  - — Increased risk for being overweight in childhood

- Although sorting out the individual effects of the nicotine versus other toxins in tobacco smoke is difficult, it is clear that at least some of the fetal harm is caused by the nicotine component, which suggests that use of electronic nicotine delivery systems (electronic cigarettes, others) can lead to important fetal harms.

Postnatal Tobacco Smoke Exposure

- Increases asthma prevalence and severity
- Decreases effectiveness of inhaled corticosteroids for asthma control
- Increases severity of viral respiratory illness, including bronchiolitis
- Increases risk for pneumonia
- Increases risk for cough
- Lowers lung function

Other Harms of Tobacco Smoke Exposure in Children

- Increases risk for middle ear disease
- Higher rate of preclinical atherosclerosis
- Increased risk for childhood cancers

Electronic Nicotine Delivery Systems

- The emissions of electronic nicotine delivery systems, such as e-cigarettes, e-hookahs, and vape pens, are not safe to breathe.
- Besides nicotine, the emissions (technically an aerosol, but often incorrectly called *vapor*) contain chemicals that are respiratory irritants, as well as chemicals that are known toxins and carcinogens.
- Recent case reports have demonstrated severe lung damage associated with the use of these devices.
- Inhaled nicotine from electronic cigarettes has been shown to cause emphysema-like changes in the lungs of laboratory animals.

Diagnostic Considerations

- Pediatricians should inquire about *(a)* tobacco product and electronic nicotine delivery system use and *(b)* emission exposure as a routine part of health supervision visits and for illnesses or diseases that may be caused or exacerbated by exposure to tobacco smoke.
- Screening questions include the following:
  - Does your child live with anyone who uses tobacco or e-cigarettes (vapes)?
  - Does anyone who provides care for your child smoke tobacco or use e-cigarettes?
  - Does your child visit places where people smoke or use tobacco or e-cigarettes?
  - Do you ever smell smoke from your neighbors in or near your home?
  - Do you have a “no-smoking, no e-cigarette, no vaping” policy for your home and car?

Management

Best Practices

- The best way to reduce or eliminate a child's exposure to tobacco smoke is for parents, caregivers, and close family members to become nonsmokers.
- Recommend tobacco dependence treatment for tobacco-dependent parents, caregivers, and close family members. Parents and close family members may be motivated to take action to protect the health of their child and reduce their child's need for medication. (See Chapter 27, Preventing and Treating Tobacco Dependence.)
- The combination of counseling and medication is more effective at treating tobacco dependence than using either strategy alone.
- With appropriate assessment, documentation, and counseling, pediatricians can recommend or prescribe tobacco dependence treatment medications for parents.
- The nicotine patch, nicotine gum, and nicotine lozenge are over-the-counter medications that are effective for tobacco dependence treatment when used properly.
- Telephonic tobacco use cessation support can help. Refer individuals to the national smokers' help line: 1-800/QUIT-NOW.
- Pediatricians should be familiar with local and state resources for tobacco dependence counseling and treatment.

Second-Best Practices

If parents and caregivers are not ready to stop smoking:

- Having a smoke-free (and electronic nicotine delivery system emission–free) home and car policy can reduce a child's exposure to tobacco smoke, although it is unlikely to completely eliminate exposure.
- The use of high-efficiency particulate air (HEPA) filters in the home can reduce, but not eliminate, the harm to a child with asthma from a household member smoking. The cost is not usually covered by health insurance. HEPA filters require periodic filter changes, as well.
- Implement office systems to identify and offer counseling, treatment, treatment recommendations, and/or referral for tobacco-dependent parents.
  - Tools provided by the Clinical Effort Against Secondhand Smoke Exposure (CEASE) can facilitate screening and referral.
    - Ask ("Does your child live with anyone who uses tobacco?")
    - Assist ("As your child's doctor [or nurse], I can help you quit using tobacco and help you have a tobacco-free home and car.")
    - Refer (The national smokers' help line can be reached at 1-800/QUIT-NOW).
    - CEASE program materials are available at www.ceasetobacco.org.

Prevention

- Encourage children to never smoke or use electronic nicotine delivery systems and to avoid exposure to tobacco and nicotine products.
- Help the child to find personally relevant reasons to be tobacco and nicotine free.
- Pediatricians can be important advocates for public policies to protect children from tobacco smoke exposure and improve children's respiratory health.
- Evidence-based policies to protect children from tobacco smoke exposure include the following.
  - — Comprehensive smoking bans should be enforced.
    - ▪ Smoking and use of tobacco products that produce an emission should be prohibited in all workplaces, including bars, restaurants, and health care facilities. Smoking and use of tobacco products that produce an emission should be banned in outdoor areas frequented by children, including sidewalks, recreational and sports facilities, entertainment venues, and parks.
  - — Smoking in multi-unit housing should be prohibited.
    - ▪ Smoking in 1 unit involuntarily exposes those in nearby units.
  - — Prohibitions on smoking and the use of tobacco products should include prohibitions on the use of electronic nicotine delivery systems.
    - ▪ The vapor emitted from electronic nicotine delivery systems contains toxic and carcinogenic substances, in addition to nicotine. Use of these products involuntarily exposes others to these hazardous substances.

Resources for Families

- National smokers' help line. 1-800/QUIT-NOW
- Julius B. Richmond Center of Excellence (American Academy of Pediatrics). www.aap.org/RichmondCenter
- Campaign for Tobacco Free Kids. www.tobaccofreekids.org
- Smokefree.gov (U.S. Department of Health and Human Services). www.smokefree.gov
- Patient Fact Sheets (American Thoracic Society). www.thoracic.org/patients
- Freedom From Smoking (American Lung Association). www.lung.org/stop-smoking
- Secondhand Tobacco Smoke and Smoke-free Homes (U.S. Environmental Protection Agency). www.epa.gov/indoor-air-quality-iaq/secondhand-tobacco-smoke-and-smoke-free-homes

Clinical Pearls

- Children are harmed by tobacco and nicotine from gestation onward. There is no safe level of tobacco smoke exposure.
- Inquire about tobacco product and electronic nicotine delivery system use and exposure as part of health supervision and as part of care for tobacco-related diseases.
- Implement office systems to identify and offer counseling, treatment, treatment recommendations, and/or referral for tobacco-dependent parents.
- Encourage children to make a commitment to being tobacco and nicotine free. Help the child to find reasons that are personally relevant.

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Chapter 27

Preventing and Treating Tobacco Dependence

Harold J. Farber, MD, MSPH, FAAP, and
Marianna M. Sockrider, MD, DrPH, FAAP

Introduction/Etiology/Epidemiology

- Tobacco dependence is a severe chronic illness. Nicotine changes brain structure and chemistry.
- Tobacco causes disease and premature death when used exactly as intended.
- In addition to conventional cigarettes, oral tobacco (also called *dip, chew,* and *snuff*), hookahs (nargiles, water pipes), cigars (often inexpensive and candy flavored), and electronic nicotine delivery systems (ENDS) are popular among youth. Many young people regularly use more than 1 type of tobacco product. Table 27-1 shows the different tobacco products currently available in the United States.
- Tobacco promotion is an important cause of tobacco use initiation and escalation. Flavoring agents, including menthol, increase the appeal of tobacco products to youth.
- In the United States, close to 90% of current adult smokers started their tobacco use prior to 18 years of age, and 99% started prior to 26 years of age. Earlier age at tobacco use initiation is associated with more severe addiction and lower rates of stopping tobacco use.
- Sexual minority (lesbian, gay, bisexual, and transgender) youth and Native American youth have higher rates of tobacco use and are therefore at substantially increased risk for developing tobacco dependence. This may be due in part to the stresses and social discrimination they face; however, another contributing factor is marketing efforts by the tobacco industry that directly target these communities.

Electronic Nicotine Delivery Systems

- ENDS (eg, e-cigarettes, e-hookahs, vape pens) are rapidly rising in popularity among youth.
- Toxic and carcinogenic chemicals, including acrolein and benzene, as well as metallic nanoparticles, have been found in ENDS emissions.
- Flavoring agents can have clinically significant pulmonary toxicity, the full extent of which is not yet known.

Table 27-1. Tobacco Products	
Product	**Description**
Cigarette	A small roll of paper that is filled with cut tobacco and smoked
Cigar, little cigar	A tightly rolled bundle of dried and fermented tobacco, wrapped in a tobacco leaf; cigars marketed to youth come in a variety of flavors, including "cherry," "peach," and "grape"
Pipe	A tube with a small bowl at one end, used for smoking tobacco that is marketed in different flavors
Hookah or narghile	A single-stemmed or multistemmed instrument in which the smoke is cooled by passing through water; flavors are commonly added to the tobacco. Charcoal is used to keep the tobacco burning.
Bidi or beedi	A thin, South Asian cigarette filled with tobacco flake and wrapped in a tendu leaf, tied with a string at 1 end
Kretek	Cigarettes made with a blend of tobacco, cloves, and other flavors
Chewing tobacco	Loose leaves, plugs, or twists of tobacco that are placed between the cheek and gum and are commonly sweetened
Snuff	Finely ground tobacco packaged in cans or pouches, which can be sold dry (a powdered form that is sniffed) or moist (placed between the lower lip or cheek and gum) and is commonly flavored
Snus	A moist powder tobacco product originating from a variant of dry snuff, usually not fermented and commonly flavored
Dissolvable tobacco	Dissolves in the mouth, unlike ordinary chewing tobacco; orbs or pellets resemble a small breath mint; sticks similar to toothpicks are inserted between the upper lip and gum; strips administer nicotine through thin-film drug delivery technology and look similar to breath-freshening strips
Electronic nicotine delivery system: e-cigarette, hookah stick, e-hookah, vape pen, other	Battery-powered devices that heat a solution to create an aerosol that can be inhaled; content is not regulated; devices usually contain nicotine from tobacco, propylene glycol, and flavoring agents; heating the mixture creates other toxins

- Youth who would not otherwise be at risk for smoking are initiating their nicotine addictions with these devices.
- Youth who use ENDS are more likely to become combustible tobacco users and are less likely to stop smoking.

Clinical Features

Nicotine Withdrawal Symptoms

- Cravings
- Irritability, frustration, anger
- Anxiety, restlessness
- Difficulty concentrating, slowed cognitive performance
- Insomnia
- Increased appetite
- Constipation
- Tremors
- Dysphoric or depressed mood
- Anhedonia—inability to feel pleasure

Usual Clinical Course

- Tobacco dependence almost always starts in the pediatric years.
- Symptoms of dependence can develop rapidly—even after just 1 cigarette and with smoking occuring less than monthly.
- Symptoms of nicotine dependence can be used to predict progression from intermittent to daily smoking.
- Early symptoms of tobacco use include coughing, bad breath, yellow stains on the fingers and teeth, and impaired sports performance.
- Tobacco smoking and exposure to tobacco smoke exacerbate asthma and decrease the effectiveness of inhaled and oral corticosteroid medications for asthma control.

Diagnostic Considerations

- The best way to establish the diagnosis is to ask the patient and the parents about their own tobacco and nicotine product use. When possible, talk with the teen separately from his or her parents (or alone) about tobacco and nicotine use.
- The tobacco product used may not be cigarettes and may not be smoked. A person may not consider him- or herself a "smoker," even if he or she smokes.
- After establishing the diagnosis, the next step is to assess the severity of tobacco dependence, readiness to change, and treatments the patient would be willing to accept.
- Questions to screen for tobacco and nicotine use include
  - "Do any of your friends use tobacco?"
  - "Have you ever tried (name of tobacco product)?"
  - "How often do you use (name of tobacco product)?"
  - "Do your friends use hookahs, cigars, e-cigarettes, e-hookahs, or vapes?"
  - "Have you tried hookahs, cigars, e-cigarettes, e-hookahs, or vapes?"
- An algorithm for assessing severity of tobacco dependence appears in Table 27-2.

Table 27-2. Classification of Tobacco Dependence Severity: Clinical Features Before Treatment

Severity of Tobacco Dependence	Cigarette Use	Nicotine Withdrawal Symptoms	Fagerström Score for Nicotine Dependence
Very severe	>40 cigarettes per day Time to first cigarette, 0–5 min	Constant	Score of 8–10
Severe	20–40 cigarettes per day Time to first cigarette, 6–30 min	Constant	Score of 6–7
Moderate	6–19 cigarettes per day Time to first cigarette, 31–60 min	Frequent	Score of 4–5
Mild	1–5 cigarettes per day Time to first cigarette, >60 min	Intermittent	Score of 2–3
Non-daily or social	Non-daily Social settings only Time to first cigarette, >60 min	None	Score of 0–1 Healthy

The presence of 1 feature of severity is sufficient to place the patient in that category. If chronic medical or psychiatric disease is present in the smoker, escalate severity assessment—more intensive treatment is needed. Adapted with permission from Sachs DPL, Leone FT, Farber HJ, et al. American College of Chest Physicians Tobacco-Dependence Treatment Tool Kit. 3rd ed. Northbrook, IL: American College of Chest Physicians; 2010. http://tobaccodependence.chestnet.org.

- Simple questions to screen for nicotine dependence that can easily be used in the office setting include
  - "How long is it between when you wake up in the morning and your first (tobacco product use)?"
  - "How much (tobacco product) do you use a day?"
  - "If you go long enough without using (tobacco product), how bad does your withdrawal get?"
- If the patient first uses tobacco within 1 hour of waking and/or smokes half a pack per day of cigarettes, then addiction is at least moderately severe.
- If withdrawal is so bad that without tobacco or nicotine the patient can't focus, gets very irritable, and can't get tobacco out of his or her mind, then dependence is very severe.

Prevention

- Counseling from a health care provider reduces the risk for tobacco product initiation. The U.S. Preventive Services Task Force recommends that primary care physicians provide interventions, including education or brief counseling, to prevent initiation of tobacco use in children and adolescents.
- Messages should be clear, personally relevant, and age appropriate.

Messages for Tobacco and Nicotine Use Prevention

- Smoking causes bad breath.
- Smoking hurts sports performance.
- Tobacco addiction costs a lot of money.
- Nicotine addiction can develop very quickly.
- Nicotine is one of the most difficult addictions to kick.
- The tobacco industry deceives youth into thinking their products are attractive.
- E-cigarettes, e-hookahs, vapes, and other ENDS are not safe. A number of toxins are added, are generated by heating the liquid, or come off of the solder or casing (such as metalic nanoparticles) when using these products. To date, there are no manufacturing, quality, or safety standards for ENDS. Just because a flavoring agent is safe to eat does not mean it is safe to inhale.
- Ask children and adolescents to make a commitment to be tobacco and nicotine free.
- Ask the child to identify his or her own reasons for being tobacco and nicotine free.

Evidence-Based Public Policy Recommendations

- Pediatricians can be powerful advocates for effective public policy to control the tobacco epidemic.
- Recommendations for effective public policy include the following.
  - — Tobacco control should be adequately funded.
  - — The minimum age to purchase tobacco should be increased to 21 years.
  - — Tobacco product prices should be increased to reduce youth tobacco use initiation.
  - — Tobacco product advertising and promotion in forms that are accessible to children and youth (including point of service advertising) should be prohibited.
  - — Depictions of tobacco products in movies and other media that can be viewed by youth should be restricted.
  - — Flavoring agents, including menthol, should be prohibited in all tobacco products.

Treatment

Pediatricians may be in the best position to counsel, recommend treatment, and/or treat patients and parents who wish to stop smoking. The pediatrician may be the health care provider that the parents see the most, as the physician for their child.

Behaviorally Based Treatments

- Behaviorally based treatments are most effective for those with mild levels of addiction.
- Effective behaviorally based strategies focus on problem-solving skills and providing support and encouragement.
- ASK NOW (Box 27-1) is an approach to negotiating behavioral change.

Box 27-1. ASK NOW for Behavioral Change

A: ***A**ssess* the health behavior of concern.
S: Determine the patient's ***S**tage of change.*
K: Keep in mind ***K**ey facts*, such as previous experience with making the change, social stresses, barriers, areas of resistance, etc.
N: Jointly ***N**egotiate* an action plan.
O: ***O**bserve outcomes* in follow-up. Does the action plan need to be updated or modified? Learn from slips and lapses.
W: ***W**ork toward the next stage*. Acknowledge and reinforce any progress. Jointly negotiate a plan to consolidate gains and move forward.

Pharmacotherapy

- The limited research on pharmacotherapy for treatment of tobacco dependence in adolescents shows that medications are effective when they are used, but nonadherence is common. Relapse rates are high after stopping the medications.
- Although off label, pharmacotherapy documented to be highly effective in adults can be considered an option for moderate to severely addicted adolescents who want to stop smoking.
- As with any severe chronic illness, patients should be monitored for adverse effects of therapy, medication adherence, and achievement of treatment goals.
- Tobacco dependence may coexist with other substance abuse and/or mental health disorders; referral to appropriate behavioral health resources may be needed.
- Pharmacotherapy is initiated on the basis of the severity of tobacco dependence and adjusted on the basis of control of nicotine withdrawal.
- Long-acting medications are used as controllers (nicotine patch [over the counter], bupropion [prescription], and varenicline [prescription]).
- Shorter-acting medications can be used for relief of nicotine withdrawal symptoms and as premedication before situations that trigger smoking (nicotine gum and lozenges [over the counter], nicotine inhaler [prescription], and nicotine nasal spray [prescription]).

- The combination of 2 or more of these medications is more effective than 1 medication alone. For individuals with moderate or greater tobacco dependence, both a controller (long-acting) and a reliever (shorter-acting) medication is recommended.
- Duration of therapy is based not on a fixed timetable but on control of the underlying disease (nicotine withdrawal).
- ENDS should *not* be recommended for tobacco dependence treatment, since they have not been shown to be effective, and there are concerns about their safety. Further, evidence to date indicates that youth who use both combustible tobacco and ENDS are less likely to stop combustible tobacco use.
- Figure 27-1 provides an algorithm for initiating pharmacotherapy on the basis of the severity of tobacco dependence (Table 27-2 addresses severity assessment).

Prognosis

- Untreated tobacco dependence leads to disease, disability, and premature death.
- Earlier age at stopping tobacco use substantially reduces the risk for tobacco-related morbidity and premature mortality, but not to the level of someone who has never smoked.

When to Refer

- Refer the patient for appropriate behavioral health services if
  - Other substance abuse is present
  - Other psychiatric disorders are present

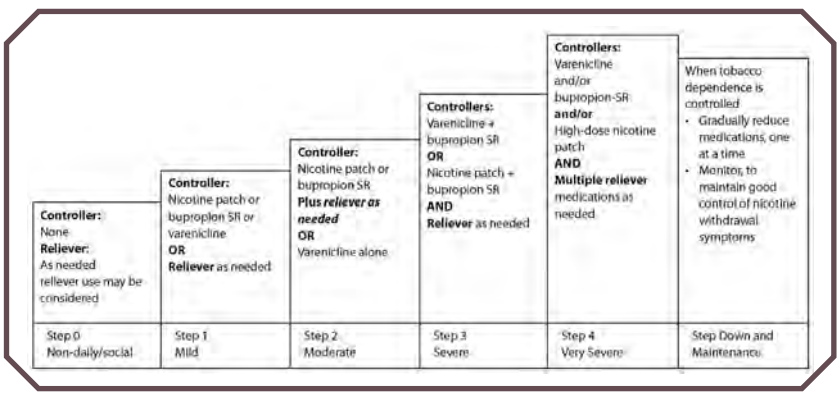

Figure 27-1. Pharmacological management of tobacco dependence. Adapted with permission from Sachs DPL, Leone FT, Farber HJ, et al. *American College of Chest Physicians Tobacco-Dependence Treatment Tool Kit.* 3rd ed. Northbrook, IL: American College of Chest Physicians; 2010. http://tobaccodependence.chestnet.org.

- Provide tobacco-dependent patients and parents with a referral for telephonic cessation support:
  - 1-800/QUIT NOW is the national smokers' help line; it will connect callers to their state Quitline.
- Refer the patient and/or parents to good-quality tobacco dependence treatment programs if they are available in your community.

Resources for Families

- Julius B. Richmond Center of Excellence (American Academy of Pediatrics). www.aap.org/RichmondCenter
- ASPIRE Program (MD Anderson Cancer Center). www.mdanderson.org/about-md-anderson/community-services/aspire.html
- Smoke Free Teen (U.S. Department of Health and Human Services). teen.smokefree.gov
- QuitSTART app (U.S. Department of Health and Human Services). smokefree.gov/apps-quitstart
- Truth Initiative. www.thetruth.com

Clinical Pearls

- Tobacco dependence starts in adolescence. Close to 90% of current adult smokers started their tobacco use prior to 18 years of age.
- Tobacco dependence is a severe chronic illness. Nicotine changes brain structure and chemistry.
- In the interest of protecting their child's health, tobacco-dependent parents may be receptive to treatment recommendations and/or prescriptions from their child's pediatrician.
- Tobacco dependence pharmacotherapy should be initiated on the basis of readiness to change and severity of tobacco dependence. Treatment should be stepped up or stepped down, based on control of nicotine withdrawal.
- ENDS should NOT be recommended for tobacco dependence treatment.

Chapter 28

Nonpharmacological Management and Use of Complementary and Alternative Medicine Therapies for Asthma

Yehudit Pollack, MD, and Christy Kim, MD

Introduction

- Use of nonpharmacological therapies for asthma, as well as complementary and alternative medicine (CAM), are increasing.
- Asthma ranked eighth among pediatric conditions, prompting the use of complementary health approaches.
- Clinicians should routinely ask patients about the use of nonpharmacological and CAM therapies.
- Conventional medical treatments are very effective in managing asthma, while the evidence for CAM for asthma is limited.

Physical Techniques

Acupuncture

- Points on the body are stimulated with needles, pressure, or lasers.
- A few studies indicate small benefits, but most show no difference in asthma symptoms or lung function between actual and simulated ("sham") acupuncture.
- At this time, there is little evidence that acupuncture is an effective treatment for asthma.
- Potential risks include pain, burns, infectious disease transmission from improperly sterilized needles, and delay in seeking more effective care.

Breathing Exercises and/or Respiratory Retraining

- Buteyko and other breathing techniques are aimed at reducing hyperventilation through various breathing exercises.
  - — There is some evidence that hyperventilation reduction techniques may reduce asthma symptoms and use of reliever medication in adults, but there is insufficient evidence in children.

- Other methods include yoga breathing techniques to control the depth, flow, or timing of breathing and physical therapy methods to increase respiratory muscle strength.
  - Evidence is insufficient to determine whether these techniques improve asthma outcomes in children.
- Some adult studies have shown improvement in quality of life scores with respiratory retraining in asthmatic patients.
  - In patients in whom emotional stress is a substantial asthma trigger, breathing exercises may have an indirect benefit as a stress-reduction strategy.
- Breathing exercises are low-risk approaches that may provide some benefit in terms of perceived well-being, but they should not replace conventional asthma medications.

Vitamins and Herbal Treatment

Herbal Treatments

- In Asia, herbal remedies have been used in traditional Chinese medicine and Ayurvedic medicine to treat asthma for centuries.
- Studies of some herbal remedies have shown improvement in subjective measures of asthma control. However, most of the studies are of poor quality and do not show changes in objective asthma measures.
- Overall, current evidence is inadequate to recommend the use of herbal products as treatment for asthma.
- Furthermore, herbal products have potential risk of toxicity and drug interactions.
- Because of lack of regulation and oversight, there is also the potential for contamination and inconsistent dosing.

Vitamins and Supplements

Vitamins A, C, and E

- Evidence is limited, but overall, studies do not support the use of vitamins A, C, or E for treatment of asthma.

Vitamin D

- Studies have shown a correlation between low serum vitamin D levels and severe asthma.
- In patients with mild to moderate asthma, vitamin D supplementation has been associated with decreased frequency of severe asthma exacerbations that require systemic steroids, emergency department visits, or hospitalization. Most of the studies were conducted in adults, so caution must be used in generalizing this effect to children.
- Studies have not shown improvement in lung function or daily asthma symptoms.

- Further studies are needed to determine whether this effect is limited to those with low baseline vitamin D levels.

Magnesium

- Evidence is insufficient to determine whether magnesium supplementation improves asthma outcomes in children.

Fish Oil

- Populations with diets rich in fish have low rates of asthma.
- A few small studies suggest possible benefit from fish oil supplementation.
- Overall, however, there is insufficient evidence to recommend the use of fish oil to improve asthma control. There is also no evidence of risk.

Soy Isoflavone

- A multicenter trial in which a soy isoflavone supplement was used in children and adults with poorly controlled asthma did not show improved lung function or improved clinical outcomes.

Probiotics

- There is insufficient evidence to recommend the use of probiotics for prevention or treatment of asthma.

Honey

- Honey is not a treatment for asthma, but it has been studied for treatment of acute cough due to upper respiratory tract infections in children.
- Studies have shown that honey may help reduce cough frequency and severity, resolve bothersome cough, and improve sleep quality for children and parents.
- Honey should not be given to infants <1 year of age.
- Honey should not replace the use of bronchodilators.

Dietary Changes

- A healthy diet that includes fruits and vegetables is advisable for all children, including those with asthma.
- Food elimination diets are not recommended for asthma treatment.

Weight Loss

- Obesity has been associated with increased rates of asthma and increased asthma severity.
- A few small studies of weight loss in overweight and obese adults with asthma showed some improvement in asthma symptoms and lung function. Overall, the quality of evidence is low.
- Current data are insufficient to recommend weight loss as an intervention for asthma control. Studies in children and adolescents are lacking.

Dairy-Free Diet

- Elimination of dairy is not recommended, as there is no evidence for a correlation between milk consumption and asthma; further, milk has many health benefits to children.
- There are no valid studies that link milk consumption and mucus production, despite this commonly held belief.

Homeopathy

- Homeopathy involves the use of minute doses of natural substances that cause symptoms in the undiluted form.
- There is inadequate evidence to reliably assess the role of homeopathy in asthma.
- The U.S. Food and Drug Administration warns consumers to avoid over-the-counter homeopathic products, as they have not been evaluated for safety or effectiveness.

Clinical Pearls

- Studies have shown that asthmatic patients treated with placebo may report clinically significant improvements in symptoms and perception of dyspnea, without actual improvement in lung function. This is an important distinction, because these patients are still at risk from poorly controlled asthma.
- Therefore, CAM should never be used in place of standard therapy in the treatment of asthma, even when there is a perceived benefit.
- Since patients are likely to try a variety of unproven therapies, it is important to emphasize that these approaches should always be considered complementary and should not replace therapies proven to be effective.
- Despite the popular perception that CAM is safer than conventional medications, patients should be reminded that CAM is not free of side effects or potential risks.

Resources for Families

- National Center for Complementary and Integrative Health. nccih.nih.gov/health/asthma/facts
- Over-the-Counter Asthma Products Labeled as Homeopathic: FDA Statement—Consumer Warning About Potential Health Risks (U.S. Food and Drug Administration). www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm439014.htm

Chapter 29

Allergic Rhinitis

Andrew G. Ayars, MD, and Mathew C. Altman, MD, MPhil

Introduction/Etiology

- Allergic rhinitis manifests with symptoms such as congestion, rhinorrhea, sneezing, itching, and conjunctivitis.
- It is caused by an immunoglobulin E (IgE)–mediated hypersensitivity to aeroallergens, including pollens, dust mites, cockroaches, pets, molds, and fungi.
- Allergic rhinitis is one of the most common chronic illnesses in developed countries.
- It results in marked morbidity that includes decreased quality of life, missed school or work days, and substantial treatment-related costs.
- Treatment strategies include medications, environmental controls, and immunotherapy (subcutaneous and sublingual).

Pathophysiology

- Allergic rhinitis is driven by an IgE antibody–mediated allergic hypersensitivity to aeroallergens.
- IgE signals delivered through the high-affinity type I Fcε receptor on inflammatory cells such as mast cells, eosinophils, and basophils cause the rapid release of inflammatory mediators, such as histamine and leukotrienes.

Clinical Features

- Rhinitis is characterized by >1 of the following nasal symptoms:
  - Congestion, rhinorrhea, postnasal drip, sneezing, and itching
  - Allergic conjunctivitis symptoms, such as itchy, watery eyes
- Allergic rhinitis symptoms can be variable, depending on
  - Seasonal exposure due to pollens from trees, grasses, molds, fungi, and weeds
  - Perennial symptoms, which can be triggered by allergens such as dust mites, molds, fungi, cockroaches, and pets
- Allergic rhinitis most commonly develops prior to the age of 20, but it can manifest at any age.

Differential Diagnosis

- Other forms of rhinitis symptoms can include
  - — Infectious rhinitis and/or sinusitis
  - — Nonallergic rhinitis
  - — Medication-induced rhinitis
  - — Nonallergic rhinitis with eosinophilia
    - ▪ This is a form of nonallergic rhinitis with associated nasal eosinophilia, most often documented by means of nasal smear.
    - ▪ Causes of medication-induced rhinitis can include antihypertensives, nonsteroidal anti-inflammatory drugs, and overuse of α-adrenergic decongestants.
- These other forms often manifest without a seasonal component or without a worsening of symptoms related to environmental exposures.
- Allergy testing is often required to differentiate allergic from nonallergic forms of rhinitis (see Table 29-1).

Table 29-1. Differentiating Factors for Common Causes of Rhinitis in Children

	Allergic Rhinitis	Nonallergic Rhinitis	Anatomic Abnormalities	Recurrent Viral Upper Respiratory Infections
Age of onset	≥12 mo for perennial 2–3 y for seasonal	≥6 mo	Can be present from birth	≥6 mo
Itching	Severe itching	No itching	No itching	No itching
Mucus	Always clear	Clear	Clear	Clear or yellow/green
Congestion	Some congestion	Severe congestion	Some congestion	Some congestion
Fever	Never	No fever	No fever	Can occur with or without fever
Duration	Weeks to months	Months	Months	10–14 d

Courtesy of David Stukus, MD.

Diagnostic Considerations

- Two elements are often necessary to establish the diagnosis of allergic rhinitis.
  - — Symptoms consistent with allergic rhinitis
  - — Positive skin test results or serum IgE test results for seasonal and/or perennial aeroallergens, which need to correlate with the clinical history

- The diagnosis can also be assigned with a strong clinical history associated with known exposures, such as
  - Worsening of symptoms around pets
  - Seasonal symptoms that correlate with a known regional pollen season
- Testing for allergic sensitizations may be performed with either of the following methods:
  - Skin prick testing
    - Bioassay to evaluate the presence of allergen-specific IgE
    - Involves scratching the skin with individual concentrated aeroallergens
    - Results available within 20 minutes
  - Serum IgE testing
    - Another option for assessing specific IgE to aeroallergens
    - Sometimes less sensitive than skin testing for aeroallergens

Management

- H_1-antihistamines
  - An inexpensive, safe, and generally effective therapy for allergic rhinitis
  - Can be delivered as oral or topical nasal agents
  - First-generation antihistamines
    - Work well but are often limited by the side effect profile
    - Sedation is a common limiting side effect
  - Second-generation antihistamines
    - Well tolerated with similar effectiveness when compared with the first-generation H_1-antihistamines
    - Do not have the systemic effect profile associated with first-generation H_1-antihistamines
- Corticosteroids
  - Topical (intranasal) corticosteroids
    - Considered the most effective medication class for controlling allergic rhinitis symptoms, such as congestion, rhinorrhea, and postnasal drip
    - Safe and are generally well tolerated
  - Oral and intramuscular steroids
    - While oral and intramuscular corticosteroids are effective short-term treatments in severe allergic rhinitis, they are not appropriate for long-term use.
- Topical anticholinergics
  - Ipratropium can reduce rhinorrhea in some patients but often has minimal effects on other nasal symptoms.

- Decongestants
  - Examples include oxymetazoline, pseudoephedrine, and phenylephrine.
  - Nasal decongestants
    - Work well for short-term relief but should not be used at high doses regularly
    - If used consistently, can cause a rebound effect called "rhinitis medicamentosa"
  - Oral decongestants
    - Can be beneficial as a short-term treatment
    - Caution should be used with consistent use of these medications due to side effects, including insomnia and hypertension
- Leukotriene antagonists
  - Can improve rhinorrhea, sneezing, and pruritus in patients with allergic rhinitis
  - Generally not recommended as first-line agents
  - Often used if there is concomitant asthma
- Common medications used to treat allergic rhinitis are discussed in Table 29-2.

Table 29-2. Common Medications Used to Treat Allergic Rhinitis

Drug Type	Common Examples	Discussion
Antihistamines		
First-generation H_1-antihistamines	Diphenhydramine, chlorpheniramine	Effective agents for rhinitis symptoms but often limited by side effect profiles Side effects can include sedation, dry eyes, dry mouth
Second-generation H_1-antihistamines	Loratadine, fexofenadine, cetirizine	First-line therapy for rhinitis Inexpensive and safe Safe for long-term use, given the side effect profile
Intranasal antihistamines	Azelastine, olopatadine	Used as an add-on therapy in allergic rhinitis and often effective in other types of rhinitis, such as nonallergic rhinitis
Corticosteroids		
Topical (intranasal) corticosteroids	Beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone furoate, fluticasone propionate, mometasone, triamcinolone	Intranasal corticosteroids are an effective medication class for controlling symptoms of allergic rhinitis The regular use of intranasal corticosteroids is generally preferred over as-needed use Some agents are approved for use as in patients as young as 2 y of age

Table 29-2. Common Medications Used to Treat Allergic Rhinitis, *continued*

Drug Type	Common Examples	Discussion
Leukotriene blockers		
	LTRAs: montelukast, zafirlukast 5-LO inhibitor: zileuton	Not a first-line treatment for rhinitis but can have a role as an add-on therapy LTRAs are generally preferred over 5-LO inhibitors, given that liver function needs to be monitored with 5-LO inhibitor Montelukast is approved in patients as young as 6 mo of age Zafirlukast is approved in patients ≥5 y of age Zileuton is approved in patients ≥12 y of age
Decongestants		
	Oxymetazoline, phenylephrine, pseudoephedrine	While these agents work well for short-term relief of congestion, they should not be used long-term, given the side effect profile Medications such as oxymetazoline are approved in children ≥6 y of age

LTRA, leukotriene receptor antagonist; 5-LO, 5-lipoxygenase

- Other treatments for allergic rhinitis
  - Environmental controls
    - When a sensitivity to an aeroallergen has been established via a history, skin testing, and/or serum IgE testing, then efforts should be made to decrease exposure to specific aeroallergens.
    - Environmental controls can be effective in decreasing symptoms due to perennial allergens, such as dust mites, pets, and cockroaches.
    - For those with known pollen sensitivities, caution should be taken with outdoor activities when pollen counts are high.
  - Immunotherapy (subcutaneous and sublingual)
    - Allergen immunotherapy may be considered for patients with allergic rhinitis and documented allergic sensitivities to aeroallergens with an appropriate history.
    - Allergen immunotherapy is the only treatment that has been shown to alter the underlying immune response to aeroallergens.

Treating Associated Conditions

- Allergic conjunctivitis
  - — Manifests with ocular pruritus, erythema, and discharge when exposed to sensitized aeroallergens
  - — Treatment options
    - Oral H_1-antihistamines
    - Nasal steroids (in many patients, nasal steroids can improve ocular symptoms)
    - Topical (eye drops) antihistamines and/or mast cell stabilizers
      ~ Olopatadine, bepotastine, azelastine, epinastine (prescription only
      ~ Ketotifen (nonprescription)
    - Immunotherapy (allergy shots)
- Allergic asthma (Please see the chapters on asthma)

When to Refer

- Uncontrolled symptoms despite first-line therapies, such as antihistamines, intranasal corticosteroids, antileukotrienes, and nasal antihistamines
- When patients want to try and limit medication use by avoiding specific allergens
- If immunotherapy is being considered

Resources for Families

- Rhinitis (American Academy of Allergy, Asthma, and Immunology). www.aaaai.org/conditions-and-treatments/allergies/rhinitis
- Allergic Rhinitis (American College of Allergy, Asthma, and Immunology). acaai.org/allergies/types/hay-fever-rhinitis
- Allergic Rhinitis Symptoms and Treatment (European College of Allergy and Immunology). www.eaaci.org/patients/allergic-and-immunologic-diseases-and-causes/allergic-conditions/rhinitis/about-rhinitis.html

Chapter 30

Asthma Guidelines: Overview

Suzette T. Gjonaj, MD

Introduction

- Asthma is a chronic disease of the airways that includes chronic inflammation, which leads to bronchial hyperresponsiveness, airflow obstruction and limitation, respiratory symptoms, and chronicity of the illness.
- Asthma is one of the most common childhood chronic illnesses, affecting more than 7 million children in the United States.
- In 1991, the first National Asthma Education and Prevention Program clinical practice guidelines were released, which were updated in 1997.
- Since then, despite the increasing prevalence of asthma, the number of asthma-related deaths has declined.

The 2007 Third Expert Panel Report

Goals of the Guidelines

- The National Heart, Lung, and Blood Institute Third Expert Panel Report (EPR-3) guidelines were published in 2007.
- The EPR-3 guidelines assist practitioners in improving and standardizing the quality of asthma care, thereby achieving better quality of life and decreasing asthma burden.
- The guidelines address long-term asthma management and management of exacerbations.
- Effective management of asthma includes the following 4 components of care:
  - Assessment and monitoring
  - Patient education
  - Control of factors that contribute to asthma severity
  - Pharmacological treatment

Assessment and Monitoring

- Assessment and monitoring are closely linked to asthma severity, control, and responsiveness.
- *Severity* refers to the intensity of the disease process. It must be accurately assessed prior to initiating therapy.

- *Control* indicates the degree to which the symptoms, functional impairments, and risks of untoward events are minimized.
- *Responsiveness* means the degree to which control is obtained with treatment.
- Severity and control are defined according to the measure of impairment previously and currently experienced, the risk of exacerbations, the decline in lung function, and the adverse effects of medications.
- Measures such as patient history, physical examination, and spirometry are used to diagnose and assess the severity of illness and to monitor whether control is achieved and maintained.
- Children ≥5 years of age should undergo spirometry to help assess disease severity and quantify the risk of exacerbations.
- Level of severity, whether intermittent or persistent, and degree of severity of persistent asthma (mild, moderate, or severe) determine the type and amount of therapy instituted.
- Intermittent asthma is classified as experiencing symptoms <2 days per week, experiencing nocturnal symptoms <2 times per month, symptoms not interfering with normal activities, and normal spirometry values and/or peak flow.
- Periodic monitoring is necessary to determine whether the goals of management are being achieved and whether the asthma is well controlled.

Patient Education

- Successful education enables patients and parents to understand and institute complicated pharmacological regimens, optimize environmental control measures, detect and manage exacerbations, and communicate with health care providers effectively.
- The patient and parents must be educated in self-management skills to control asthma and improve outcomes.
- Education should be initiated at the time of diagnosis, with consistent and constant reinforcement and repetition at follow-up visits.
- At every opportunity, education should include basic facts about asthma, roles in preventive management and in the event of an exacerbation, identification and reduction of environmental allergens and irritants, differences between various medications, and review of patient skills (proper use of inhalers, spacers, and peak flow meters).
- All health care team members should be included in education efforts. This involvement can occur in clinics, office visits, emergency department visits or hospital visits, pharmacies, and the community.
- It is important that an asthma action plan be created and reviewed at every visit. It should include daily management strategies and how to recognize and treat worsening asthma.
- Regular follow-up is necessary to review the status of asthma control, continue patient and parent education, develop a relationship with the patient and parents, and encourage treatment adherence.

- Customizing the approach to self-management with the individual patient and parents is necessary to achieve success with treatment goals and adherence.

Control of Environmental Factors and Comorbid Factors

- To achieve success in the long-term management of asthma, it is crucial to identify and decrease exposure to allergens and irritants that can trigger exacerbations or increase asthma symptoms.
- These factors include inhalant allergens, irritants, occupational exposure, and comorbid conditions, among others.
- Inhalant allergens include indoor allergens (animal dander, dust mites, cockroaches, mice, and mold) and outdoor allergens (tree, grass and weed pollens, and mold).
- Food allergies are unlikely to trigger asthma symptoms and exacerbations.
- Irritants include tobacco (environmental tobacco smoke) and smoke from fireplaces and wood-burning stoves.
- In patients who have difficulty achieving asthma control, evaluation for comorbid factors should be undertaken.
- Comorbid factors include gastroesophageal reflux disease, obesity, obstructive sleep apnea syndrome, allergic bronchopulmonary aspergillosis, sinusitis, rhinitis, chronic stress, and depression.
- Other factors include viral (respiratory syncytial virus, rhinovirus, and influenza) and atypical (*Mycoplasma* and chlamydia) infections.

Medications

- Pharmacotherapy is used to prevent and control asthma symptoms, improve quality of life, decrease the frequency and severity of exacerbations, and reverse airflow obstruction.
- Long-term controller medications are used to achieve and maintain control of persistent asthma.
- Quick-relief medications treat acute symptoms and exacerbations by promptly reversing airflow obstruction and relieving bronchoconstriction.

Long-term Controllers

- Patients with persistent asthma require long-term controller medication.
- Because inflammation is part of the pathophysiology of asthma, the most effective long-term controller attenuates inflammation.

Inhaled Corticosteroids

- See also Chapter 35, Pharmacological Management: Inhaled Corticosteroids.
- Inhaled corticosteroids (ICS) are the most potent and unfailingly effective controllers for mild, moderate, and severe persistent asthma.
- ICS are more effective as a single long-term controller than other controllers.

- Benefits include decrease in severity of symptoms; improved asthma control and quality of life; improved peak expiratory flow and spirometry values; decrease in airway hyperresponsiveness; decrease in frequency and severity of exacerbations; reduction in use of systemic steroids, emergency department visits, hospitalizations, and deaths due to asthma; and possibly attenuation of loss of lung function in adults.
- ICS have fewer side effects than systemic steroids.
- The effectiveness outweighs the small but potential risk of side effects. The reduction of potential side effects can be achieved with the use of a spacer or holding chambers, the use of the lowest dose possible to achieve asthma control, and/or combination therapy.
- The addition of a long-acting β-adrenergic agonist (LABA) is a more effective add-on medication with ICS than other controllers in combination therapy.

Inhaled LABA

- See also Chapter 34, Pharmacological Management: Long-acting β_2-Adrenergic Agonists.
- An adjunct to ICS therapy for persistent asthma
- Not used as monotherapy for persistent asthma
- Not used for acute symptoms and exacerbation

Antileukotriene Agents

- See also Chapter 36, Pharmacological Management: Leukotriene Receptor Antagonists.
- An alternative, but not preferred, treatment for mild persistent asthma
- May be used as an adjunct with ICS
- Provide modest improvement in lung function as a single agent

Omalizumab

- Used as adjunct therapy for severe persistent asthma and allergies when high-dose ICS and LABA do not achieve control of asthma symptoms
- Currently approved for use in patients >6 years of age

Methylxanthines

- Sustained-release theophylline is an alternative but not preferred medication for mild persistent asthma.
- Methylxanthines are an alternative but not preferred adjunct with ICS for moderate and severe persistent asthma.

Quick-Relief Medications

- For rapid relief of symptoms of bronchoconstriction
- Includes short-acting β_2-agonists (SABAs), anticholinergics, and systemic corticosteroids

Short-acting β_2-Adrenergic Agonists

- See also Chapter 33, Pharmacological Management: Short-Acting β_2-Adrenergic Agonists.
- These are the drug of choice in the treatment of acute asthma symptoms and exacerbations and in the prevention of exercise-induced bronchospasm.
- Within 3–5 minutes, the airway smooth muscle relaxes and airflow increases.
- Daily long-term use is NOT recommended.
- Use more than 2 times per week for symptomatic relief is an indication for initiating or adjusting anti-inflammatory preventive medication.

Anticholinergics

- See also Chapter 37, Pharmacological Management: Anticholinergic Agents
- Provide additional benefit when added with a SABA in moderate to severe exacerbations

Systemic Corticosteroids

- See also Chapter 38, Pharmacological Management: Systemic Corticosteroids.
- Systemic corticosteroids are used in moderate to severe exacerbations.
- Although the onset of action is relatively slow (1–2 hours), systemic corticosteroids are used for moderate and severe exacerbations to prevent progress of flare, speed recovery, and avoid relapse.
- Multiple courses (>2 per year) indicate the need to initiate or adjust a preventive anti-inflammatory regimen.

When to Refer

- After a life-threatening exacerbation
- Goals of treatment not met after an interval of management
- Atypical signs or symptoms
- Presence of confounding comorbidities
- Additional specialized diagnostic testing indicated
- Additional guidance and education warranted
- According to guidelines, patient requires Step 3 care in a 0–4-year-old and Step 4 care in a >4-year-old
- Patient received 2 courses of oral steroids in 1 year or 1 hospitalization
- Patient desires confirmation of diagnosis and/or complex management that may require comanagement

Summary of EPR-3 Guidelines

- The goal for management is reducing impairment and risk of exacerbations.
- Institute pharmacological therapy in a stepwise manner to achieve and maintain control of asthma.

- Institute environment control measures to minimize exposure to indoor allergens and pollutants.
- There is an essential need for follow-up and monitoring.
- A detailed, written action plan should be created and individualized for every patient to feature treatment, recognition and treatment of symptoms, and exacerbations.
- Refer the patient to an asthma specialist for consultation or comanagement when control of asthma is difficult to achieve or maintain, when more patient and parent education is warranted to improve treatment adherence, when the patient requires a higher level of care, and when the patient has experienced a clinically significant exacerbation.
- Updated guidelines detail management for the age groups 0–4 years, 5–11 years, and ≥12 years.
- The classification of severity of asthma determines the treatment option to initiate for long-term management.
- Adjusting therapy and maintaining control is determined by the degree of asthma control.
- There are 6 steps to asthma treatment in the guidelines, which will be discussed in subsequent chapters.

The 2016 Global Initiative for Asthma Report: Global Strategy for Asthma Management and Prevention

- The Global Initiative for Asthma (GINA) Report, revised and updated in 2016, is an approach to the management of asthma, rather than a guideline.
- Management starts with establishing the correct diagnosis of asthma with a detailed history and physical examination and obtaining spirometry values to demonstrate variable airflow limitation and reversibility with a bronchodilator.
- Management goals are asthma control and risk reduction.
- Assess the patient at every visit for the following:
  - Asthma control
    - Assess symptom control.
    - Identify and reduce exposure to risk factors (allergens and pollutants).
  - Comorbidities: Determine if any are present, because they may confound or contribute to poor asthma control.
  - Treatment issues: Review the asthma action plan and possible side effects, the administration of medications, and adherence to the treatment plan. Discuss mutual goals of treatment and create a written action plan.
- The GINA strategy involves the use of control-based asthma management, which is a continuous cycle of assessing, adjusting treatment, and reviewing the response.

Five-Step Approach to the Treatment of Children >6 Years of Age

- The severity of asthma is assessed retrospectively, from the level of management required to control symptoms.
- The severity is classified as mild, moderate, or severe.
- Determine if the asthma is well controlled, partly controlled, or uncontrolled.
- Identify and reduce exposure to risk factors, which include indoor and outdoor allergens, indoor pollutants, viral infections, and drugs.
- Mild asthma is controlled with Step 1 and 2 management.
- Moderate asthma is controlled with Step 3 management.
- Severe asthma requires Step 4 and 5 management to achieve control.

Step 1: Use of a SABA With No Daily Controller

- Infrequent symptoms with no nocturnal symptoms, no exacerbations in 1 year, and normal forced expiratory volume in 1 second values
- If there is a risk for exacerbation, low-dose ICS may be added

Step 2: Regular Low-Dose ICS With SABA as Needed

- Leukotriene receptor antagonist (LTRA) or low-dose theophylline are less effective alternatives
- Another option is medium-dose ICS

Step 3: Regular Low-Dose ICS or LABA Maintenance Plus SABA as Needed

- Primary options are the following:
  - Medium- or high-dose ICS
  - Low-dose ICS or LABA with LTRA, with or without theophylline
  - ICS or formoterol, used as a preventive and reliever medication if the patient is >12 years of age
- If the patient is >12 years of age, may add tiotropium

Step 4: Medium- or High-Dose ICS or LABA as Maintenance Plus SABA as Needed

- An option is to use high-dose ICS and LTRA, with or without theophylline.
- Refer children <12 years of age to an asthma specialist.
- In children >12 years of age, an option is to use medium-dose ICS or formoterol as maintenance and reliever.
- An option is to add tiotropium in patients with exacerbations who are >12 years old.

Step 5: Refer the Patient to an Asthma Specialist for Extra Treatment and Further Evaluation

- Additional treatment with tiotropium in patients >12 years of age
- Additional treatment with omalizumab for patients >6 years of age with severe allergic asthma
- Additional treatment with mepolizumab for patients >12 years of age with severe eosinophilic asthma
- May consider low-dose systemic corticosteroids, but these will likely cause systemic side effects

Adjust and Review

- At follow-up visits, adjustments depend on the patient's level of asthma control, response to prior treatment, and capability and motivation to follow the action plan.
- Consider adjustments initially 1–3 months after starting treatment, then every 3–12 months afterward.
- Consider adjustments within 1 week after an exacerbation.

Stepping Treatment Up

- Sustained step-up (2–3 months) should be used for difficult-to-control symptoms or a breakthrough exacerbation.
  - Review the technique used with medication and spacer.
  - Review the treatment administration for poor adherence.
  - Review the treatment plan for modifiable risk factors like environmental tobacco smoke.
  - Evaluate the patient for comorbidities.
- Short-term step-up (1–2 weeks) should be used with concomitant viral infection or allergen exposure.
- Make day-to-day adjustments if needed.

Stepping Treatment Down

- Consider stepping treatment down when good asthma control is achieved for 2–3 months.
- Use a minimal treatment dose to achieve control of symptoms and exacerbations and minimize side effects.

Four-Step Approach to Treatment of Children <6 Years of Age

Step 1: If Symptoms Are Triggered by Viral Infections or There Are Few or No Interval Symptoms

- Use a SABA as needed.
- Use of ICS, in addition to SABA, may negate the need for oral steroids.

Step 2: If Symptoms Are Consistent With Asthma, Symptoms Are Not Well Controlled, and/or There Are ≥3 Exacerbations Per Year

- The preferred treatment is daily low-dose ICS.
- Daily LTRA or intermittent low-dose ICS is an option.
- A SABA may be used as needed.

Step 3: If Symptoms Are Consistent With Asthma and Not Well Controlled With Low-Dose ICS

- Re-evaluate adherence to treatment, medication and spacer skills, diagnosis, exposures, and comorbidities.
- Double the low dose of ICS.
- Adding LTRA to low-dose ICS is an option.
- Adding LABA to low-dose ICS is an option.
- A SABA may be used as needed.

Step 4: If Symptoms Are Consistent With Asthma and Not Well Controlled With a Double Dose of ICS

- Re-evaluate adherence to treatment, medication and spacer skills, diagnosis, exposures, and comorbidities.
- Refer the patient to an asthma specialist.
- Add LTRA, with or without intermittent additional ICS.

Acute Exacerbations

Guidelines for the management for acute exacerbations have been outlined in the updated 2016 GINA recommendations.

General Management Principles

- Both the EPR-3 and GINA recommendations strongly suggest achieving symptom control and risk reduction in patients.
- Asthma control is achieved with environmental control measures and pharmacological therapy.
- After step-up therapy achieves excellent symptom control, slowly step the therapy down to maintain control.
- Initial accurate diagnosis, followed by continued monitoring at follow up visits, is essential.
- The following are vital to the successful management of asthma: continually educating the patient and parents about the pathophysiology of the disease, reviewing the treatment plan and correct use of medication and devices, maintaining a partnership with the patient and parents regarding the goals of management, adhering to the treatment plan, and formulating written asthma action plans.
- With the use of guidelines, physicians can accomplish standardized care and achieve success in the management of asthma.

Resource for Families

- Asthma: Parents (U.S. Centers for Disease Control and Prevention). www.cdc.gov/asthma/parents.html

Clinical Pearls

- Once an accurate diagnosis of asthma is established, schedule routine periodic follow-up visits.
- The patient should be re-evaluated at every visit to ascertain whether excellent asthma control is being achieved.
- Review environmental control measures to reduce patient exposure to allergens and pollutants, both indoors and outdoors.
- Encourage and devise strategies at every visit to facilitate adherence to the treatment plan.
- At every visit, review the proper use of metered-dose inhalers with spacer, dry-powder inhalers, and nebulizers.
- Listen to the parents and the patient and include them in the management plan.

Chapter 31

Asthma Guidelines: Management of Acute Asthma

Hiromi Yoshida, MD, MBA, FAAP

Introduction/Etiology/Epidemiology

- In 2014, the asthma attack rate among U.S. children with active asthma <18 years of age was about 48%.
- Viral upper respiratory tract infections are the most common trigger for wheezing in children.

Pathophysiology

- Hyperresponsiveness of the airways, which is caused by external stimuli (irritants, exercise, chemicals, allergens, and infection), leads to bronchospasm and inflammation that results in airflow obstruction.
- Mucosal edema, hypersecretion of mucus, infiltration of inflammatory cells, vasodilation, hypertrophy of the mucus gland, desquamation of the airway epithelium, and mucus plugging leads to decrease in expiratory airflow.

Clinical Features

- History
  - Recent or current viral illness
  - Environmental or airborne allergens
- Early signs
  - Cough, breathlessness
- Common signs and symptoms
  - Persistent cough
  - Increased respiratory rate
  - Retractions (belly breathing, subcostal retractions, intercostal retractions, tracheal tugging, nasal flaring, head bobbing)
  - Audible wheezing, dyspnea
  - Inability to drink and/or eat
- Peak expiratory flow usually <80% of predicted or personal best

Differential Diagnosis

- Pneumonia
- Bronchiolitis in younger children
- Bacterial tracheitis
- Anaphylaxis
- Foreign-body aspiration
- Esophageal foreign body
- Bronchitis
- Vocal cord dysfunction

Diagnostic Considerations and Severity Assessment

- Asthma severity scores help stratify the severity of asthma exacerbation.
- Scores are based on a variety of signs and symptoms, including respiratory rate, work of breathing, lung examination (air entry, wheezing), degree of dyspnea, oxygen saturation, inspiratory-to-expiratory time ratio, respiratory rate, and peak expiratory flow rate.
- Several validated asthma severity scores have been developed, but no one score has been adopted universally (Box 31-1 and Table 31-1).

Management

- Early recognition of an asthma exacerbation and early intervention are crucial.
- Reverse airway obstruction
  - Inhaled bronchodilators
    - Albuterol: Selective short-acting β_2-adrenergic agonist (SABA) is the most effective bronchodilator for reversing bronchospasm in asthma.
      - This medication facilitates smooth muscle relaxation and dilation of the bronchial passages.
      - Onset occurs in <5 minutes, and the effects last 2–4 hours.
      - The delivery method is a metered-dose inhaler (MDI) or nebulizer.
        - Using a spacer or holding chamber can improve the delivery of inhaled medications through an MDI, especially in younger children.
      - Repetitive administration leads to incremental bronchodilation.
      - Use of this medication does not alter the inflammatory process.
      - Dosage:
        - For nebulizer solution: 2.5–5.0 mg per dose
        - For MDI with spacer (90 mg per puff): 4–8 puffs per dose
        - 2.5 mg = 4 MDI puffs
        - 5.0 mg = 8 MDI puffs
      - Give the patient ≤3 doses of inhaled SABA over 1 hour and reassess after each dose.

Box 31-1. Respiratory Scoring Tools

- Pediatric Asthma Severity Score ("PASS"): Ages 1–18 years
  - Gorelick MH, Stevens MW, Schultz TR, Scribano PV. Performance of a novel clinical score, the Pediatric Asthma Severity Score (PASS), in the evaluation of acute asthma. *Acad Emerg Med.* 2004;11(1):10–18.
- Pediatric Respiratory Assessment Measure ("PRAM"): Ages 2–17 years
  - Ducharme FM, Chalut D, Plotnick L, et al. The Pediatric Respiratory Assessment Measure: a valid clinical score for assessing acute asthma severity from toddlers to teenagers. *J Pediatr.* 2008;152(4):476–480.
- Pulmonary Index Score ("PIS"): Ages 1–18 years
  - Scarfone RJ, Fuchs SM, Nager AL, Shane SA. Controlled trial of oral prednisone in the emergency department treatment of children with acute asthma. *Pediatrics.* 1993;92(4):513–518.
- Pulmonary Score: Ages 5–17 years
  - Smith SR, Baty JD, Hodge D III. Validation of the pulmonary score: an asthma severity score for children. *Acad Emerg Med.* 2002;9(2):99–104.
- Respiratory rate, Accessory muscle use, Decreased breath sounds ("RAD") Score: Ages 5–17 years
  - Arnold DH, Gebretsadik T, Abramo TJ, Moons KG, Sheller JR, Hartert TV. The RAD score: a simple acute asthma severity score compares favorably to more complex scores. *Ann Allergy Asthma Immunol.* 2011;107(1):22–28.
- Respiratory Clinical Score: Ages 0–19 years
  - Liu LL, Gallaher MM, Davis RL, Rutter CM, Lewis TC, Marcuse EK. Use of a respiratory clinical score among different providers. *Pediatr Pulmonol.* 2004;37(3):243–248.
- Grading scale (Table 31-1)
  - Mild: Dyspnea with activity, end-expiratory wheeze, mild work of breathing, tachypnea
  - Moderate: Dyspnea at rest that interferes with usual activity, wheezing, moderate work of breathing, tachypnea
    - Mild to moderate exacerbations may be managed in the office setting
  - Severe: Dyspnea at rest, wheezing or diminished lung sounds, clinically significant work of breathing, tachypnea, possible hypoxia
    - For severe exacerbations, initiate treatment while arranging for transfer of the patient to an emergency department.

Table 31-1. Formal Evaluation of Asthma Exacerbation Severity in the Urgent and Emergency Care Setting

	Mild	Moderate	Severe	Subset: Respiratory Arrest Imminent
Symptoms				
Breathlessness	While walking	While at rest (in an infant, a softer, shorter cry is indicative, with difficulty feeding)	While at rest (an infant will stop feeding)	
	Can lie down	Prefers sitting	Sits upright	
Speech difficulty	Speaks in sentences	Speaks in phrases	Speaks in words	
Alertness	May be agitated	Usually agitated	Usually agitated	Drowsy or confused
Signs				
Respiratory rate	Increased	Increased	Often >30 breaths/min	
		Guide to rates of breathing in awake children:		
		Age <2 mo 2–12 mo 1–5 y 6–8 y	Normal rate <60 breaths/min <50 breaths /min <40 breaths /min <30 breaths /min	
Use of accessory muscles; suprasternal retractions	Usually not	Commonly	Usually	Paradoxical thoraco-abdominal movement
Wheeze	Moderate, wheeze often only end-expiratory	Loud, wheeze throughout exhalation	Usually loud, wheeze throughout inhalation and exhalation	Absence of wheeze
Pulse rate	<100 beats/min	100–200 beats/min	>120 beats/min	Bradycardia
		Guide to normal pulse rates in children:		
		Age 2–12 mo 1–2 y 3–8 y	Normal rate <160 beats/min <120 beats /min <110 beats /min	

Table 31-1. Formal Evaluation of Asthma Exacerbation Severity in the Urgent and Emergency Care Setting, *continued*

	Mild	Moderate	Severe	Subset: Respiratory Arrest Imminent
Pulsus paradoxus	Absent at <10 mm Hg	May be present at 10–25 mm Hg	Often present at >25 mm Hg in an adult and 20–40 mm Hg in a child	Absence suggests respiratory muscle fatigue
Functional Assessment				
PEF (percentage predicted or percentage personal best)	≥70%	Approximately 40%–69% or response lasts <2 h	<40%	<25% (Note: PEF testing may not be needed in very severe attacks)
PaO_2 (on air)	Normal (test not usually necessary)	≥60 mm Hg (test not usually necessary	<60 mm Hg: possible cyanosis	
and/or PCO_2	<42 mm Hg (test not usually necessary	<42 mm Hg (test not usually necessary)	≥42 mm Hg: possible respiratory failure	
SaO_2 percentage (on air) at sea level	>95% (test not usually necessary)	90%–95% (test not usually necessary)	<90%	
	Hypercapnia (hypoventilation) develops more readily in young children than in adults and adolescents.			

PaO_2, arterial oxygen pressure; PCO_2, partial pressure of carbon dioxide; PEF, peak expiratory flow; SaO_2, arterial oxygen saturation. The presence of several but not necessarily all parameters indicates the general classification of the exacerbation. Many of these parameters have not been systematically studied, especially as they correlate with each other. Thus, they serve only as general guides. The emotional effect of asthma symptoms on the patient and family is variable but must be recognized and addressed and can affect approaches to treatment and follow-up. From National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. https://www.nhlbi.nih.gov/files/docs/guidelines/asthsumm.pdf.

- ~ Continuous albuterol nebulization is typically not administered in the outpatient office setting.

- Levalbuterol, or (R)-albuterol, is an active isomer of albuterol.
  - ~ It has the same mechanism as albuterol.
    - Some patients experience less tachycardia, although most studies have not shown a difference in mean heart rates.
  - ~ Dosage: one-half the dose of albuterol
    - For nebulizer solution: 1.25–2.50 mg per dose
    - For MDI with spacer (45 mg per puff): 4–8 puffs per dose

~ Give the patient ≤3 doses of inhaled SABA over 1 hour and reassess after each dose.
~ This medication may not be readily available in outpatient settings.
~ Continuous levalbuterol nebulization has not been studied.

▪ Ipratropium bromide is a short-acting anticholinergic.
~ It inhibits bronchoconstriction and mucus secretion.
~ Onset is 15–30 minutes, and the effects last 3–5 hours.
~ The delivery method is an MDI or nebulizer.
~ Dosage for nebulizer solution:
◆ <20 kg: 250 mg per dose
◆ ≥20 kg: 500 mg per dose
◆ Dosage for MDI with spacer (18 mg per puff): 4–8 puffs per dose
~ Give the patient ≤3 doses over 1 hour and reassess after each dose.
~ Start in patients with moderate to severe symptoms who are being transferred to the emergency department (ED).
◆ The addition of ipratropium to albuterol in the ED setting has been shown to decrease hospital admissions.

▪ SABA and ipratropium can be administered via nebulizer with oxygen at a flow rate of 6–8 L/min or an MDI inhaler with spacer.

• Reverse inflammation
— Systemic glucocorticoids
▪ Anti-inflammatory effect
▪ Greatest effect within 2–4 hours of administration
▪ Given orally in the outpatient setting (may be given intramuscularly)
▪ Prednisone or prednisolone
~ Dosage: 1–2 mg/kg (maximum 60 mg/d) orally for the first dose
▪ Dexamethasone
~ Dosage: 0.6 mg/kg (maximum 16 mg/d) orally or intramuscularly
▪ There is no evidence that outcomes differ between oral prednisone or prednisolone and oral dexamethasone, although dexamethasone has a shorter treatment course, and some children find dexamethasone more palatable.
~ Adding flavoring to prednisolone can be helpful in promoting adherence to treatment.
▪ Administer in patients with mild symptoms if they have not responded to the first 2 doses of SABA or if they have recent steroid use.
▪ Administer early in patients with moderate to severe symptoms.
~ Early administration of steroids has been shown to decrease ED visits and hospitalizations for acute asthma attacks.

• Correct hypoxemia

  - Hypoxemia is often a result of mucus plugging and ventilation-perfusion mismatch.
  - Provide supplemental oxygen to maintain oxygen saturation ≥92%.
- Mild symptoms
  - Give the patient 2.5–5.0 mg via nebulizer or 4–8 puffs of albuterol every 20 minutes for ≤3 doses.
    - Reassess after every dose.
  - Consider oral steroids if there is no improvement after 2 doses of SABA.
  - Provide oxygen as needed to keep the arterial oxygen saturation (Sao_2) level >90%.
  - If the symptoms improve, send the patient home with 1.25–2.50 mg via nebulizer or 2–4 puffs every 4 hours for 24 hours and then as needed.
- Moderate symptoms
  - Give the patient 2.5–5.0 mg or 4–8 puffs of albuterol every 20 minutes for ≤3 doses.
    - Reassess after every dose.
  - Give the patient oral steroids.
  - Provide oxygen as needed to keep Sao_2 levels >90%
  - Consider administering ipratropium, especially if the patient needs to be transferred to an ED.
  - If symptoms are still improved 30–60 minutes after the most recent dose of bronchodilators, send the patient home with the following:
    - Albuterol: 2.5 mg via nebulizer or 4 puffs every 4 hours for 24 hours and then as needed
    - Oral corticosteroids:
      - ~ Prednisone or prednisolone: 0.5–1.0 mg/kg (maximum, 60 mg/d) administered orally twice daily for 3–5 days
        or
      - ~ Dexamethasone: 0.6 mg/kg (maximum, 16 mg/d) orally for 1 dose given the following day (2 total doses)
    - Consider starting inhaled glucocorticoids
    - Follow-up within 1 week
- Severe symptoms
  - Give the patient 5 mg via nebulizer or 8 puffs of albuterol every 20 minutes, then switch to a continuous albuterol nebulizer if available.
  - Give the patient ipratropium.
  - Give the patient oral steroids or intramuscular steroids if giving the patient oral medication would be unsafe.
  - Provide oxygen to keep Sao_2 levels >90%.
  - Expedite transfer of the patient to an ED via advanced life support.
    - ED management may include administration of continuous albuterol and ipratropium, intravenous magnesium for smooth muscle relaxation, and intravenous glucocorticoids.

- Consider obtaining a chest radiograph to rule out pneumonia in the presence of focal lung examination findings, fevers, continued tachypnea, hypoxemia, or chest pain after initial asthma therapy.

Expected Outcomes/Prognosis

- Most asthma attacks resolve with adequate bronchodilator and steroid therapy.
- About 50% of children have improvement in their asthma symptoms as they become adolescents.

When to Transfer

Transfer the patient to the hospital via an advanced life support ambulance in the following situations.

- Transfer patients with severe exacerbations.
- Transfer patients who are having mild or moderate exacerbations but are worsening or not responding to SABA and oral glucocorticoid therapies given in the first 1–2 hours of their care in the office.
- Transfer patients with continued hypoxia after 1–2 doses of SABA therapy and if supplemental oxygen therapy is needed.
- Transfer patients if there are risk factors for severe, uncontrolled disease, such as history of frequent ED visits, hospital and intensive care unit admissions, intubation, repeated courses of oral glucocorticoids, history of rapid progression of exacerbations, and food allergies.
- Transfer infants <1 year of age.
- Transfer patients who have contributing social factors, such as those with difficulty regarding access to care, those with medication adherence issues, and those with lack of social supports.

Discharge Considerations

- Discharge patients with mild to moderate symptoms who have good response to therapy within the first 1–2 hours of therapy.
  - — Discharge patients who have sustained improvement at least 30–60 minutes after the most recent dose of bronchodilators.
- Discharge instructions
  - — The patient should return for care if he or she has worsening shortness of breath, difficulty speaking, increased work of breathing, or inability to maintain hydration.
  - — Provide and review the asthma action plan or revise and update the plan if following the current plan did not prevent the exacerbation.
  - — Perform follow-up within 1 week for those with moderate exacerbations.

Prevention

- Identify, control, and avoid asthma triggers, such as respiratory infections, allergens (dust, pollens, animal fur), irritants (tobacco smoke, aerosol sprays, cleaning products), exercise, and cold air.
- Practice good asthma management and have a written asthma action plan for home and school.
- Educate patients and families about how to monitor signs and symptoms of asthma exacerbation to allow for early detection and early intervention.
  - Acute asthma exacerbations are often preventable with good asthma control.
  - Each exacerbation is an opportunity to review and update asthma action plans to decrease the risk of another exacerbation.
- Administer routine immunizations.

Resources for Families

- Allergies & Asthma (American Academy of Pediatrics). www.healthychildren.org/English/health-issues/conditions/allergies-asthma/Pages/default.aspx
- Asthma (American Academy of Allergy, Asthma, and Immunology). www.aaaai.org/conditions-and-treatments/asthma
- Learn How to Control Asthma (U.S. Centers for Disease Control and Prevention). www.cdc.gov/asthma/faqs.htm

Asthma Action Plan Examples

- National Heart, Lung, and Blood Institute. www.nhlbi.nih.gov/files/docs/public/lung/asthma_actplan.pdf
- American Lung Association. www.lung.org/assets/documents/asthma/AsthmaActionPlan-JUL2008-high-res.pdf
- American Academy of Allergy, Asthma, and Immunology. www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Libraries/NEW-WEBSITE-LOGO-asthma-action-plan_HI.pdf
- Asthma and Allergy Foundation of America. www.aafa.org/media/asthma-action-plan-aafa.pdf
- Tools for Asthma Control (U.S. Centers for Disease Control and Prevention). www.cdc.gov/asthma/tools_for_control.htm

Clinical Pearls

- Having good asthma action plans with early recognition and intervention for exacerbations can prevent ED visits.
- Not all wheezing represents an asthma exacerbation.
- Chest radiography is not routinely necessary at the onset of asthma exacerbation.

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Chapter 32

Asthma Guidelines: Management of Chronic Asthma

James W. Stout, MD, MPH, FAAP

Introduction

- Once the diagnosis of asthma is established, the foundations of chronic asthma care are an initial assessment of asthma severity, followed by planned preventive visits to assess symptom control and adjust therapy over time. (See also Chapter 30, Asthma Guidelines: Overview.)
- In primary care, a main objective is determining which patients with asthma should use a bronchodilator only when needed for symptoms and which patients should also take a daily controller medication, typically an inhaled corticosteroid. This is achieved with a structured approach to severity and symptom control.

Assessing Asthma Severity and Control

- Severity and control are assessed by using a structure of impairment and risk with the following metrics.
  - Impairment metrics
    - Symptom frequency (daytime and nighttime), short-acting bronchodilator use for symptoms
    - Lung function (forced expiratory volume in 1 second [FEV_1] percentage predicted and ratio of FEV_1 to forced vital capacity [FVC])
  - Risk metrics
    - Exacerbations that require a "burst" of oral corticosteroids increase risk.
    - Abnormal lung function may also be considered a predictor of future risk.

Severity

- At an initial visit, assess asthma severity. Although this may change over time, it is meant to represent the intrinsic severity of disease.
- The asthma guidelines provide 4 levels of asthma severity: intermittent, mild persistent, moderate persistent, and severe persistent (severity and control tables can be found at www.nhlbi.nih.gov/files/docs/guidelines/asthgdln.pdf, on pages 71–77)

Control

- Control assessment involves essentially the same metrics as severity, but they are applied over time.
- If the patient is using controller therapy, assess whether he or she is adhering to the treatment plan and confirm that the inhaler delivery technique is correct before adjusting medication dose.

Metrics for Assessment

- A Venn diagram (Figure 32-1) shows the main markers of asthma impairment and risk, which reflect the decision-making structure for assessment of asthma severity and control presented in the National Heart, Lung, and Blood Institute Third Expert Panel Report tables.
- Only one of these criteria needs to be positive for asthma to be classified as persistent in severity or not well controlled (both classifications warrant daily controller medication), although 2 or 3 criteria may often overlap.
- For children <5 years of age, a careful history of impairment and risk is used to assess severity and control, and lung function information is typically unavailable.

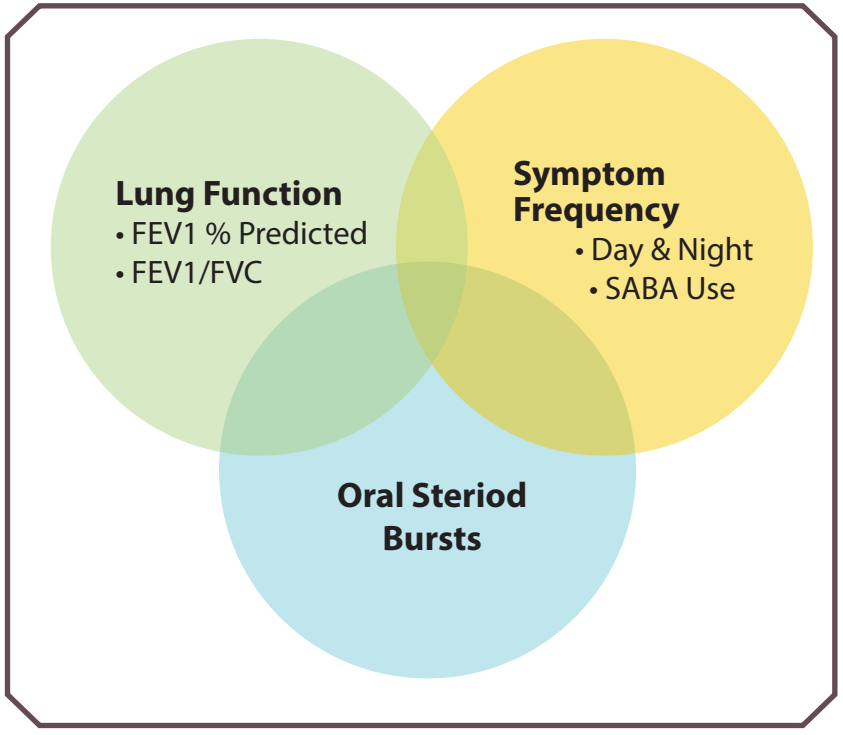

Figure 32-1. Venn diagram of the drivers of asthma severity and control. FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, SABA = short-acting β_2-adrenergic agonist.

Lung Function

- Spirometry has several indications in primary care pediatrics. These include
  - — Diagnosis and severity assessment of asthma in patients ≥5 years of age
  - — Follow-up of asthma control (especially when changing medications)
  - — Evaluation of chronic cough
  - — Evaluation of shortness of breath and other chronic respiratory complaints
  - — Evaluation of baseline lung function in a patient with exercise-induced bronchospasm

The goal is for the patient to have normal or near-normal lung function during periods of wellness.

- First and most importantly, assess whether the FEV_1 percentage predicted and/or the FEV_1/FVC ratio represents obstruction for the patient. (See Table 32-1; see also Figure 4-4 in Chapter 4, Office Pulmonary Function Testing.)

Table 32-1. Spirometry and Asthma

Asthma Severity	Spirometry Measurements					
	FEV_1 (Percentage Predicted)	FEV_1/FVC (Absolute Ratios)[a]				
		Age 5–11	Age 12–19	Age 20–39	Age 40–59	Age 60–80
Normal	≥0.80	≥0.85	≥0.85	≥0.80	≥0.75	≥0.70
I: Mild persistent	≥0.80	0.80–0.84	≥0.85	≥0.80	≥0.75	≥0.70
II: Moderate persistent	0.60–0.79	0.75 ≤ 0.80	0.80 ≤ 0.85	0.75 ≤ 0.80	0.70 ≤ 0.75	0.65 ≤ 0.70
III: Severe persistent	<0.60	<0.75	<0.80	<0.75	<0.70	<0.65

[a]Use actual ratios (not percentage of predicted values).

Symptom Frequency

- A careful, structured history of symptom frequency is critical for assessing severity and control.
- Chronic cough, wheeze, or trouble breathing (daytime and nighttime) or bronchodilator use for symptoms that persist for at least half of a typical week represents asthma that is persistent in severity and not well controlled.

- Brief, validated questionnaires are available for assessing control over time.
  - Two such tools are the Asthma Control Test (ACT) and the Childhood ACT (C-ACT) (Box 32-1). Scores from these tools can be used to assess this domain of asthma control.

Box 32-1. Symptom Frequency

Asthma Control Test (ACT): 5 items, 12 years of age through adulthood

Scoring:
- 20 and higher: Well controlled
- 16–19: Not well controlled
- 15 or lower: Very poorly controlled

Childhood Asthma Control Test (C-ACT): 7 items, 4–11 years of age

Scoring:
- 20 and higher: Well controlled
- 13–19: Not well controlled
- 12 or lower: Very poorly controlled

- The ACT and C-ACT have good reliability, validity, and responsiveness to changing clinical conditions. They are also easy to administer and interpret.
- Other examples of available and validated scoring tools include the Asthma Therapy Assessment Questionnaire (available at https://evidencebasedpractice.osumc.edu/Documents/Guidelines/ATAQChecklist.pdf) and the Asthma Control Questionnaire (available at https://www.qoltech.co.uk/acq.html).

Oral Steroid Bursts

- Two or more exacerbations in a 12-month period that require an oral corticosteroid burst is the main marker for future risk, because the best predictor of a future exacerbation is a recent one.
- An intensive care unit stay, even if brief, implies a life-threatening exacerbation and is its own marker for future risk.

Decision-making Support

- Decision-making support tools for prompting correct decisions are available online.
- Although not directly tied to treatment decision-making, measuring quality of life can also be meaningful and helpful. Validated tools for this include the Pediatric Asthma Quality of Life and Pediatric Asthma Caregiver Quality of Life questionnaires (available at http://www.qoltech.co.uk).

Planned Asthma Visits

- At regularly planned office visits, asthma control is assessed with 3 categories: well controlled, not well controlled, and very poorly controlled.
- A treatment plan is initiated and adjusted over time by using these same metrics. Treatment choices are made on the basis of these assessments of severity and control. (See Chapter 30, Asthma Guidelines: Overview.)
- A pragmatic approach is to schedule planned visits with a frequency aligned with the patient's asthma severity.
  - Intermittent: Assess at the child's annual health supervision check.
  - Mild persistent: Assess twice yearly—the beginning and end of the school year are logical times.
  - Moderate persistent: Assess 3 times a year, such as at the beginning of the school year, midwinter, and at the end of the school year. This is a responsibility that may be shared with or assumed by a specialist.
  - Severe persistent: Assess 3 or 4 times a year. This is a responsibility that should be shared with or assumed by a specialist.

Assessing Asthma Triggers

- See Chapter 30, Asthma Guidelines: Overview, for discussion about common allergens.
- Most children with asthma also have respiratory allergies that frequently manifest as allergic rhinitis. It is important to collect objective information about these (see the Diagnostic Considerations section in Chapter 29, Allergic Rhinitis).
- Consider treatment and avoidance options with the patient and family, bearing in mind the family's means and ability to make substantial environmental changes.

Treating Associated Conditions

- Atopic dermatitis: See Chapter 43, Recurrent Wheezing in Infants, Toddlers, and Preschoolers.
- Allergic rhinitis: See Chapter 29, Allergic Rhinitis.
- Gastroesophageal reflux disease: A history and physical and/or empirical, time-limited medical therapy is usually sufficient to establish a diagnosis, although objective studies are sometimes indicated. Treatment with acid suppressant therapy—histamine-2 receptor antagonists or proton pump inhibitors—is the most common approach. (See also Chapter 74, Gastroesophageal Reflux and Recurrent Small-Volume Aspiration, and the 2013 AAP Clinical Report on Gastroesophageal Reflux: Management Guidance for the Pediatrician.)
- Obstructive sleep apnea: See Chapter 98, Obstructive Sleep Apnea.

- Obesity
  - — Heath supervision
    - Encourage parents and caregivers to promote healthy eating patterns by offering nutritious snacks, such as vegetables and fruits, low-fat dairy foods, and whole grains; encouraging children's autonomy in self-regulation of food intake and setting appropriate limits on choices; and modeling healthy food choices.
    - Routinely promote physical activity, including unstructured play at home, in school, in child care settings, and throughout the community.
    - Recommend limitation of television and video time to a maximum of 2 hours per day.
    - Recognize and monitor changes in obesity-associated risk factors for adult chronic disease, such as hypertension, dyslipidemia, hyperinsulinemia, impaired glucose tolerance, and symptoms of obstructive sleep apnea syndrome.
  - — Advocacy
    - Help parents, teachers, coaches, and others who influence youth to discuss health habits, not body habitus, as part of their efforts to control excess weight and obesity.
- Sinusitis: This diagnosis should be considered when poorly controlled asthma is not responding to typical therapy.
  - — Clinicians should assign a presumptive diagnosis of acute bacterial sinusitis when a child with an acute upper respiratory infection presents with the following:
    - Persistent illness: nasal discharge (of any quality) or daytime cough or both lasting >10 days without improvement
      or
    - Worsening course: worsening or new onset of nasal discharge, daytime cough, or fever after initial improvement
      or
    - Severe onset: concurrent fever (temperature ≥39°C [≥102.2°F]) and purulent nasal discharge for ≥3 consecutive days
  - — Clinicians should prescribe amoxicillin with or without clavulanate as first-line treatment when a decision has been made to initiate antibiotic treatment of acute bacterial sinusitis. See also the 2013 AAP Clinical Practice Guideline for the Diagnosis and Management of Acute Bacterial Sinusitis in Children Aged 1 to 18 Years.
- Allergic bronchopulmonary aspergillosis: This diagnosis should be considered when asthma is not responding to typical therapy. (See Chapter 44, Allergic Bronchopulmonary Aspergillosis in Asthma.)

Patient Education

- Education and partnership with the patient and family are essential. It is important for the patient and the family to have a clear understanding of how rescue and control medicines address different aspects of asthma pathophysiology and how they differ greatly in response times.
- A picture can be a very helpful teaching aid.
- This education also includes developing a written asthma action plan that should be used as a teaching tool at the end of the encounter. These are available online in a variety of languages (www.rampasthma.org/info-resources/asthma-action-plans).
- The following self-management issues should be addressed:
  - When and where to integrate use of controller medications
  - What should be done at home to reduce allergic triggers and airborne irritants
  - Proper use and maintenance of medication delivery devices, most notably holding chambers with or without a face mask (see Chapter 109, Spacers and Holding Chambers)
- These issues often need to be reinforced at subsequent planned asthma visits.
- Working as a team, support staff can collect relevant data, such as the ACT score and spirometry data, prior to the pediatrician's visit, and educate the patient and/or family in specified areas during a planned asthma visit once an assessment and plan have been made.

Resources for Families

- Allergy and Asthma Network. www.allergyasthmanetwork.org
- Asthma (U.S. Centers for Disease Control and Prevention). cdc.gov/asthma
- Asthma (Medline Plus). nlm.nih.gov/medlineplus/asthma.html

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Chapter 33

Pharmacological Management: Short-Acting β_2-Adrenergic Agonists

Josh Akers, PharmD, BCACP, and Amy Brown, MD, MBe

Introduction

- Short-acting β_2-adrenergic agonists (SABAs) are rapid-acting bronchodilators, administered as a "rescue" medication for respiratory exacerbations that involve symptoms of cough, wheezing, dyspnea, and shortness of breath.
- The differences in response to bronchodilators between infants, children, and adults are not likely due to differences in pharmacological response but are rather due to other issues related to mechanism of airway obstruction, device delivery, or other patient-specific factors.
- SABAs are meant to be used not as chronic therapy but on an "as needed" basis to relieve symptoms.
- Available SABAs include albuterol, levalbuterol, and terbutaline.
  - Albuterol is available as an oral inhalation, injection, and tablet. The most common usage in pediatrics is via oral inhalation.
  - Levalbuterol is only available as an oral inhalation. It is mainly reserved for patients with heart disease or those who have adverse effects of tachycardia with the administration of albuterol.
  - Terbutaline is only available as an injection solution or tablet, not as an inhalation.

Mechanism of Action and Pharmacology

- Bronchodilators work by relaxing smooth muscles in the airways and inhibiting release of rapidly acting hypersensitivity mediators from mast cells.
- SABAs selectively target β_2-adrenergic receptors, a G protein–coupled transmembrane receptor, through agonist binding.
- Selectivity for β_2 is equivalent across the available SABAs.
- Peak effect from inhalation usually occurs in 25–30 minutes.
- Duration of action is generally 4–6 hours.
- Continued stimulation by an agonist may result in desensitization that occurs within 1–2 weeks of regular administration, at which point it levels off, and there may be no further worsening over time.

Indications for Use

- U.S. Food and Drug Administration (FDA)–approved indications for asthma and bronchospasm
  - 2 years of age and older: Nebulized inhalation solutions
  - 4 years of age and older: Hydrofluoroalkane, or HFA, metered-dose inhalers (MDIs)
  - 6 years of age and older: Oral tablets
- Non–FDA-approved indication for asthma and bronchospasm
  - Nebulized albuterol solution is commonly used in young infants who present with onset of first-time wheeze and have a history suspicious for asthma.
  - MDIs with a holding chamber and face mask are often used in children <4 years of age because of ease of use and a faster response.
  - Using appropriate demonstration and teach-back techniques with patients, parents, and/or guardians can ensure appropriate use of medications.
- Terbutaline is FDA approved for children >12 years of age. Typical usage of terbutaline is in the intensive care unit and emergency department settings when inhaled bronchodilators are not tolerated or ineffective—most commonly for severe status asthmaticus.
- Daily administration of SABAs as a preventative approach is not indicated for persistent asthma symptoms.
- If a patient is using a SABA more than 2 days per week, except in the case of prevention of exercise-induced bronchoconstriction (see Chapter 41, Exercise-Induced Bronchoconstriction), then step-up therapy per National Heart, Lung, and Blood Institute asthma guidelines should be considered.

Dosage and Availability

- Several preparations of albuterol are available via different modes of inhalation (ie, ProAir HFA [Teva Respiratory, Frazer, PA] vs ProAir RespiClick [Teva Respiratory]), so ensuring proper technique for each type of inhaler is important. See the "Drug Administration" section in this chapter for more device-specific information.
- Dosage recommendations for routine outpatient use of inhaled agents are found in Table 33-1.
- Oral tablets are not preferred for treatment of asthma because of slow onset of action and increased prevalence of side effects.
- Pirbuterol, previously available as MaxAir Autohaler (Graceway Pharmaceuticals), is no longer available on the market.
- Inhaled albuterol is also formulated as a combination product with ipratropium, an anticholinergic agent.
- Albuterol comes as a racemic mixture of both the (*S*)- and (*R*)-enantiomers. Levalbuterol contains only the (*R*)-enantiomer, which is considered the therapeutically active component.

Table 33-1. Dosages According to Age for Routine Outpatient Use of Inhaled SABAs				
Medication and Delivery Method	**Dose**	**Dosage Administration**		
		<5 Years of Age	**5–11 Years of Age**	**≥12 Years of Age**
Albuterol				
MDI	90 μg/puff, 60 or 200 puffs per canister	2 puffs with valved holding chamber and mask every 4–6 h as needed for symptoms and 5 min prior to exercise	2 puffs as needed every 4–6 h for symptoms and 5 min prior to exercise	2 puffs as needed every 4–6 h for symptoms and 5 min prior to exercise
Nebulizer	0.63 mg/3 mL saline 1.25 mg/3 mL saline 2.5 mg/3 mL saline 5.0 mg/mL saline (0.5%)	0.63–2.5 mg in 3 mL saline every 4–6 h as needed 0.1–0.2 mg/kg in 1–2 mL saline every 4–6 h for bronchopulmonary dysplasia	1.25–5.0 mg in 3 mL saline every 4–8 h as needed	1.25–5.0 mg in 3 mL saline every 4–8 h as needed
Levalbuterol				
MDI	45 μg/puff, 200 puffs per canister	2 puffs with valved holding chamber and mask every 4–6 h as needed for symptoms and 5 min prior to exercise	2 puffs as needed every 4–6 h for symptoms and 5 min prior to exercise	2 puffs as needed every 4–6 h for symptoms and 5 min prior to exercise
Nebulizer	0.31 mg/3 mL saline 0.63 mg/3 mL saline 1.25 mg/0.5 mL saline 1.25 mg/3 mL saline	0.31–1.25 mg in 3 mL saline every 4–8 h as needed	0.31–0.63 mg every 8 h as needed	0.63–1.25 mg every 8 h as needed

MDI, metered dose inhaler.

- Levalbuterol does not appear to have any superior effectiveness or safety over albuterol for acute asthma.
  - Some patients and families note less jitteriness and tachycardia with levalbuterol than with albuterol, but studies typically show no difference in side effects between these medications when provided in equivalent doses.
- In settings of increased inflammation in the outpatient management of bronchospasm, such as virus-induced exacerbations and nocturnal asthma, the usual dose of SABAs may be insufficient to reverse the bronchospasm, and the doses may be increased.
- In the acute management of asthma exacerbations in the home, emergency department, or hospital, doses and frequency may be increased (see Table 33-2).

Drug Administration

- Oral inhalation is the preferred delivery method for SABAs over injections or tablets in respiratory conditions because of decreased incidence of side effects, faster onset of action, and site-specific activity.
- Drug administration device and patient factors affect the delivery of aerosol medications (for both nebulized medications and oral inhalation). See Chapter 106, Small-Volume Nebulizers; Chapter 107, Metered-Dose Inhalers; and Chapter 109, Spacers and Holding Chambers, for details on devices.

Adverse Effects (Most Notable)

- Tremor and/or jitteriness: Incidence, 5%–7% of patients (>12 years of age)
- Central nervous system excitation: Incidence, 20% of patients (ages 2–14 years)
- Headache: Incidence, 5%–7% of patients (>12 years of age)
  - Tachycardia: Incidence, 3%–7% of patients (typically higher incidence from birth to 4 years). Mean heart rate increase of 10–15 beats per minute has been observed.
    - Note: Levalbuterol has lower incidence (3%).

Warnings and Precautions

- Hypokalemia: Albuterol results in an intracellular shift of potassium. This is a transient effect, and no supplementation is generally required, although caution should be taken in hypokalemic patients.
- Bronchospasm: While rare, paradoxical bronchospasm may occur with the use of inhaled bronchodilating agents. This may be a specific formulation effect, not a generalized class effect.
- Frequent use of SABAs in persistent asthma may mask the underlying inflammatory condition. Appropriate stepwise therapy with a long-acting controller medication may be necessary.

Table 33-2. Inhaled SABA Bronchodilator Medication Dosing Chart for Severe Acute Exacerbations (Management in the Home, Emergency Department, and Hospital)

Medication and Delivery Method	Dose	Dosage Administration		
		<5 Years of Age	5–11 Years of Age	≥12 Years of Age
Albuterol nebulizer	0.63 mg/3 mL saline 1.25 mg/3 mL saline 2.5 mg/3 mL saline 5.0 mg/mL saline (0.5% diluted with 2–3 mL of normal saline)	**Home:** 1.25–2.5 mg up to every 20 min with face mask for ≤3 doses, then every 2–4 h as needed **ED:** 0.15 mg/kg (minimum, 2.5 mg) every 20 min 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 via continuous nebulization **Hospital:** 0.15–0.3 mg/kg up to 10 mg every 1–4 h as needed or 0.5 mg/kg/h via continuous nebulization **Bronchiolitis:** 0.15 mg/kg up to 5 mg every 30 min for 3 doses, then every 2 h if patient responds	**Home:** 1.25–2.5 mg up to every 20 min for ≤3 doses, then every 2–4 h as needed **ED:** 0.15 mg/kg (minimum, 2.5 mg) every 20 min for 3 doses, then 0.15–0.3 mg/kg up to 10 mg every 1–4 h as needed or 0.5 mg/kg/h via continuous nebulization **Hospital:** 0.15–0.3 mg/kg up to 10 mg every 1–4 h as needed or 0.5 mg/kg/h via continuous nebulization	**Home:** 2.5–5 mg up to every 20 min for ≤3 doses then every 2–4 h as needed **ED:** 2.5–5.0 mg every 20 min for 3 doses, then 2.5–10 mg every 1–4 h as needed or 10–15 mg/h via continuous nebulization **Hospital:** 2.5–10 mg every 1–4 h as needed or 10–15 mg/h via continuous nebulization
Levalbuterol MDI	45 mg/puff, 200 puffs per canister	See albuterol MDI doses	See albuterol MDI doses	See albuterol MDI doses

Continued

Table 33-2. Inhaled SABA Bronchodilator Medication Dosing Chart for Severe Acute Exacerbations (Management in the Home, Emergency Department, and Hospital), *continued*

Medication and Delivery Method	Dose	Dosage Administration		
		<5 Years of Age	5–11 Years of Age	≥12 Years of Age
Levalbuterol nebulizer	0.31 mg/3 mL saline 0.63 mg/3 mL saline 1.25 mg/0.5 mL saline 1.25 mg/3 mL saline	**Home:** 0.63–1.25 mg up to every 20 min via face mask for ≤3 doses, then every 2–4 h as needed **ED:** 0.075 mg/kg (minimum, 1.25 mg) every 20 min for 3 doses, then 0.075–0.15 mg/kg up to 5 mg every 1–4 h as needed or 0.25 mg/kg/h via continuous nebulization **Hospital:** 0.075–0.15 mg/kg up to 5 mg every 1–4 h as needed or 0.25 mg/kg/h via continuous nebulization	**Home:** 0.63–1.25 mg up to every 20 min for ≤3 doses, then every 2–4 h as needed **ED:** 0.075 mg/kg (minimum, 1.25 mg) every 20 min for 3 doses, then 0.075–0.15 mg/kg up to 5 mg every 1–4 h as needed or 0.25 mg/kg/h via continuous nebulization **Hospital:** 0.075–0.15 mg/kg up to 5 mg every 1–4 h as needed or 0.25 mg/kg/h via continuous nebulization	**Home:** 1.25–2.5 mg up to every 20 min for ≤3 doses, then every 2–4 h as needed **ED:** 1.25–2.5 mg every 20 min for 3 doses, then 1.25–5 mg every 1–4 h as needed or 5–7.5 mg/h via continuous nebulization **Hospital:** 1.25–5 mg every 1–4 h as needed or 5–7.5 mg/h via continuous nebulization
Injectable terbutaline	1 mg/mL saline	**ED:** 0.01 mg/kg up to 0.3–0.5 mg subcutaneously every 20 min for 3 doses, then every 2–6 h as needed	**ED:** 0.01 mg/kg up to 0.3–0.5 mg subcutaneously every 20 min for 3 doses, then every 2–6 h as needed	**ED:** 0.25 mg subcutaneously every 20 min for 3 doses
Intravenous terbutaline			**ED, PICU:** 0.01 mg/kg IV over 1–2 min; continuous infusion starting at 0.001 mg/ kg/min, titrated to effect and heart rate	**ED, PICU:** 0.01 mg/kg IV over 1–2 min; continuous infusion starting at 0.001 mg/kg/min, titrated to effect and heart rate

ED, emergency department; IV, intravenously; MDI, metered-dose inhaler; PICU, pediatric intensive care unit; SABA, short-acting β_2-agonist; VHC, valved holding chamber. All doses are for asthma, unless otherwise indicated. Table 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).* Washington, DC: U.S. Department of Health and Human Services, National Institutes of Health; 2007. https://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines.

- Effects of SABAs may be diminished in patients taking nonselective β-blockers (eg, carvedilol, labetalol, nadolol, propranolol, sotalol).
- Use with caution in patients with seizure disorders, since β-agonists may result in central nervous system stimulation or excitation.

Resources for Families

- Lung Diseases (National Heart, Lung, and Blood Institute). www.nhlbi.nih.gov/health/resources/lung
- Asthma: Parents (U.S. Centers for Disease Control and Prevention). www.cdc.gov/asthma/parents.html

Clinical Pearls

- Proper instruction, including teach-back methods and demonstrations, is necessary to ensure proper adherence to treatment and use of the various SABA devices.
- Review of proper device use and indication at least yearly may be warranted.
- SABAs are the "rescue" inhaler medications used to relieve asthma symptoms. All patients with asthma should be given a written asthma action plan in which details of when to administer SABAs are properly outlined.
- Children and their families should receive education on the proper use and therapeutic function of all of their inhalers (controllers and rescue).
- Have patients bring asthma inhalers to outpatient visits to review the use of rescue and controller medications. Alternatively, reviewing pharmacy dispensation records of albuterol inhalers can reveal possible overuse and/or lack of control of asthma symptoms.
- The Asthma Control Test, Childhood Asthma Control Test, Asthma Control Questionnaire, and Asthma Therapy Assessment Questionnaire are validated assessment tools that can be easily implemented during an encounter to assess current symptom control.
- Albuterol inhaler formulations are most typically covered by insurance at the lowest copay level, although some plans may prefer levalbuterol.

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Chapter 34

Pharmacological Management: Long-Acting β_2-Adrenergic Agonists

Amy Ly, PharmD, Hannah Y. Mak, PharmD, and Amy Brown, MD, MBe

Introduction

- Long-acting β_2-adrenergic agonists (LABAs) (Table 34-1) are used to prevent symptoms of asthma from becoming severe.
- These agents work by stimulating β_2-adrenergic receptors in the lungs to open the airways.
- These agents are not used for quick relief of asthma symptoms. See Chapter 33, Pharmacological Management: Short-Acting β_2-Adrenergic Agonists, for quick-relief medications.
- Two agents, salmeterol and formoterol, are approved by the U.S. Food and Drug Administration (FDA) for use in children ≥12 years of age.
- Children <12 years of age may be prescribed LABAs by their provider on the basis of recommendations by the National Asthma Education and Prevention program.

Table 34-1. Long-Acting β_2-Adrenergic Agonists

Drug	Available Dosages	Formulation
Fluticasone or salmeterol	100/50 µg 250/50 µg 500/50 µg	Dry-powder inhaler
Fluticasone or salmeterol	45/21 µg 115/21 µg 230/21 µg	Metered-dose inhaler
Budesonide or formoterol	80/4.5 µg 160/4.5 µg	Metered-dose inhaler
Mometasone or formoterol	100/5 µg 200/5 µg	Metered-dose inhaler

Mechanism of Action and Pharmacology

- Stimulates β_2-receptors in the lungs to relax airway smooth muscle that inhibits bronchoconstriction

- Onset: 20 minutes
- Peak effect: 1–4 hours
- Duration: ≤12 hours; approximately 5 hours with chronic use
  - Lipophilicity ("lipid-loving" property) of the drug prolongs the retention of LABAs in the lung tissue
- Systemic absorption is minimal; thus, there is low risk for drug-drug interaction
- Dose-dependent adverse effects include tremor and hyperglycemia
- Powder inhalation contains lactose; use caution in children with severe milk protein allergy
- Monitoring:
  - Use of as-needed rescue asthma medications
  - Frequency of exacerbations
  - Lung function tests (ratio of forced expiratory volume in 1 second [FEV_1] to forced vital capacity and FEV_1 precentage predicted)

Indications and Administration

- LABAs are not a first-line medication for treatment of asthma. They should be used adjunctively for maintenance control of asthma.
- LABAs are indicated for use in combination with an inhaled corticosteroid (ICS) (fluticasone, budesonide, mometasone) for long-term control and prevention of symptoms in moderate or severe persistent asthma.
- LABAs are not used as monotherapy because they have been shown to increase the risk of asthma-related deaths and carry an FDA black box warning.
- LABAs are indicated in Step 3 care and higher in children ≥5 years old with poorly controlled asthma who are already taking a low to medium dose of ICS as defined by the National Asthma Education and Prevention Program, Expert Panel 3.
- LABAs are ineffective for acute symptoms of asthma.
- The dose should not exceed 100 mg per day for salmeterol or 24 mg per day for formoterol.
- LABAs can be prescribed in several preparations, including a metered-dose inhaler (MDI) and a dry-powder inhaler (DPI).
- The most commonly used preparation for young children is an MDI. When using an MDI, be sure to instruct the patient and caregiver on the proper use and maintenance of a holding chamber, also known as a "spacer" (see Chapter 109, Spacers and Holding Chambers).
- DPIs have the advantage of not requiring a holding chamber; however, the child must be able to develop sufficient inspiratory flow to activate a DPI to deliver sufficient medication. When using a DPI, be sure to instruct the patient to rinse and spit with water each time after inhaling the dose.

- While studies have shown that young children *can* develop sufficient inspiratory flow to activate DPIs to deliver sufficient medication, there is concern whether they *will* consistently use proper technique on a daily basis, over time. For this reason, many specialists limit DPIs to children at least 8–12 years of age and only after they are able to demonstrate proper technique in the office.

Resources for Families

- How Is Asthma Treated and Controlled? (National Heart, Lung, and Blood Institute). www.nhlbi.nih.gov/health/health-topics/topics/asthma/treatment
- Treatment: Childhood Asthma (Mayo Clinic). www.mayoclinic.org/diseases-conditions/childhood-asthma/diagnosis-treatment/treatment/txc-20193128.
- Know How to Use Your Asthma Inhaler (U.S. Centers for Disease Control and Prevention). www.cdc.gov/asthma/inhaler_video/default.htm

Clinical Pearls

- LABAs are "controller" medications for asthma and should not be used to treat acute asthma symptoms.
- The use of LABAs is never indicated as monotherapy; LABAs should always used in combination with ICS therapy.
- LABAs are indicated for persistent asthma as a step-up therapy when patients are not able to control symptoms with ICS alone.
- Frequent asthma visits with symptom assessment is important for patients with persistent asthma, especially when it is hard to control. If improvement is noted with an ICS and LABA combination, then steps should be taken to continue to step down the LABA treatment, if the patient tolerates it.

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Chapter 35

Pharmacological Management: Inhaled Corticosteroids

Jeffrey M. Kintner, PharmD, and Elizabeth de la Riva-Velasco, MD

Introduction

Inhaled corticosteroids (ICS) are generally considered first-line therapy for all patients with persistent asthma.

Mechanism of Action

- The potent anti-inflammatory activity of ICS is likely related to their broad effect on many aspects of the inflammatory process.
- The primary action of the corticosteroid occurs at the cellular level, where the interaction with the glucocorticoid receptor leads to a reduction in multiple inflammatory substances (cytokines, chemokines, adhesion molecules, inflammatory enzymes, receptors, and proteins).
- Clinically, these actions translate into
  - Reduced severity of asthma symptoms
  - Better asthma control and an improvement in quality of life
  - Improvement in peak expiratory flow and spirometry values
  - Diminished airway hyperresponsiveness
  - Prevention of exacerbations
  - Reduction in systemic corticosteroid courses, emergency department care, hospitalizations, and death

Indications for Use

- ICS are indicated for the maintenance treatment of asthma as prophylactic therapy and are NOT indicated for the relief of acute bronchospasm.
- Both the National Asthma Education and Prevention Program and the Global Strategy for Asthma Management and Prevention guidelines consider ICS to be the superior long-term asthma control medication and are listed as the first-line agents of choice for persistent asthma.

Dosing

- A critical component of asthma management is frequent assessment of asthma control and subsequent adjustments to the therapeutic regimen.

- The goal of therapy is to achieve asthma control while minimizing exposure to medications.
- ICS are available in both a metered-dose inhaler (MDI) and a dry-powder inhaler (DPI); there are advantages and disadvantages to each dosage form.
  - MDI contents are secured in a pressurized aerosol dispenser that is more resistant to changes in temperature and humidity, whereas storage of DPIs is critical to maintain potency.
  - DPIs have the advantage of not requiring a holding chamber. While studies have shown that young children can develop sufficient inspiratory flow to activate DPIs to deliver sufficient medication, there is concern whether children will consistently use proper technique on a daily basis, over time. For this reason, many specialists limit DPIs to children at least 8–12 years of age and only after they are able to demonstrate proper technique in the office.
- Table 35-1 lists ICS doses and corresponding steroid potencies.

Table 35-1. Low, Medium, and High Daily Doses of ICS Products

Steroid or Medication Type	Product Strengths	Age (y)	Low Daily Dose (µg)	Medium Daily Dose (µg)	High Daily Dose (µg)	Typical Dosing
Beclomethasone HFA	40 mg 80 mg	5–11	80–160	>160–320	>320	Twice daily
		≥12	80–240	>240–480	>480	Twice daily
Budesonide DPI	90 mg 180 mg	5–11	180–400	>400–800	>800	Twice daily
		≥12	180–600	>600–1,200	>1,200	Twice daily
Budesonide HFA	160/4.5 mg[ab] 80/4.5 mg[ab]	5–11	ND[c]	ND[c]	ND[c]	ND
		≥12	ND[c]	ND[c]	ND[c]	Twice daily
Ciclesonide HFA	80 mg[b] 160 mg[b]	6–11	ND[c]	ND[c]	ND[c]	ND
		≥12	80–160	>160–320	>320	Twice daily
Flunisolide HFA	80 mg	5–11	160	320	≥640	Twice daily
		≥12	320	>320–640	>640	Twice daily
Fluticasone furoate DPI	100 mg[b] 200 mg[b] 100/25 mg[de] 200/25 mg[de]	6–11	ND[c]	ND[c]	ND[c]	ND
		≥12	100	ND	200	Once daily
Fluticasone propionate DPI	100/50 mg[f] 250/50 mg[f] 500/50 mg[cf] 50 mg 100 mg 250 mg	5–11	100–200	>200–400	>400	Twice daily
		≥12	100–300	>300–500	>500	Twice daily

Table 35-1. Low, Medium, and High Daily Doses of ICS Products, *continued*

Steroid or Medication Type	Product Strengths	Age (y)	Low Daily Dose (µg)	Medium Daily Dose (µg)	High Daily Dose (µg)	Typical Dosing
Fluticasone propionate HFA	115/21 mg[f] 230/21 mg[f] 45/21 mg[f] 110 mg 220 mg 44 mg	5–11	88–176	>176–352	>352	Twice daily
		≥12	88–264	>264–440	>440	Twice daily
Mometasone DPI	110 mg 220 mg	6–11	110–220	220–440	>440	Once or Twice Daily
		≥12	110	≥220–440	≥440	Once daily
Mometasone HFA	100 mg[b] 200 mg[b] 100 mg[ab] 200 mg[ab]	6–11	100–200	>200–400	>400	ND
		≥12	100–200	>200–400	>400	Twice daily

DPI, dry-powder inhaler; HFA, hydrofluoroalkane; ICS, inhaled corticosteroids; LABA, long-acting β_2-adrenergic agonist; ND, no data.

Some of these products are a combination of inhaled corticosteroids and LABAs. The steroid referenced in addition to the LABA is indicated by the footnotes.

[a] Product contains formoterol.
[b] Product not approved for patients <12 years of age.
[c] Product contains salmeterol.
[d] Product contains vilanterol.
[e] Product not approved for patients <18 years of age.
[f] No guideline recommendations for ICS dosage form or specified age group.

Adverse Effects

- ICS have little systemic absorption and are subsequently associated with fewer and less severe adverse effects than orally administered glucocorticoids, which make them favorable chronic asthma control medications.
- However, their use is not completely devoid of adverse effects, which can occur both locally and systemically.
- Using a holding chamber and rinsing the mouth can minimize the risk of systemic and local adverse effects.

Systemic Adverse Effects

- While ICS are intended to act exclusively in the lungs, if a valved holding chamber (for an MDI) or spacer (for a DPI) is not used, approximately 80% of the doses inhaled do not reach their target destination but are deposited in the oropharynx, swallowed, and subsequently absorbed from the gastrointestinal tract.
- Most ICS have poor bioavailability (<1% for ciclesonide to 15% for beclometasone dipropionate) and, when subjected to first-pass metabolism, are converted into inactive metabolites.

- The remaining ICS is free for systemic absorption and is responsible for observed systemic adverse effects (Table 35-2).

Table 35-2. Potential Systemic Adverse Effects of ICS

Adverse Effect	Description
Adrenal suppression	Chronic administration of ICS may reduce cortisol secretion from the adrenal gland via negative feedback inhibition of the HPA axis. The degree of HPA suppression depends on the dose, duration, and frequency of ICS administration. Symptoms include Cushingoid features, anorexia, weight loss, fatigue, growth failure, and hypoglycemia.
Linear growth deceleration	ICS therapy may be associated with an adverse effect on linear growth in children. This adverse effect is dose dependent, occurs in the first several months of therapy, and is generally small and not progressive. This phenomenon may be confounded by the observation that poorly controlled asthma may also delay linear growth. The minor growth risks are considered to be outweighed by the respiratory benefits.
Reduction in bone mineral density	ICS have mild effects on bone mineral density that typically do not reach clinical significance. Children at highest risk are those with chronic disease, malnutrition, or use of long-term medications that reduce bone mineral density.

HPA, hypothalamic-pituitary-adrenal; ICS, inhaled corticosteroids.

Local Adverse Effects

- Table 35-3 shows the most common local adverse effects associated with ICS.
- While not generally as serious as systemic side effects, they have the ability to affect patient quality of life and adherence to treatment and may mask symptoms of more serious disease.
- The incidences of local adverse effects are highly variable and are dependent on the type and/or dose of ICS used, the mode of delivery (MDI vs DPI), the use of valved holding chamber devices, and inhaler technique.

Strategies to Minimize Risks of Adverse Effects

- Recommend the routine use and cleaning of valved holding chambers with all MDIs, especially in children. For younger children who are unable to deeply inhale voluntarily, spacers with face masks are available.
- Advise patients to have the child "rinse and spit" and wash the face after administration of inhaled medications.
- Use the lowest effective dose of ICS that maintains asthma control to reduce unnecessary steroid excess
  - There are few long-term head-to-head comparison studies with sufficient sample sizes to determine whether growth effects might be less with different brands overall or if an individual child might have improved growth if switched from 1 formulation to another.

Table 35-3. Potential Local Adverse Effects of ICS

Adverse Effect	Description
Dysphonia (hoarseness)	Has been reported in 5%–50% of patients using ICS. While the etiologic origin of dysphonia is unclear, it has been suggested that pharyngeal deposition of steroid particles may induce myopathy of vocal cord muscles, subsequently triggering bowing of the vocal folds on phonation. The risk of dysphonia may be dose dependent, and symptoms can be reversed after discontinuation of therapy.
Oropharyngeal candidiasis (thrush)	May result from local deposition of ICS particles on the mucosal surface of the oropharyngeal cavity. Thrush is thought to be the consequence of local immunosuppression or an increase in salivary glucose levels, which may stimulate growth of *Candida albicans*. Symptoms of thrush tend to be mild, and the primary clinical manifestation is local discomfort (altered taste sensation, sore throat, etc); however, the risk of fungemia increases in immunocompromised populations or if left untreated. Thrush can occur in ≤70% of patients using ICS, and risk increases at higher doses, with more frequent dosing, or in patients taking concomitant oral glucocorticoids and/or antibiotics.
Cough	Can occur in >30% of children treated with ICSs, although cough may be difficult to differentiate from poor asthma control. It has been proposed that coughing may be due to the exposure to excipient ingredients (specifically oleic acid) and nonspecific irritating properties of ICS. Dry-powder inhalers typically have a lesser incidence of coughing owing to a larger proportion of fine particles.
Perioral dermatitis	An erythematous, eczematoid eruption that occurs around the mouth, nostrils, or eyes has been described with ICS use, most notably with budesonide. Perioral dermatitis is thought to be due to a direct local effect of ICS on facial skin and occurs infrequently in children. Wash the face after the use of ICS to avoid this side effect. Topical erythromycin or metronidazole should be considered in severe cases.
Tongue hypertrophy	A seldom-reported adverse effect thought to be caused by ICS-induced hypertrophy and local fat accumulation. This phenomenon has been described in infants treated with nebulized beclometasone dipropionate and in asthmatic children treated with nebulized budesonide. Tongue hypertrophy resolves after cessation of ICS treatment.
Thirst sensation	Occurring in >20% of children using ICS, a thirsty feeling after delivery of the drug may be caused by throat irritation or as a manifestation of oral thrush. Combination treatment with a long-acting β_2-adrenergic agonist may increase risk.

ICS, inhaled corticosteroids.

  - Some specialists and limited data suggest that there may be fewer growth effects with either flunisolide or ciclesonide, but the need for more data is urgent.
- Before increasing the ICS dose, assess the following:
  - Inhaler technique
  - Adherence to the prescribed regimen
  - Environmental control measures
  - Whether the addition of a long-acting β_2-adrenergic agonist, antileukotriene agent, or alternative adjunctive therapy to low- or medium-dose ICS should be considered, rather than using high-dose ICS to minimize steroid exposure
  - Whether allergic sensitizations are being assessed and treated appropriately

Resources for Families

- Allergy & Asthma Network. www.allergyasthmanetwork.org
- American Academy of Allergy, Asthma, and Immunology. www.aaaai.org
- American Association for Respiratory Care. www.aarc.org
- American Lung Association. www.lung.org
- Association of Asthma Educators. www.asthmaeducators.org
- Asthma and Allergy Foundation of America. www.aafa.org

Chapter 36

Pharmacological Management: Leukotriene Receptor Antagonists

Amarachi Uzosike, PharmD, and Bindu George, MD

Mechanism of Action

- Antileukotriene agents are also referred to as *leukotriene modifiers.*
- Airflow obstruction in asthma is the result of numerous pathologic processes.
- Inflammatory infiltrates and exudates distinguished by eosinophils, but also including other inflammatory cell types (neutrophils, monocytes, lymphocytes, mast cells, basophils), can fill and obstruct the airways and induce epithelial damage and desquamation into the airway lumen.
- Leukotrienes are potent proinflammatory mediators that can induce bronchospasm, mucus secretion, altered cellular activity, and airway edema.
- Two classes of leukotriene modifiers exist: inhibitors of leukotriene synthesis (5-lipoxygenase inhibitor [5-LOX]) and leukotriene receptor antagonists (LTRAs).
  - Zileuton is the 5-LOX inhibitor used in the management of asthma.
  - Montelukast and zafirlukast are LTRAs used in the management of asthma.
- LTRAs reduce the proinflammatory (increased microvascular permeability and airway edema) and bronchoconstriction effects of leukotriene D4, especially in exercise, aspirin, and allergen-induced bronchoconstriction.

Indications, Administration, and Dosing

- LTRAs are suggested as alternative therapy for mild persistent asthma and as add-on medication with inhaled corticosteroids (ICS) for moderate or severe persistent asthma.
- If a child's asthma is not adequately controlled with ICS alone, either an antileukotriene agent or a long-acting β_2-adrenergic agonist (LABA) may be added. Most studies indicate that overall, the addition of a LABA is more effective, but there are some children for whom the addition of an antileukotriene agent may be the best choice.
- LTRAs have been shown to help prevent exercise-induced bronchospasm (EIB), although most specialists first try pretreatment with albuterol or another short-acting β_2-adrenergic agonist.

- LTRAs are less effective than low-dose corticosteroids.
- They are not used to treat acute exacerbations.
- Montelukast is administered orally as granules mixed with liquid or food or as a chewable or regular tablet.
- Take zafirlukast at least 1 hour before or 2 hours after meals, since administration with meals decreases its bioavailability.
- When choosing an anti-leukotriene agent, montelukast is attractive because it is prescribed once daily (Table 36-1), and monitoring of liver function tests is not routinely needed.

Table 36-1. Dosing of Antileukotriene Agents

Drug	Dosage		
	1–5 Years of Age	6–14 Years of Age	Adolescents
Montelukast	4 mg at bedtime	5 mg at bedtime (6–14 y)	10 mg at bedtime (≥15 y)
Zafirlukast	NA	10 mg twice daily (5–11 y)	40 mg daily (≥12 y)
Zileuton	NA	NA	1,200 mg twice daily (≥12 y)

NA, not applicable.

Adverse Effects

- Dizziness, fever, headache
- Increased liver function enzyme levels
- Churg-Strauss syndrome
- Mood changes, including irritability, depression, and anxiety
  - In 2009, the U.S. Food and Drug Administration issued an alert that children and adolescents may be at increased risk for neuropsychiatric events with antileukotriene agents, including suicide. Since suicide and suicidal behavior are not uncommon in the general adolescent population, the significance of this association has not yet been definitively clarified.
- Nightmares
- Abdominal pain and/or nausea
- Cytochrome P450 system drug interactions, such as theophylline and warfarin (zileuton)

Resources for Families

- How Is Asthma Treated and Controlled? (National Heart, Lung, and Blood Institute). www.nhlbi.nih.gov/health/health-topics/topics/asthma/treatment
- Treatment: Childhood Asthma (Mayo Clinic). www.mayoclinic.org/diseases-conditions/childhood-asthma/diagnosis-treatment/treatment/txc-20193128

Clinical Pearls

- A stepwise approach, in addition to clinical decision-making, should be used to meet individual patient needs.
- Antileukotriene agents are alternative medications used in the treatment of asthma and allergic rhinitis.
- If alternative treatment is selected and well-controlled asthma is not achieved, discontinue the therapy and use the preferred treatment or trial of a different add-on therapy before stepping up the treatment. First assess adherence, technique, and environmental control.
- It is preferable to schedule daily, long-term medications so that they are not taken at school. However, prompt access to medication is essential to treat acute symptoms or to prevent exercise-induced bronchoconstriction that may develop during physical education class, school recess, or organized sports.
- Routine consideration for step down to intermittent therapy should be given to those with well-controlled asthma, especially in children 0–4 years of age.

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Chapter 37

Pharmacological Management: Anticholinergic Agents

Kelsey Hawkins, PharmD, and Bindu George, MD

Introduction

- There are many medications with anticholinergic properties that are approved for a wide variety of indications. Anticholinergic medications can be classified as *(a)* antimuscarinic agents that act on muscarinic acetylcholine receptors and *(b)* antinicotinic agents that act on nicotinic acetylcholine receptors. Inhaled anticholinergic agents are prescribed for children with respiratory disease to decrease airway secretions and/or act as cough suppressants.
- This chapter is limited to a discussion of *inhaled* anticholinergic (antimuscarinic) agents and their role in respiratory disease in children.
- Currently, inhaled anticholinergic agents are approved by the U.S. Food and Drug Administration (FDA) for the treatment of chronic obstructive pulmonary disease (COPD) in adults, and tiotropium is FDA approved for the treatment of asthma in children ≥6 years old.
- Although not all agents are FDA approved, anticholinergic agents have been used off-label in children with asthma and bronchopulmonary dysplasia (BPD).
- Inhaled anticholinergic agents include
  - Ipratropium bromide (short acting)
  - Tiotropium (long acting)
- Several newer inhaled long-acting muscarinic antagonists (LAMAs) have been approved for the treatment of COPD in adults and are being studied in both adults and children for the treatment of asthma. These agents include
  - Aclidinium bromide
  - Umeclidinium bromide
  - Glycopyrrolate

Mechanism of Action/Pharmacology

- Inhaled anticholinergic agents cause bronchodilation through competitive blockade of muscarinic receptors in the airways, resulting in airway smooth muscle relaxation.

- Ipratropium bromide and tiotropium are poorly absorbed across respiratory and gastrointestinal tract membranes, resulting in few to no systemic effects.
- The duration of action for ipratropium is approximately 6 hours; it is therefore referred to as a *short-acting muscarinic antagonist (SAMA)*. The duration of action of tiotropium is approximately 24 hours; it is therefore referred to as a *long-acting muscarinic antagonist (LAMA)*.

Indications and Administration

- Dosage forms include a metered-dose inhaler (MDI), nebulizer solution, and inhaled aerosol solution.
- A holding chamber may be used with an MDI, although this recommendation is not universal. While most asthma specialists recommend that a holding chamber be used with all MDIs, there is lack of agreement regarding clinical effectiveness.
- Potential benefits of a holding chamber include:
  - Decreased need to coordinate actuation with inhalation
  - Improved delivery of medication to the lungs
  - Decreased amount of medication deposited in the oropharynx, minimizing oral and systemic side effects
- If an older child or adolescent consistently demonstrates proper inhaler techniques, a holding chamber may not be necessary.

Treatment and Dosing

- Moderate or severe asthma exacerbations
  - Ipratropium bromide provides added effectiveness when combined with short-acting β_2-adrenergic agonists (SABAs) in moderate to severe acute asthma exacerbations. Ipratropium may be mixed with albuterol in the same nebulizer or given as an MDI in combination with a SABA (Table 37-1).
  - Ipratropium bromide does not improve outcomes in currently hospitalized patients.
  - Ipratropium bromide may be used as an alternative quick reliever in patients who do not tolerate or respond to a SABA.
- Chronic persistent asthma
  - Ipratropium bromide has not shown effectiveness as a long-term controller therapy.
  - Tiotropium has been studied and is approved for children with asthma, but it has not yet been added to national and international guidelines.
    - Tiotropium appears to be helpful as add-on maintenance therapy when inhaled corticosteroids alone are inadequate.
    - Further studies need to be conducted to elucidate the advantages and disadvantages of the addition of a LAMA in childhood asthma.

- Bronchopulmonary dysplasia
  - — Bronchodilator therapy does not improve long-term outcomes in patients with BPD.
  - — Aerosolized ipratropium bromide has been used to treat infants with BPD; however, data are limited to case reports.
  - — There is insufficient evidence to support anticholinergic therapy for the management of BPD.

Table 37-1. Anticholinergic Medication Dosing Chart for Management of Acute Respiratory Symptoms (Hospital or Emergency Department)

Medication	Dosage Form	Administration	
		≤12 Years of Age	≥13 Years of Age
Ipratropium bromide	MDI (HFA): 17 mg per puff (200 puffs per canister)	4–8 puffs every 20 minutes as needed for ≤3 hours	8 puffs every 20 minutes as needed for ≤3 hours
	Nebulizer solution: 0.5 mg/2.5 mL (0.02%)	0.25–0.5 mg every 20 minutes for 3 doses, then as needed	0.5 mg every 20 minutes for 3 doses, then as needed
Ipratropium bromide with albuterol	MDI: 18 mg of ipratropium bromide and 90 mg of albuterol per puff	4–8 puffs every 20 minutes as needed for ≤3 hours	8 puffs every 20 minutes as needed for ≤3 hours
	Nebulizer solution: Each 3-mL vial contains 0.5 mg ipratropium bromide and 2.5 mg albuterol	1.5–3.0 mL every 20 minutes for 3 doses, then as needed	3 mL every 20 minutes for 3 doses, then as needed

HFA, hydrofluoroalkane; MDI, metered-dose inhaler.

Adverse Effects

- Dry mouth
- Dry respiratory secretions
- Blurred vision if sprayed or nebulized in the eyes

Resources for Families

- How Is Asthma Treated and Controlled? (National Heart, Lung, and Blood Institute). www.nhlbi.nih.gov/health/health-topics/topics/asthma/treatment
- Treatment: Childhood Asthma (Mayo Clinic). www.mayoclinic.org/diseases-conditions/childhood-asthma/diagnosis-treatment/treatment/txc-20193128

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Chapter 38

Pharmacological Management: Systemic Corticosteroids

Calvin Huynh, PharmD, and Elizabeth De la Riva-Velasco, MD

Introduction

- Systemic corticosteroids are a U.S. Food and Drug Administration–approved treatment for asthma exacerbations that are most effective when started early in an exacerbation.
- While childhood asthma leads all other medical causes for hospitalization, its treatment, including systemic corticosteroids, is essentially the same as that which would have prevented most hospitalizations had the treatment been administered earlier.

Mechanism of Action

- Asthma is characterized by hyperresponsiveness of the airways to various stimuli, which results in varying degrees of airway obstruction secondary to bronchospasm and inflammation.
- β_2-agonists do not alter the inflammatory component of airway obstruction.
- Anti-inflammatory therapy is essential to relieve airway obstruction that is subresponsive to bronchodilators.
- Corticosteroids block late-phase reaction to allergen, reduce airway hyperresponsiveness, and inhibit inflammatory cell migration and activation.

Indications and Administration

- Systemic corticosteroids are indicated for short-term treatment of acute exacerbations (Table 38-1) to gain prompt control of inadequately controlled persistent asthma when repeated use of bronchodilator therapy leads to incomplete resolution of symptoms.
- Early administration of systemic corticosteroids for acute asthma permits earlier discharge from the hospital, decreases the likelihood of admission of patients for emergency care of asthma, and prevents progression of exacerbation of asthma in ambulatory patients at risk for requiring urgent care.
- Standard therapy for an acute asthma exacerbation is a 5–10-day course of systemic corticosteroids without a taper.
- Onset of action may begin within 1–2 hours of administration.

- Therapy with systemic corticosteroids should be re-evaluated if no improvement is seen within 5 days or if symptoms have not resolved within 10 days.
- Dexamethasone has been shown to be a viable alternative to prednisone or prednisolone, particularly in the emergency department, and has been associated with less nausea and vomiting; however, there are no studies in which extended courses of dexamethasone were used for asthma therapy.

Table 38-1. Dosing of Corticosteroids

Corticosteroid	Formulations	Dosing[a]	Adverse Effects
Prednisone	Tablet: 1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, 50 mg Oral solution: 5 mg/1 mL, 5 mg/5 mL	Doses are for prednisone, prednisolone, and methylprednisolone Infants and children <12 y (oral/IV): 1–2 mg/kg/d in divided doses 1–2 times daily for 5–10 d (maximum, 60 mg/d) Children ≥12 y and adolescents (oral/IV): 40–60 mg/d in divided doses 1–2 times daily for 5–10 d IM methylprednisolone[b] in children ≤4 y: 7.5 mg/kg as a 1-time dose (maximum dose, 240 mg) IM methylprednisolone[b] in children >4 y and adolescents: 240 mg as a 1-time dose	Short-term use: Hyperglycemia Increased appetite Fluid retention Weight gain Mood alteration Hypertension Peptic ulcer Muscle atrophy (IM injection) Long-term use: Adrenal suppression (greater risk with dexamethasone due to longer duration of activity) Growth suppression Dermal thinning Hypertension Diabetes Cushing syndrome Muscle weakness
Prednisolone	Tablet: 5 mg Orally disintegrating tablets: 10 mg, 15 mg, 30 mg Oral solution (as sodium phosphate): 5 mg/5 mL, 15 mg/5 mL, 25 mg/5 mL		
Methylprednisolone (IV formulation available)	Tablet: 2 mg, 4 mg, 8 mg, 16 mg, 32 mg IV injection (as sodium succinate salt): 80 mg/1 mL IM injection (as acetate): 40 mg/1 mL, 80 mg/1 mL		
Dexamethasone (IV formulation available)	Tablet: 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg ,4 mg, 6 mg Oral solution: 0.5 mg/5 mL, 1 mg/1 mL IV injection (as sodium phosphate salt): 4 mg/1 mL, 10 mg/1 mL	Infants, children, and adolescents (oral, IM, IV): 0.6 mg/kg once daily as a single dose or once daily for 2 d (maximum, 16 mg per dose)	

IM, intramuscular; IV, intravenous.

[a] Dosing recommendations are per National Asthma Education and Prevention Program Expert Panel Report 3.

[b] May be used in place of a short burst of oral steroids in patients who are vomiting or if adherence to treatment is a problem; IV administration is preferred in the hospital setting.

- Adverse effects associated with systemically administered corticosteroids occur at greater frequency in comparison to inhaled corticosteroids, owing to systemic delivery and higher doses administered.
- Limited data suggest that repeated short courses of oral corticosteroids (median of 4 courses in the preceding year) for asthma exacerbations in young children do not appear to cause sustained adverse effects related to bone metabolism, bone mineralization, and adrenal function.

Dosing

- Once-daily dosing is preferred to improve adherence to treatment.
- Intravenous methylprednisolone or dexamethasone may be used for patients who are unable to tolerate oral administration or in which gastrointestinal absorption is a concern.
- Corticosteroids are generally continued until resolution of symptoms or until peak expiratory flow is 70% of predicted or personal best (on average about 5 days).
- There is no evidence that tapering the dose after improvement in symptom control and pulmonary function prevents relapse.
- Prolonged therapy with daily oral corticosteroids may be considered in a rare number of children who have failed to achieve adequate control with high-dose inhaled corticosteroids and a long-acting β_2-agonist.
- For patients who require long-term therapy with systemic corticosteroids, the lowest possible dose should be used, and children should be monitored for adverse effects of corticosteroid therapy.
- A gradual taper of corticosteroids over several weeks should be seriously considered for children taking systemic corticosteroid therapy at supraphysiological doses exceeding 14 days or for children who have received multiple courses totaling >3 weeks in the last 6 months to avoid adrenal insufficiency.
- A morning cortisol level may be used to assess the presence of adrenal insufficiency in children who are at risk or in whom symptoms of adrenal insufficiency are present (corticosteroids should be tapered to a physiological dose for at least 1 week prior, and 1–2 doses should be withheld prior to testing for cortisol).

Resources for Families

- How Is Asthma Treated and Controlled? (National Heart, Lung, and Blood Institute). www.nhlbi.nih.gov/health/health-topics/topics/asthma/treatment
- Treatment: Childhood Asthma (Mayo Clinic). www.mayoclinic.org/diseases-conditions/childhood-asthma/diagnosis-treatment/treatment/txc-20193128

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Chapter 39:

Pharmacological Management: Anti–Immunoglobulin E Therapy

David Naimi, MD

Introduction

- Immunoglobulin E (IgE) plays an important role in the pathogenesis of asthma and allergic diseases.
- Most asthmatic patients are atopic, with positive skin test findings for common allergens and detectable allergen-specific IgE in the serum.
- Exposure to allergens to which patients are sensitized can contribute to asthma symptoms.
- Anti-IgE therapy is a recombinant humanized immunoglobulin G1 monoclonal antibody that binds to IgE with high affinity.
- Omalizumab is the first U.S. Food and Drug Administration (FDA)–approved biological therapy for the treatment of asthma and the only available anti-IgE therapy. It is FDA approved for the treatment of allergic asthma and chronic urticaria.
  - — Decreases rates of asthma exacerbations, annualized rates of hospital admission, total emergency department visits, unscheduled doctor's office visits, rescue therapy use, and inhaled corticosteroid dose.
  - — Improves symptom scores, quality of life, and time to first asthma exacerbation.
- More than 200,000 patients with allergic asthma have been treated with omalizumab since its approval in 2003 for people ≥12 years of age. It was approved in 2016 for people ≥6 years of age.

Mechanism of Action/Pharmacology

- Binds to circulating IgE, forming immune complexes that are subsequently cleared by the hepatic reticuloendothelial system.
- Inhibits the attachment of IgE to IgE receptors on mast cells, basophils, and other cell types, which reduces surface IgE receptor levels and the ability of these cells to be activated by allergens.
- Absorbs slowly, reaching peak serum concentrations after a mean of 7–8 days. Serum elimination half-life is approximately 26 days.

Indications and Administration

- Indicated as an additional controller medication in Step 5 and 6 care for patients ≥6 years of age who have allergies and severe persistent asthma (2007 National Asthma Education and Prevention Program asthma guidelines)
- Approved for use in patients with the following characteristics:
  - ≥6 years of age
  - Moderate to severe persistent asthma
  - Asthma symptoms that are inadequately controlled with an inhaled corticosteroid
  - A total serum IgE level between 30 and 700 IU/mL (0.07–1.68 mg/L); dosing tables allow for total IgE level >700 IU/mL (>1.68 mg/L) in younger children 6 to <12 years of age because of their lower weights
  - Some patients (≥12 years of age) with IgE levels >700 IU/mL (>1.68 mg/L) are being treated with omalizumab, but safety and effectiveness in this population have not been well studied, and concern has been expressed for potential risk associated with the formation of immune complexes in patients with very high IgE levels. Allergic sensitization is demonstrated by positive skin test or serum test results for allergen-specific IgE to a perennial allergen (dust mite, animal dander, cockroach, or mold).
- Should be administered via subcutaneous injection by a health care provider in a health care setting prepared to manage anaphylaxis
  - In general, this is accomplished in a specialist's office.
  - A minimum of 3 months is needed to determine the effectiveness for asthma.
  - A 3- to 6-month trial is appropriate.
- Therapy is typically long-term, because it is expected that the effects will wear off within 6–12 months.
- Optimal duration of therapy has not been determined.
- Omalizumab is used by some allergists as adjuvant therapy to enhance tolerance to allergy immunotherapy, including oral immunotherapy for severe food allergies.

Dosage and Availability

- A dose of 75–375 mg is given via subcutaneous injection every 2–4 weeks.
- Dose and dosing frequency are determined by serum total IgE level (measured before start of treatment) and body weight (in kilograms). Adjust the dosing for clinically significant changes in body weight during therapy.
- The cost is approximately $11,000 per patient per year (in U.S. dollars) for a minimum dose (150 mg every 4 weeks) and approximately $65,000 per patient per year for a maximum dose (375 mg every 2 weeks).

Adverse Effects

- Adverse effects include local injection site reactions (44%, similar to those of placebo), urticaria (1%), and serum sickness (few case reports).
- Adverse effects in children 6–12 years of age with asthma include upper respiratory infection symptoms, headache, fever, sore throat, otalgia, abdominal pain, nausea, vomiting, and epistaxis.
- Adverse effects in adults and children ≥12 years of age with asthma include musculoskeletal pain (mainly in the arms and legs), dizziness, fatigue, skin rash, bone fractures, and otalgia. There is a questionable risk of cerebrovascular events (transient ischemic attack, ischemic stroke).
- FDA black box warning: Anaphylaxis and anaphylactoid reactions occur at a rate of 1–2 per 1,000 patients. Because of the risk of anaphylaxis, omalizumab should be administered in a setting prepared to manage anaphylaxis. Observe patients closely for an appropriate interval after administration.
- Omalizumab should not be administered to patients who have experienced a severe hypersensitivity reaction to omalizumab.

Resources for Families

- Omalizumab (Subcutaneous Route) (Mayo Clinic). www.mayoclinic.org/drugs-supplements/omalizumab-subcutaneous-route/description/drg-20065207
- Omalizumab Injection (Nationwide Children's). healthlibrary.nationwidechildrens.org/Library/Encyclopedia/121,80107

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Chapter 40

Immunotherapy

Andrew G. Ayars, MD, and Matthew C. Altman, MD, MPhil

Introduction/Etiology/Epidemiology

- An "allergy" is an immune-mediated hypersensitivity response to an otherwise benign substance, such as aeroallergens, medications, venoms, or foods.
- Both allergic rhinitis and allergic asthma represent some of the most common chronic childhood illnesses in developed countries.
- These conditions cause clinically significant morbidity, including loss of productivity in the workplace or at school and increased treatment-related costs.
- Desensitization is a process by which a diminished responsiveness to an allergen is achieved via repeated administration of an allergen to which a patient is sensitized.
- Immunotherapy is currently the only available therapy that can result in a desensitization to aeroallergens.
  - The treatment is available as subcutaneous or sublingual immunotherapy.
  - Immunotherapy has been shown to be effective in both allergic rhinitis and allergic asthma.
- Venom immunotherapy will not be discussed in this chapter.
- Oral immunotherapy for food allergies is being increasingly studied but will not be discussed in this chapter.

Mechanism of Action

- Immunotherapy alters the underlying immune response to aeroallergens.
- Prolonged administration of immunotherapy has been associated with the following:
  - Induction of regulatory T cells, resulting in suppression of the pro-inflammatory T helper (T_h2 and T_h1) cells
  - Decreased allergen-specific lymphocyte proliferation
  - Decreased specific immunoglobulin E (IgE) and increased specific immunoglobulin G4 response to aeroallergens

Indications

- Allergic rhinitis: Characterized by periodic rhinorrhea, postnasal drip, congestion, and sneezing; often associated with allergic conjunctivitis (itchy, watery eyes)

- Allergic asthma: Characterized by periodic wheezing, chest tightness, cough and/or shortness of breath, and reversible lung obstruction
- Immunotherapy is often indicated in the following patients:
  - Patients with symptoms that are uncontrolled despite medical therapy and environmental controls
  - Those who do not tolerate medications or who would like to try to decrease medication use
  - Those with a documented IgE-mediated hypersensitivity that correlates with the clinical history
- Prescribing immunotherapy
  - Clinicians prescribing immunotherapy should have knowledge of
    - The local aeroallergens prevalent in the area
    - Cross-reactivity between aeroallergens
    - The potential for allergen degradation caused by proteolytic enzymes within aeroallergens
    - Initial dosing and subsequent titration schedules
    - Patient-specific history
    - Patient-specific IgE sensitivities
  - While most immunotherapy is administered in allergy and immunology offices, personnel in a primary care office who are properly trained in administering immunotherapy and treating anaphylaxis can administer this therapy once prescribed by a specialist.
    - This can improve patient access to care.
- Appropriate age for immunotherapy
  - While there is no age cutoff, it is recommended that children should be old enough to understand why they are receiving the injection and are willing participants, given the number of injections needed over the course of a 3–5-year treatment period.
- Figure 40-1 provides an algorithm to help decide whether immunotherapy is appropriate.

Subcutaneous Immunotherapy

- Benefits of therapy
  - Allergic rhinitis
    - Decreases nasal symptoms
    - Decreases ocular symptoms
    - Reduces medication requirements
  - Allergic asthma
    - Therapy leads to a clinically significant reduction in asthma symptoms and medication use.
    - The treatment of children with allergic rhinitis can help prevent the subsequent development of allergic asthma.
  - The clinical benefits of immunotherapy often persist after immunotherapy is discontinued.

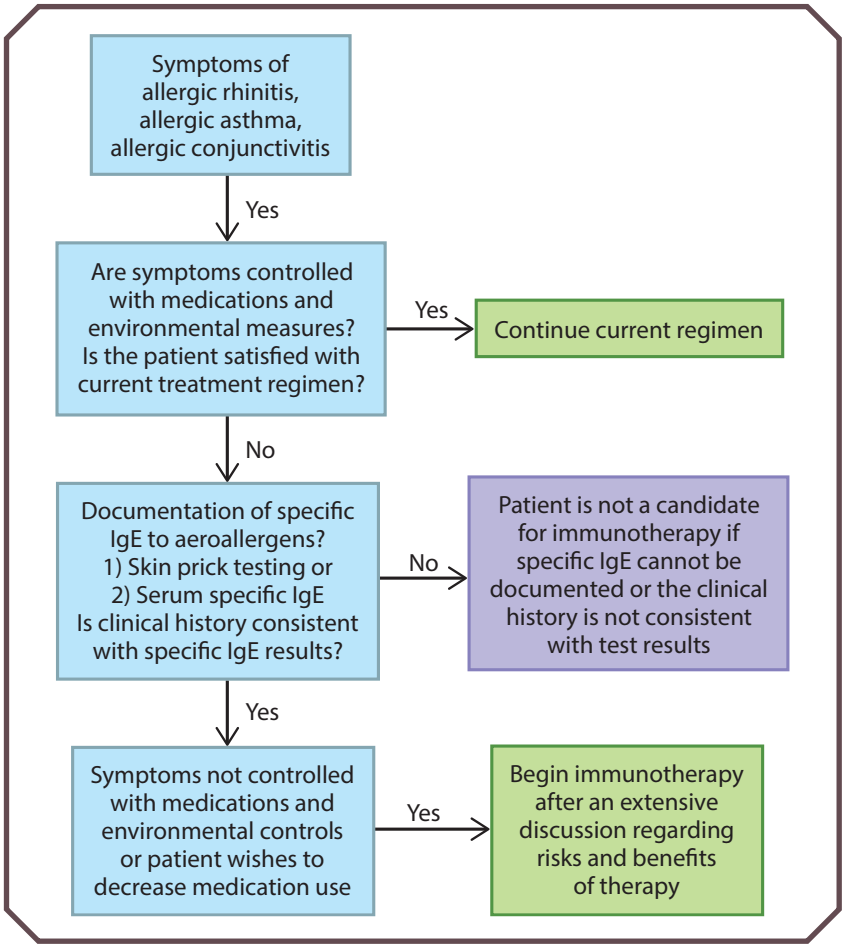

Figure 40-1. Algorithm to evaluate whether a patient is appropriate for immunotherapy. IgE = immunoglobulin E.

- Risks of therapy
  - — Local reactions
    - ▪ Most patients experience local reactions at the site of the immunotherapy injection, such as local erythema, pruritis, and swelling.
  - — Systemic reactions (anaphylaxis)
    - ▪ While the risk is very low, anaphylaxis can occur.
    - ▪ Patients need to remain in the clinic for ≥30 minutes after injections to monitor them for anaphylaxis.
    - ▪ Any clinic that administers appropriate doses of subcutaneous immunotherapy should have experience in the diagnosis and treatment of anaphylaxis and have access to advanced cardiovascular life support.

- Immunotherapy schedules
  - — Buildup phase
    - ▪ Because the risk of administering a substance to which the patient is sensitized has inherent risks, a buildup phase is needed.
    - ▪ A common buildup phase includes 1–3 shots per week to work toward a maintenance dose.
    - ▪ Allergy shots are generally divided up into multiple vials, with each vial 10-fold more concentrated than the last.
    - ▪ Patients receive injections with increasing amounts of antigen from an individual allergen vial.
      - ~ If this is tolerated, then the dose is advanced to a vial that is a 10-fold concentration higher.
    - ▪ While there are variations in the number of vials and doses per vial, most allergy and immunology specialists use similar buildup regimens and maintenance doses.
    - ▪ An example regimen is outlined in Table 40-1 and illustrated in Figure 40-2.
  - — Maintenance phase
    - ▪ Once the maintenance dose is achieved, then injections are given approximately every 4 weeks.
  - — Length of therapy
    - ▪ Treatment is generally administered for at least 3–5 years.
    - ▪ Length of therapy depends on clinical response, severity of symptoms, and patient preference.
    - ▪ There are no clinical or serologic markers that allow prediction of who will experience continued remission of symptoms versus those who will experience a recurrence of symptoms after discontinuation.

Table 40-1. Sample Subcutaneous Immunotherapy Buildup Regimen

Dilution of 1:10,000		Dilution of 1:1,000		Dilution of 1:100		Dilution of 1:10		Dilution of 1:1	
Dose No.	Dose (mL)	Dose No.	Dose (mL)	Dose No.	Dose (mL)	Dose No.	Dose (mL)	Dose No.	Dose (mL)
1	0.05	6	0.05	12	0.05	19	0.05	26	0.05
2	0.10	7	0.10	13	0.07	20	0.07	27	0.07
3	0.20	8	0.15	14	0.10	21	0.10	28	0.10
4	0.30	9	0.20	15	0.15	22	0.15	29	0.15
5	0.50	10	0.30	16	0.20	23	0.20	30	0.20
		11	0.50	17	0.30	24	0.30	31	0.25
				18	0.50	25	0.50	32	0.30

Figure 40-2. Example immunotherapy regimen.

Sublingual Immunotherapy

- Sublingual immunotherapy involves desensitization with oral administration of specific aeroallergens via either tablets or drops.
  - Local side effects include oral itching and mild swelling.
- Sublingual immunotherapy has been effectively used in Europe for many years, and several products have recently become available in the United States.
- In the United States, sublingual immunotherapy for grass allergy has been approved for the adult and pediatric patients, and sublingual immunotherapy for ragweed and dust mite allergies has been approved for adult patients.
- While subcutaneous immunotherapy is thought to be somewhat more effective than sublingual immunotherapy, both are effective treatments.

Resources for Families

- Allergy Immunotherapy: Asthma Shots (American College of Allergy, Asthma, and Immunology). acaai.org/allergies/treatment/allergy-shots-immunotherapy
- Allergen Immunotherapy (Vaccines) (European Academy of Allergy and Clinical Immunology). www.eaaci.org/patients/diagnosis-and-treatment/allergy-specific-treatment/allergen-immunotherapy-vaccines.html
- Allergy Shots (Immunotherapy) (American Academy of Allergy, Asthma, and Immunology). www.aaaai.org/conditions-and-treatments/treatments/allergy-shots-%28immunotherapy%29

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Chapter 41

Exercise-Induced Bronchoconstriction

BreAnna Kinghorn, MD

Introduction/Etiology/Epidemiology

- Exercise-induced bronchoconstriction (EIB) involves acute, transient airway narrowing that occurs during and after exercise.
- EIB is most often defined by ≥10% decline in forced expiratory volume in 1 second (FEV_1) at spirometry after exercise provocation.
- EIB occurs in 90% of individuals with asthma.
- EIB also can occur in individuals without a known diagnosis of asthma.
- Prevalence of EIB is higher in the competitive athlete population (30%–70%) than the nonathlete population (≤10%).

Pathophysiology

- Breathing dry and/or cold air causes airway narrowing via osmotic and thermal consequences of evaporative water loss from the airway surface.
- Dry or cold air in the distal airways causes hyperemia of bronchial vasculature and airway edema, which further causes airway narrowing.
- Airway narrowing causes cough.
- Although the events that trigger EIB and the role of inflammatory cells are not fully understood, a hyperosmolar environment is thought to trigger the release of inflammatory mediators, including histamine, tryptase, and leukotrienes from eosinophils and mast cells.
- Several studies have demonstrated that individuals who are prone to EIB have increased levels of exhaled nitric oxide, increased airway leukotriene levels, greater expression of mast cell genes, and/or peripheral eosinophilia.

Clinical Features

- Clinical manifestations can range from mild impairment to severe bronchospasm and, rarely, respiratory failure.
- Symptoms include coughing, wheezing, chest tightness, and dyspnea.
- More subtle symptoms include fatigue, abdominal discomfort, poor performance, and avoidance of activities.
- Exercise duration for a minimum of 5–8 minutes at 80% of maximum predicted oxygen consumption typically generates bronchospasm.

- Symptoms peak 5–10 minutes after exercise ceases and can last 60–90 minutes.

Differential Diagnosis

(Note: Children may have EIB [Figure 41-1] in addition to any of the disorders listed here.)

- Unrecognized or poorly controlled asthma
- Anxiety

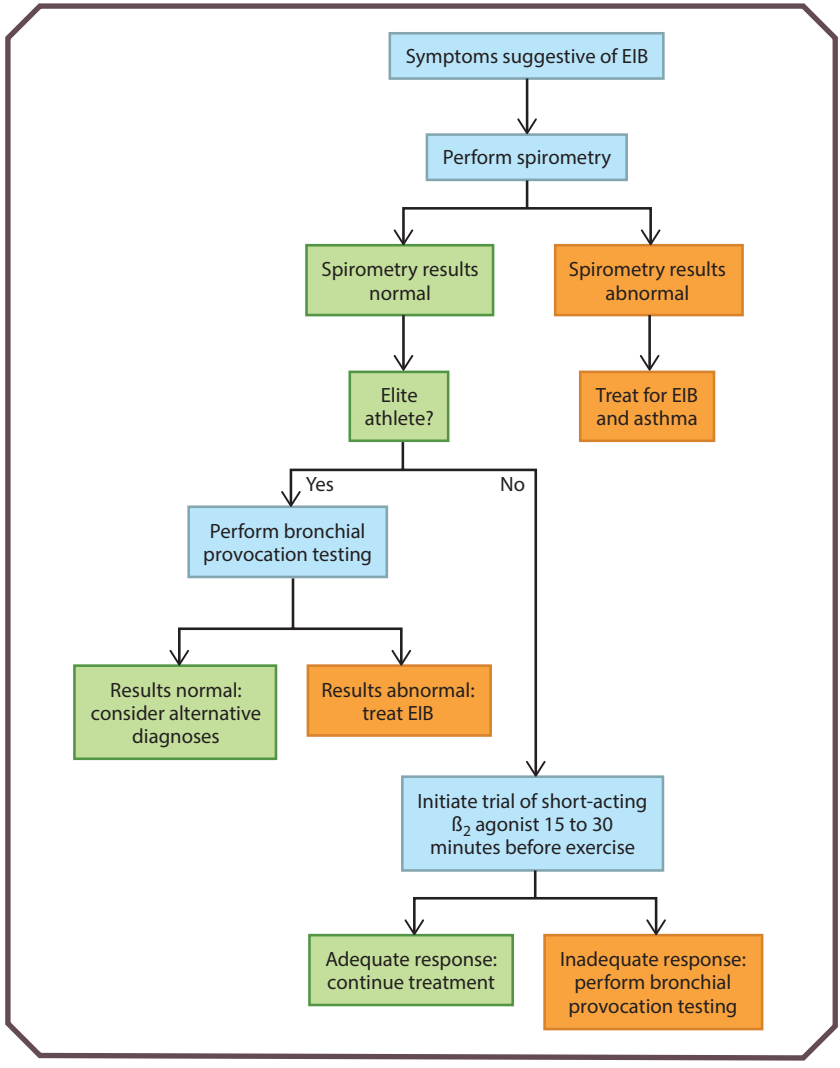

Figure 41-1. Diagnostic flowchart for exercise-induced bronchoconstriction (EIB). Reprinted with permission from Krafczyk MA, Asplund CA. Exercise-induced bronchoconstriction: diagnosis and management. *Am Fam Physician.* 2011;84(4):427–434. Copyright © 2011 American Academy of Family Physicians. All Rights Reserved.

- Deconditioning
- Vocal cord dysfunction
- Exercise-induced laryngomalacia
- Exercise-induced anaphylaxis
- Exercise-induced reflux
- Central airway obstruction arrhythmias
- Pulmonary or cardiac shunt

Diagnostic Considerations

Comprehensive History and Physical Examination

- Obtaining a history alone has been shown to lead to under- and over-diagnosis of EIB.
  - — Rule out other etiologic origins, including vocal cord dysfunction, arrhythmias, and pulmonary or cardiac shunt.
  - — Obtain a complete family history, including asthma or relatives with atopy.

Pulmonary Function Testing

While spirometry is the most important pulmonary function test, there are other tests that can be considered when evaluating a patient with exercise-related respiratory symptoms, including some that are more sensitive and/or less effort-dependent than spirometry alone. For the purpose of this review, discussion will be limited to the use of spirometry in the diagnosis of EIB.

Spirometry

- All patients with suspected EIB should perform spirometry.
  - — Assess the patient for baseline airway obstruction (ratio of FEV_1 to forced vital capacity up to the lower limit of normal for age).

Bronchodilator Responsiveness

- Identify bronchodilator responsiveness, defined as an increase of ≥12% in FEV_1 after inhalation of a short-acting bronchodilator.

Bronchoprovocation Techniques

- FEV_1 decrease ≥10% from a pre-exercise level is diagnostic of EIB, with an FEV_1 decline of ≥50% considered to indicate severe EIB.
- Indirect testing: Exercise, eucapnic voluntary hyperpnea, inhaled powdered mannitol, or nebulized hypertonic saline (see Table 41-1)
  - — Elicits inflammatory response to release mediators and provokes airway smooth muscle constriction
  - — Measurements obtained 5, 10, 15, and 30 minutes after exercise
- Direct challenges: Methacholine or histamine
  - — Acts directly with airway smooth muscle receptors to cause constriction independent of airway inflammation

Table 41-1. Indirect Testing (Performed in a Pulmonary Function Laboratory) for the Diagnosis of Exercise-Induced Bronchoconstriction

Test	Description
Exercise	Laboratory or field based Involves 2 min of warm up to 85% MVV, then sustaining for 6 min FEV_1 measured pre-exercise and at 5, 10, 15, and 30 min after exercise in the laboratory setting FEV_1 measured before and after exercise in the field
Eucapnic voluntary hyperpnea	Voluntary breathing of hypercapnic air (4.5%–5% CO_2, 21% O_2) at 85% MVV for 6 min FEV_1 measured pre-exercise and at 5, 10, 15, and 30 min after exercise
Mannitol	Inhalation of dry powder mannitol with measurement of FEV_1 1 min after inhalation Mannitol dose doubled until FEV_1 change ≥15%, in between dose decrease ≥10% FEV_1 or maximum cumulative dose
Hypertonic saline	Inhalation of 4.5% hypertonic saline with FEV_1 measured every 60 s Repeat dosing until FEV_1 change ≥15%

FEV_1, forced expiratory volume in 1 second; MVV, maximal voluntary ventilation.

Management

Pharmacological and nonpharmacological management strategies are summarized in Box 41-1.

Pharmacological Therapy

- Pretreatment before exercise
  - Short-acting β-agonists
    - First-line treatment for EIB
    - Two puffs 15 minutes prior to exercise
    - Peak bronchodilation at 15–60 minutes, coverage for 3 hours
  - Leukotriene receptor antagonist: Montelukast therapy offers protection against EIB and improvement of decrease of FEV_1 after exercise
    - Onset of action within 2 hours, with continued benefit for ≤24 hours
    - Often suggested in individuals with allergic rhinitis
  - Daily inhaled corticosteroids should be used in patients with refractory or daily symptoms or asthma
    - Long-term control of asthma with anti-inflammatory medication reduces airway responsiveness and frequency and severity of EIB
    - May take 1–2 weeks after therapy initiation to see maximal improvement
- Additional therapies
  - Antihistamine may be helpful in individuals with allergies.

Box 41-1. Management Strategies for Exercise-Induced Bronchoconstriction

Pharmacological	Nonpharmacological
Short-acting β-agonists	Adequate warm-up
Inhaled corticosteroids	Avoidance of triggers
Long-acting β_2-agonists or inhaled corticosteroids	Nasal breathing
Leukotriene receptor antagonists	Mask or face device
Antihistamines	Dietary modifications (based on limited evidence)

- — Long-acting β-agonists are never recommended as single-agent therapy, yet when used in conjunction with an inhaled corticosteroid, they may be superior to inhaled corticosteroids alone in managing EIB.
- — Anticholinergics provide some protection against EIB, yet they are usually not as effective as short-acting β_2-agonists or leukotriene receptor antagonists.

Nonpharmacological Therapy

- Since the degree of EIB is often related to the patient's depth and rate of breathing (minute ventilation), patients who are poorly conditioned may have higher rates of EIB.
  - — Recommend aerobic exercise throughout the year, even during the "off season."
- Interval or combination warm-up exercise: Warming up prior to exercise releases catecholamines such as norepinephrine and epinephrine, which are bronchodilators.
  - — Pre-exercise warm-up may attenuate bronchoconstriction by inducing a "refractory period," which typically lasts 2 hours.
- Nose breathing warms, filters, and humidifies the inspired air, which reduces airway cooling and dehydration.
  - — Since many patients with EIB also have allergic or nonallergic chronic rhinitis, therapy that helps decrease nasal congestion and inflammation can often help decrease EIB.
- Use of a face device, such as a mask or scarf, warms and humidifies the inspired air.
- Dietary modifications (based on limited evidence) include the following:
  - — Low-salt diet
  - — Fish oils
  - — Ascorbic acid

When to Refer

- Refer athletes with suspected EIB for spirometry and bronchoprovocation techniques. Competitive athletes will require documentation for medication use during organized sports activities.
- Refer any patient, regardless of athletic status, with suspected EIB who does not achieve satisfactory prevention of symptoms with pre-exercise treatment with short-acting β-agonists.
- All patients with suspected EIB should perform spirometry.

Resources for Families

- Exercise and Asthma (American Academy of Pediatrics). www.healthychildren.org/English/health-issues/conditions/allergies-asthma/Pages/Exercise-and-Asthma.aspx
- Exercise-Induced Asthma (KidsHealth). kidshealth.org/en/parents/exercise-asthma.html

Chapter 42

Recurrent Croup and Bronchitis

John Welter, MD

Recurrent Croup

Introduction/Etiology/Epidemiology

- Croup is a viral illness that causes inflammation of the upper airway, which leads to upper-airway obstruction that manifests as barky cough and stridor.
- Recurrent or atypical episodes of croup have many causes and should be distinguished from typical viral croup (see Table 42-1).
  - — Croup (acute laryngotracheitis)
    - Viral infection of the larynx, trachea, and/or bronchi (most commonly caused by parainfluenza)
    - Typically, viral upper respiratory tract symptoms followed by barky cough, hoarse voice, and stridor
    - Symptoms typically last 2–3 days
    - Symptoms often worse at night
  - — Recurrent croup
    - Not a specific diagnosis, has many causes
    - Recurrent episodes of barky cough, hoarse voice, and stridor
    - More than 2 episodes of croup per year, often atypical
    - Presence should prompt evaluation for underlying etiologic origin
    - Viral illnesses can unmask the underlying cause

Table 42-1. Differences Between Croup and Recurrent Croup

	Croup	Recurrent Croup
Age	Commonly 6 mo to 3 y of age, uncommon over 6 y of age	Any age
Time of year	Viral illness season (fall, winter)	Any time of year
Duration	1–2 days	May last days to weeks, symptoms may persist between episodes
Response to treatment	Symptoms typically resolve	Partial or no response

Clinical Features

- Stridor occurs during acute episodes.
  - Timing in the respiratory cycle can help distinguish the type of obstruction.
    - Inspiratory: Supraglottic obstruction
    - Biphasic: Glottic and/or subglottic obstruction
    - Expiratory: Tracheal obstruction
- Pharyngeal cobblestoning may be seen in allergic rhinitis and gastroesophageal reflux (GER).
- Wheezing is an indication of lower airway involvement, such as asthma.
- Reduced air entry may indicate an airway foreign body.
- It has been reported that ≤50% of children with subglottic hemangiomas have a facial or neck (beard distribution) cutaneous hemangioma.

Differential Diagnosis

- Recurrent croup should prompt obtaining a patient history to identify underlying airway abnormalities.
  - Birth history: Intubation in the neonatal period may cause subglottic stenosis that is manifesting as recurrent croup episodes.
  - Onset: Early onset before 6 months of age raises suspicion for congenital abnormalities such as tracheomalacia, subglottic hemangioma (which is often steroid responsive), or congenital subglottic stenosis. However, all of these etiologic origins can be causes of recurrent barking cough at any age.
  - Quality and volume of voice and crying: A weak cry and/or hoarse voice can be a sign of vocal cord paralysis.
  - Dysphagia, recurrent chest infections, and episodes of prolonged cough: These symptoms may be a sign of a vascular ring or other external thoracic compression of the trachea.
  - History of foreign-body aspiration: Bronchial foreign bodies may manifest as recurrent croup and are often associated with delayed diagnosis.
- Recurrent croup should also prompt obtaining a patient history to identify associated disorders.
  - GER: Symptoms of GER are often present in patients with recurrent croup (occurring 47%–100% of the time).
    - Episodes may improve with treatment; however, the incidence of GER is so high in patients with recurrent croup that other potential etiologic origins should only be discarded with caution.
  - Asthma and atopy: Between 40% and 80% of patients with recurrent croup have been reported to have symptoms of asthma and allergies.
  - Family history: Children who have a parent with a history of croup are 4.1 times as likely to have recurrent croup than a child whose parents have not had croup.

Diagnostic Considerations

- Radiographic studies
  - On chest radiographs, look for mass effect on the airway, caused by anomalies such as mediastinal masses and radiographically opaque foreign bodies (Figure 42-1).
  - Barium esophagography can be used to identify thoracic abnormalities that are causing esophageal and tracheal compression, such as vascular rings, cysts, or neoplasms.
  - Computed tomography (CT) or magnetic resonance (MR) imaging of the chest can be used to determine whether mass effect is seen on the airway, suggesting possible vascular ring or mediastinal mass.

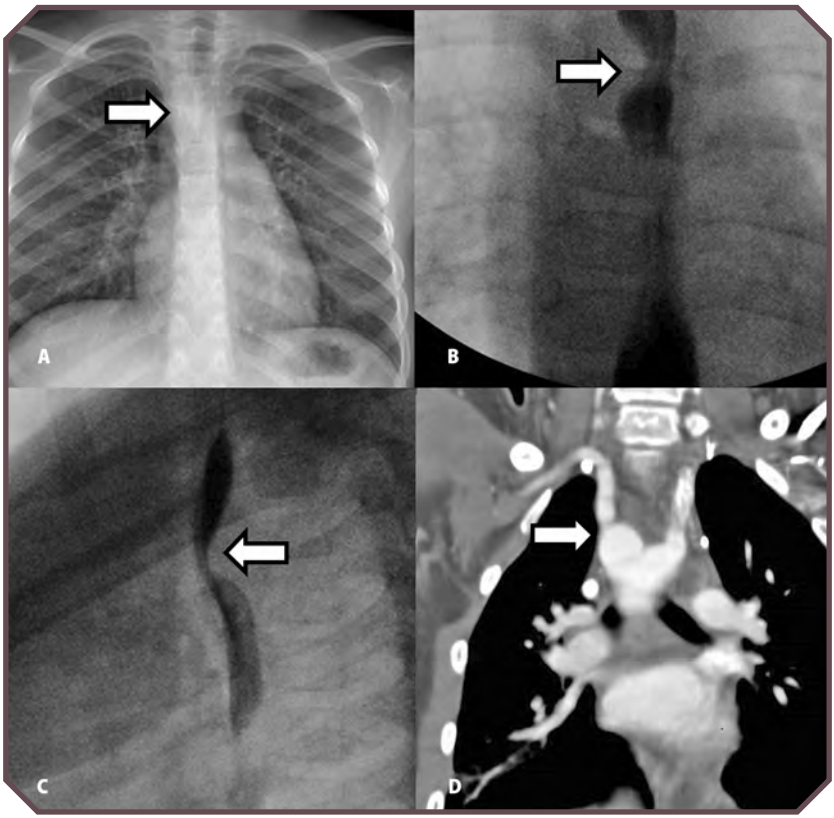

Figure 42-1. Vascular ring in a 4-year-old boy. A. Frontal chest radiograph shows mass effect on the right side of the trachea, suggesting a vascular ring (arrow). B. Frontal and C. lateral views from barium esophagraphy demonstrate mass effect on the esophagus at the level of the aortic arch (arrows). D. Coronal reformatted contrast-enhanced computed tomographic image confirms a right arch (arrow on D) with aberrant left subclavian artery.

- Laryngoscopy
  - Pro: Laryngoscopy can be performed in the ear, nose, and throat office without sedation.
  - Con: The subglottic region and trachea cannot be evaluated.
  - Laryngomalacia, glottic abnormalities, and signs of GER may be identified.
  - The presence of laryngomalacia does not rule out distal airway abnormalities (below the vocal cords).
- Rigid and flexible bronchoscopy performed with anesthesia
  - Subglottic, tracheal, and bronchial lesions may be identified, and bronchoscopy is essential for the diagnosis of tracheomalacia.
  - With rigid bronchoscopy, tracheomalacia may be underestimated or missed. Flexible bronchoscopy may cause tracheomalacia to be missed, as well, unless it is performed with minimal or light anesthesia in a spontaneously breathing patient.
  - Flexible bronchoscopy may cause subglottic hemangiomas to be missed.
  - Rigid bronchoscopy can be both diagnostic and therapeutic (ie, removal of foreign bodies).
- Pulmonary function testing
  - In older children (typically >5 years of age, but some younger patients may be able to perform testing adequately), inspiratory flows and flow volume loops can help determine the presence, degree, and site of upper-airway obstruction.

Treatment

- Assess the response to corticosteroids—most commonly dexamethasone—and nebulized epinephrine; consider further evaluation in patients with poor response.
- Assess the patient for asthma and optimally treat both asthma and allergic rhinitis if present (see Chapter 29, Allergic Rhinitis).
- Other treatment is based on the underlying condition.

When to Refer

- Frequent croup (>2 episodes per year)
- Atypical croup
  - Age <6 months or >3 years
  - Prolonged episodes beyond 1–2 days
  - Hospitalization required, especially for respiratory failure
  - No response to standard treatment
- Chronic respiratory symptoms between croup episodes
  - Weak cry, hoarse voice
  - Chronic cough
  - Frequent lower respiratory tract infections
- Suspicion of foreign-body inhalation

Recurrent Bronchitis

See also Chapter 43, Recurrent Wheezing in Infants, Toddlers, and Preschoolers.

Introduction/Etiology/Epidemiology

- Cough is one of the most common reasons parents bring their children for medical care.
- Bronchitis manifests as a wet bronchial cough and possibly wheezing caused by both infectious and noninfectious bronchial inflammation.
- Recurrent bronchitis encompasses multiple diseases and is not itself a disease entity.
- More than 2 episodes of cough lasting >10 days should prompt obtaining a further history and evaluation aimed at determining the underlying cause.

Differential Diagnosis

- By definition, asthma is a form of bronchitis (see Chapter 30, Asthma Guidelines: Overview).
  - — While asthma is the most common reason for recurrent bronchitis and therapy directed toward asthma is often successful, asthma can also be overdiagnosed. Without wheezing, it can be dangerous to assume that all children with recurrent coughing have asthma. Lack of response to asthma treatment should prompt evaluation for other causes of recurrent bronchitis.
- Premature infants with subsequent bronchopulmonary dysplasia are prone to prolonged cough and wheeze with viral illnesses that may or may not be inflammatory in nature.
- History of recurrent mild respiratory tract infections (ie, sinusitis, ear infections) or >1 serious systemic infection may be an indication of an immune deficiency.
- Classic cystic fibrosis (CF) typically manifests as failure to thrive, symptoms of fat malabsorption, and chronic cough that is typically responsive to antibiotics. However, some patients may not have symptoms of fat malabsorption.
- Primary ciliary dyskinesia was previously referred to as *immotile cilia syndrome*.
  - — Most patients with primary ciliary dyskinesia have a history of chronic or recurrent otitis and/or sinusitis.
  - — While still considered rare, mild cases have been increasingly recognized with symptoms attributed to asthma for many years, even into adolescence or adulthood.
- Foreign-body aspiration may not elicit a history suggestive of aspiration, which could delay diagnosis.
- Extrinsic airway compression, such as vascular rings, can be associated with dysphagia at times, but not always. Extrinsic airway compression

leads to poor bronchial airway clearance and difficulty clearing lower respiratory tract infections.
- In chronic aspiration, neurological weakness or laryngeal anatomic abnormalities can lead to chronic aspiration that places children at risk for recurrent bronchitis.
- Bacterial bronchitis is not common in pediatric patients; however, children with a wet cough for >4 weeks may have evidence of lower-airway bacterial infection at bronchoscopy that is responsive to antibiotics (protracted bacterial bronchitis).

Diagnostic Considerations

- Consider further diagnostic studies as dictated by the clinical history or if the patient has prolonged or severe episodes that are not responsive to therapy.
- Pulmonary function testing is extremely helpful; it can be used to identify airway obstruction, as well as responsiveness to bronchodilators such as albuterol, which is consistent with the diagnosis of asthma.
  - If pulmonary function shows an obstructive pattern after the use of inhaled albuterol, it is less likely that recurrent bronchitis can be attributed to asthma alone and should prompt a more extensive workup.
- Radiographic studies may be performed.
  - Chest radiography may be used to identify hyperinflation associated with either upper- or lower-airway obstruction, as well as signs of bronchial inflammation or atelectasis.
  - If extrinsic airway compression is suspected, barium esophagography may be performed to evaluate the presence of possible vascular ring.
  - There is a trend for pediatric radiologists to recommend MR arteriography instead of barium esophagography to evaluate the presence of a possible vascular ring, depending on local resources, including adequate anesthesia support.
  - Perform modified barium swallow or flexible endoscopic evaluation of swallow if concerns for aspiration exist.
    - Recurrent aspiration can occur in children who appear otherwise normal neurologically.
  - Perform CT of the thorax if there is concern for possible bronchiectasis.
- Laboratory studies
  - Allergy testing
  - Immunology studies
- Sweat test
  - Still the standard of reference when ruling out CF
  - Should always be performed at a Cystic Fibrosis Foundation–accredited laboratory
- Flexible or rigid bronchoscopy

Treatment

- Treatment of recurrent bronchitis is aimed at the underlying diagnosis.

When to Refer

- Refer the patient to a specialist if there is difficulty establishing the diagnosis.
- Refer if specialized testing, such as bronchoscopy, is needed.
- Refer for interpretation of abnormal pulmonary function test results.
- Refer if the patient is not responding adequately to therapy, particularly if coughing is not resolved within 2–3 weeks at most and/or if a child has a chronic cough, even if mild in nature, in between episodes.

Clinical Pearls

- Barium esophagography is technically dependent, and the radiologist should be alerted to the concern for thoracic compression of the trachea, such as a vascular ring. Many pediatric radiologists suggest MR imaging, MR arteriography, or chest CT, since these modalities provide more information than barium esophagography. In young children, this may vary, depending on resources and availability of pediatric anesthesiology.
- If there is clinical suspicion for CF, then further evaluation, such as sweat testing, should be pursued, even if there is a negative newborn screening result.

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Chapter 43

Recurrent Wheezing in Infants, Toddlers, and Preschoolers

Miles Weinberger, MD, FAAP

Introduction

- *Bronchiolitis* is the name given to the first episode of symptomatic airway obstruction in infancy and is associated with lower respiratory tract infection.
- The affected infant typically presents with increased work of breathing manifested by retractions and associated with polyphonic wheezing heard audibly, with or without a stethoscope.
- The term *bronchiolitis* should not be applied to repeated episodes of wheezing that are seen in infants and toddlers with an asthma phenotype.
- Asthma includes several phenotypical disorders that share a common end-organ pathway, characterized by an increased responsiveness of the trachea and bronchi to various stimuli and manifested by a widespread narrowing of the airways that changes in severity, either spontaneously or as a result of therapy.

Pathophysiology

- Bronchial smooth muscle constriction causes narrowing of the airways.
- Airway inflammation in predisposed individuals with mucosal edema and mucous secretions results in decreased lumen diameter of the airways.
- Airway responsiveness to various stimuli increases.
- Airway obstruction results from inflammation and bronchospasm.
- Evidence for a defect of innate immunity related to deficient airway epithelial interferon production seems to be why common cold viruses, rhinovirus, respiratory syncytial virus, coronavirus, and others cause infection and inflammation of the lower airways, whereas those without such a defect have only typical upper respiratory symptoms commonly associated with a cold.

Clinical Features

- The sequence of symptoms during an exacerbation (which may or may not progress beyond cough and/or wheezing) are as follows.
  - Rhinorrhea
  - Cough
  - Wheezing, an expiratory musical sound
  - Increased work of breathing, manifested by intercostal, suprasternal, and substernal retractions
  - Hypoxemia from continued perfusion of poorly ventilated areas of the lung that result from areas of increased airway obstruction
  - Respiratory failure manifested by increased P_{CO_2}
  - Asphyxia and death
- Symptoms vary greatly in severity, from mild to life-threatening.
- Frequency of symptoms varies greatly, from occasional to frequently episodic to continuously persistent.

Differential Diagnosis

- Protracted bacterial bronchitis, an infection in the peripheral airways from the same bacteria that causes otitis media, is primarily seen in infants and toddlers; it is commonly associated with airway malacia, which may be an important contributing mechanism.
- Cystic fibrosis (see Chapter 67, Cystic Fibrosis) is a congenital disease caused by a defect in innate immunity of the airways that results in chronic bacterial infection, with inflammation and viscous mucous that interferes with airway clearance.
- Primary ciliary dyskinesia (see Chapter 70, Primary Ciliary Dyskinesia) is a congenital disease that results in absent ciliary mucous airway clearance.
- Anatomic causes of cough and/or wheeze include tracheal or bronchial malacia and intra-airway polyps.

Diagnostic Considerations and Characterizing the Clinical Pattern

- Obtain a careful and detailed history, including
  - Age of onset of symptoms
  - Description of symptoms
  - Duration of symptoms if currently symptomatic
  - Chronic and persistent or intermittent clinical pattern
  - Frequency of symptomatic periods if not persistent since onset
  - Duration of symptoms when they occur
  - Presence of related comorbidities
    - Atopic dermatitis
    - Immunoglobulin E (IgE)–mediated food allergies

- Diagnosis of asthma is supported by complete response of current symptoms to an observed initial administration of an inhaled bronchodilator such as albuterol, but failure to respond to a bronchodilator does not exclude the diagnosis of asthma, since albuterol has no effect on the airway obstruction from airway inflammation.
- The diagnosis of asthma is supported by complete response of current prolonged or increasing symptoms to a short course (7–10 days maximum) of an oral corticosteroid.
- Response to a prolonged course of an inhaled corticosteroid is not a reliable means of establishing the diagnosis.
- Once the diagnosis is confirmed, use the obtained historical information to identify common asthma phenotypes present in the preschool child on the basis of the clinical pattern.
  - The recurrent viral respiratory infection (VRI)–induced pattern of asthma has a complete clearing between acute episodes.
    - This is the most common asthma phenotype, particularly in the preschool-aged child.
    - Fall and spring exacerbations are most common because of the seasonality or the common cold viruses.
    - These children are typically much more free of symptoms during the summer months, when VRIs are less frequent.
    - There is no evidence for chronic airway inflammation from asthma for most children during extended periods when they are completely asymptomatic.
  - A chronic, persistent phenotype is less common in this age group and is most likely associated with development of inhalant allergy from allergen-specific IgE.
  - The atopic triad is a distinct phenotype that manifests early with atopic dermatitis, commonly has allergen-specific IgE to foods (eggs and cow milk most common) in infancy, frequently manifests inhalant allergy early, and has a chronic and persistent pattern of asthma.
  - Identification of allergen-specific IgE by means of allergy skin testing or appropriate blood tests is important for children with persistent symptoms (Figure 43-1).

Management

- Inhaled bronchodilator with a β_2-agonist such as albuterol, administered with a valved holding chamber (Figure 43-2), is the initial treatment for relief of acute wheezing, cough, and dyspnea.
  - Repeating use when needed is appropriate, but a bronchodilator has no disease-modifying properties beyond relief of acute symptoms.
  - Scheduled repetitive use has no therapeutic advantage over as-needed use and may promote down-regulation of the β_2-receptor.

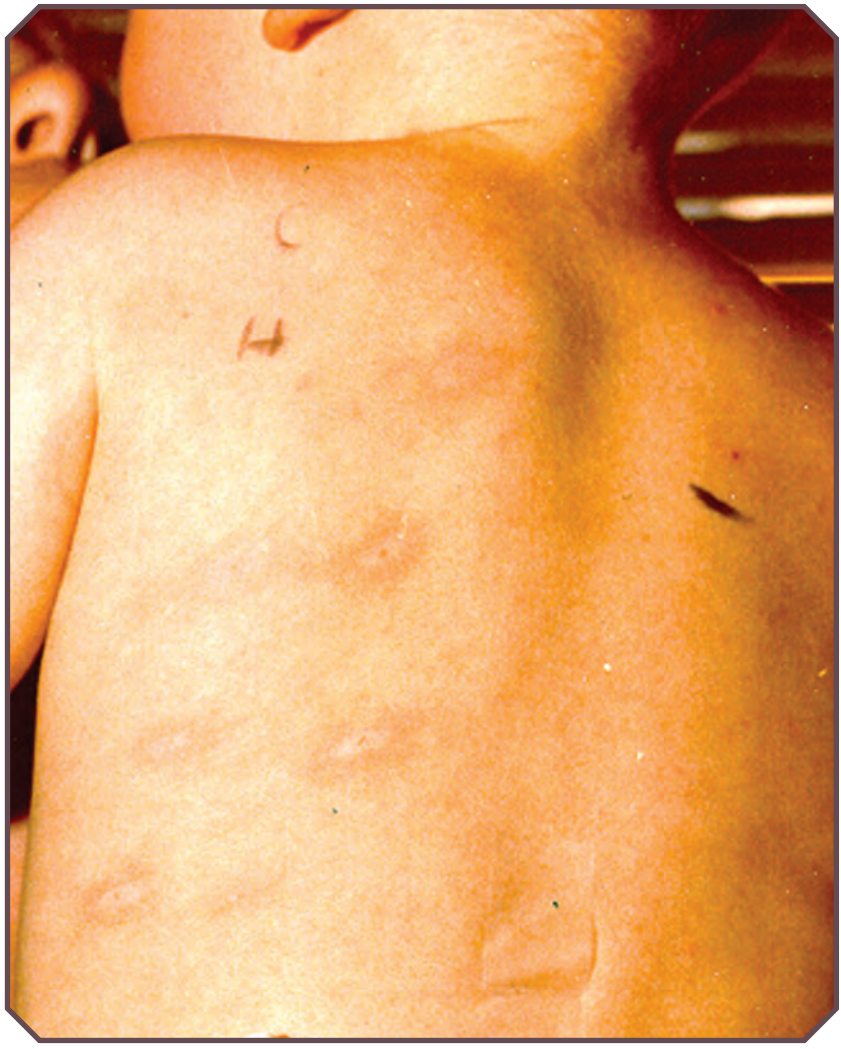

Figure 43-1. Skin test in an 11-month old infant. This infant was hospitalized at 9 months of age with severe acute asthma preceded by rhinoconjunctivitis during the peak of the grass pollen season in a Northern California valley area. At skin testing, the typical wheal and flare of the multiple related species of grass pollen native to that area are seen 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 test results on the right side of the back for other common inhalant allergens were all negative.

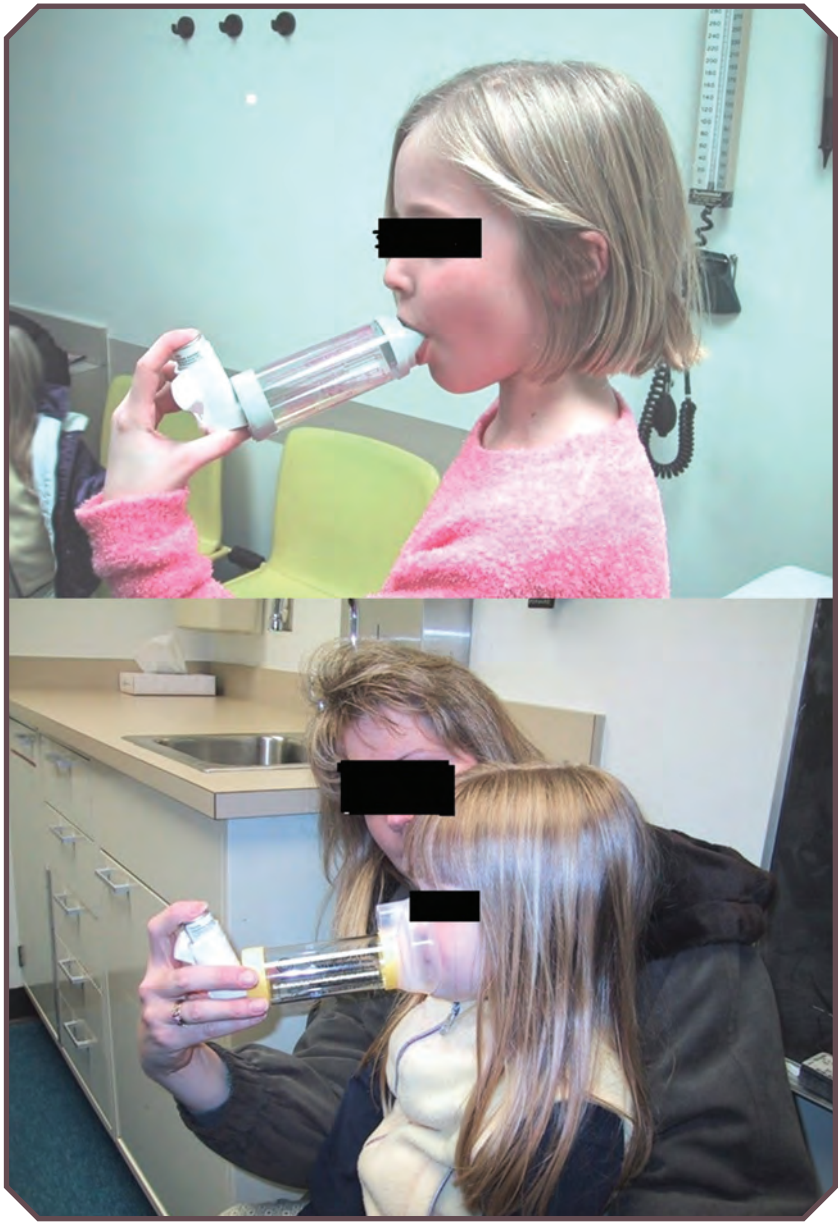

Figure 43-2. Demonstration of inhaled medication from a metered-dose inhaler (MDI) with a valved holding chamber in a preschool-aged child (upper photo) and with a face mask in a toddler (lower photo). The MDI injects aerosol into the chamber with a one-way valve that permits inhalation of the medication from the chamber while exhalation occurs into the ambient air. Four to 6 actuations of albuterol (90 µg per actuation) in this manner with at least 3–4 breaths after each actuation to evacuate the chamber provides bronchodilator effectiveness equivalent to 2.5 mg of albuterol via open nebulizer, with greater convenience and lower cost.

- If sufficiently symptomatic (troublesome cough or labored breathing), clear with a short course of an oral corticosteroid; a systemic corticosteroid is disease modifying, since it decreases inflammation, which secondarily decreases airway hyperresponsiveness.
  - Traditional dosing (milligrams per kilograms of body weight per day), while appropriate for older children, serves to underdose small children.
  - A higher dose provides more rapid onset and greater degree of effect; twice-daily dosing of prednisolone appears to be more reliable for quickly relieving an exacerbation than once-daily dosing.
- Empirically determined dosage with apparent optimal effectiveness is 15 mg twice daily for infants, 20 mg twice daily for 1–3 years of age, and 30 mg twice daily for >3 years of age; while lower doses may be adequate for some children with some exacerbations, these doses appear to provide the greatest likelihood of maximal effect. If dexamethasone is used, one-fifth of the dose in milligrams is equivalent.
- If clearing doesn't occur with the oral corticosteroid, consider an alternative diagnosis and referral to a pediatric pulmonologist.
- If symptoms completely clear with the oral corticosteroid, follow up closely and start an inhaled corticosteroid at the first sign of symptoms returning in the absence of an apparent VRI.
- Because exacerbations are predominantly from VRIs (common cold viruses), which are quite common in preschool-aged children, provide a plan and measures to treat exacerbations prior to the need for emergency care and hospitalization.
- Although acute VRI-induced exacerbations of asthma are commonly misdiagnosed as pneumonia, antibiotics are rarely indicated.
- Educate parents about the sequence of symptoms associated with VRI-induced exacerbations.
  - Nasal symptoms are the most common initial symptom but cannot be used reliably to predict subsequent increased severity.
  - Troublesome cough (cough affecting sleep and/or activity, often recognized as "asthma cough") is the most reliable predictor of progression to increased work of breathing.
  - Use troublesome cough as an indication to begin oral corticosteroids for patients at risk for emergency care or hospitalization on the basis of prior history.
  - If an oral corticosteroid was not started for troublesome cough, administer one immediately if symptoms progress to increased work of breathing.
- Since inhaled corticosteroids, even in high doses, don't reliably prevent progression of exacerbations that cause emergency care visits and hospitalizations, oral corticosteroids should be provided for VRI-induced exacerbations, at least for children who have previously experienced emergency department visits and hospitalization from exacerbations of their asthma.

- Provide the patient's parents and caregivers with information regarding asthma and its treatment (see uichildrens.org/health-library/managing-asthma-patients-and-families).
- Provide printed instructions (an action plan) for beginning oral corticosteroid treatment of an exacerbation.
- Monitor criteria for control at regular follow-up visits.
  - — Absence of wheeze or chronic cough
  - — Rare interference with activity
  - — Rare interference with sleep
  - — Use of bronchodilator for symptom relief no more than twice weekly
  - — No use of oral corticosteroids for exacerbations other than acute VRI-induced ones

Treating Associated Conditions

Rhinitis

- Rhinitis is the most common associated condition.
- Rhinorrhea is associated with symptoms from a cold caused by the same virus that triggers asthma; oral medications are of little value for rhinorrhea from a VRI.
- Ipratropium nasal spray stops rhinorrhea from a VRI but doesn't otherwise alter the clinical course of the cold.
- Allergic rhinitis, which is less common in this age group than rhinorrhea from a cold virus, includes symptoms of rhinorrhea, sneezing, and conjunctivitis that may respond well to antihistamines; nasal stuffiness responds best to topical nasal corticosteroid sprays when used correctly on the basis of nasal anatomy (see Chapter 105, Delivery of Inhaled Medications).
- Cetirizine and its prodrug, hydroxyzine, are the most effective antihistamines for allergic rhinitis. They are inherently long acting, so once- or twice-daily dosing is appropriate. For preschool-aged children, begin with 5 mg cetirizine or 10 mg hydroxyzine once daily and increase, if needed, to twice daily.
- Although cough is as common as wheezing with asthma, nonprescription cough and cold medications are ineffective and unnecessary.

Atopic Dermatitis

- This condition is also known as *atopic eczema.*
- Hydration of the skin is of extreme importance for normalizing the defective skin barrier characteristic of this disorder; the patient should take a soaking daily bath, followed by a generous use of emollient over the whole body.
- Systemic antibiotics are available for impetiginized eczema; *Staphylococcus aureus* methicillin sensitive or resistant bacteria are most common, but group A β-hemolytic *Streptococcus* can also be present.

- Topical corticosteroids should be used judiciously.
- Use topical calcineurin inhibitors, tacrolimus, or pimecrolimus when needed to minimize topical corticosteroid usage.

Expected Outcomes/Prognosis

- While individual episodes of acute asthma are frequently benign and self-limited, they can also progress to respiratory failure and become life-threatening or even fatal.
- Experiencing symptoms beyond preschool age is much more likely for children with allergen-specific IgE (Figure 43-3).
- Long-term outcome varies with the initial clinical pattern and frequency of symptoms (Figure 43-4).

When to Refer

- Refer the patient if current care is not preventing urgent care or hospitalization.
- Refer the patient if the criteria for control are consistently not met (see the Management section in this chapter).

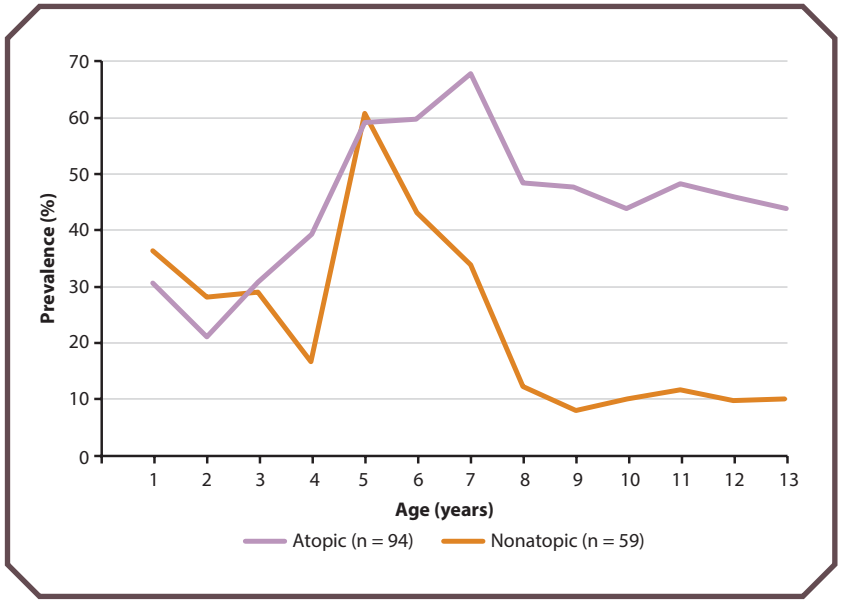

Figure 43-3. The frequency of wheezing episodes from birth up to the age of 5 years is equivalent for children with atopic and nonatopic wheeze but then decreases in the nonatopic group and increases in the atopic group. From Illi S, von Mutius E, Lau S, et al. Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study. *Lancet.* 2006;368:763–770. Copyright 2006, with permission from Elsevier.

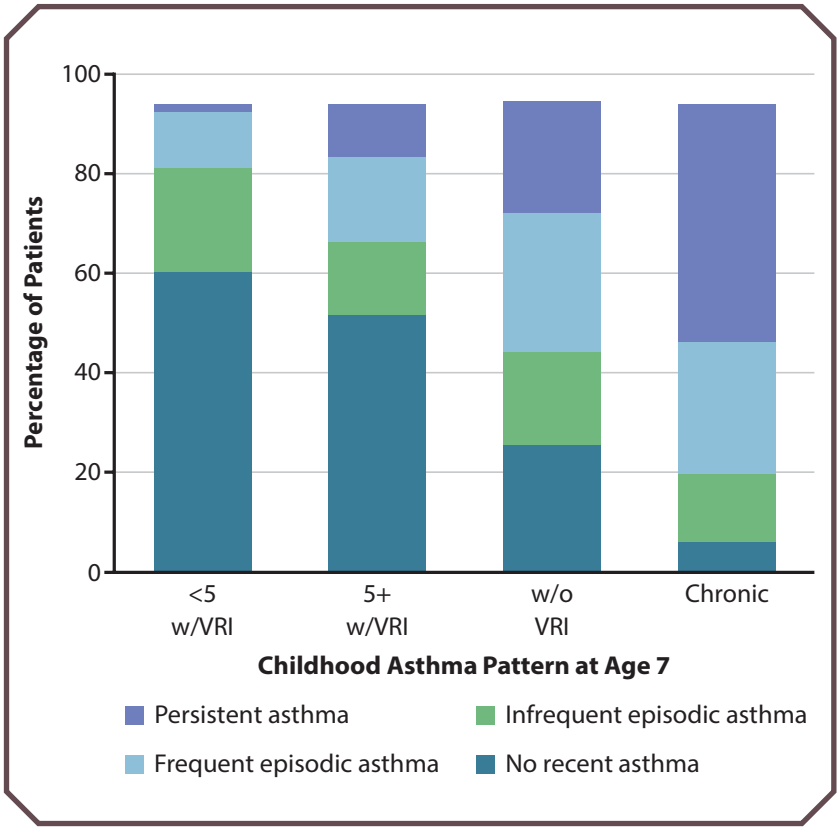

Figure 43-4. Clinical expression of asthma at age 42 years among patients who had various patterns of preschool-aged wheezing. A stratified random sample from a population of 30,000 children was surveyed at entry to first grade, about 20% of whom had a history of wheezing in the preschool-aged period. The sample included 75 children with <5 episodes of preschool-aged wheezing with viral respiratory infections (VRIs) *(<5 w VRI),* 104 children with ≥5 episodes of preschool-aged wheezing with VRIs *(5+ w VRI),* 113 children with recurrent preschool-aged wheezing not limited to VRIs *(w/o VRI),* and 83 children from the same population who had severe chronic asthma since age 3 *(chronic).* Adapted from Phelan PD, Robertson CF, Olinsky A. The Melbourne Asthma Study 1964–1999. *J Allergy Clin Immunol.* 2002;109–194. Copyright 2002, with permission from Elsevier.

When to Admit

- Admit a patient who has acute respiratory distress with hypoxemia that is not responding promptly to bronchodilator and oral corticosteroid.
- Because hospitalization may require intensive care, hospitalization should occur at a facility with a pediatric intensive care unit and personnel experienced in treating acute respiratory failure from asthma.

Prevention

- Since there is currently no reliable prevention for acute exacerbation from common cold viruses, the need for emergency care or hospitalization can be prevented by providing measures on hand, including inhaled bronchodilator and oral corticosteroid, with careful instruction and reliable monitoring of its early use.
- The patient should avoid breathing secondhand smoke and other airborne irritants, such as smoke from open fires.
- Identify inhalant allergy and avoid exposure if possible.

Resource for Families

- Managing Asthma for Patients and Families (University of Iowa Stead Family Children's Hospital). uichildrens.org/health-library/managing-asthma-patients-and-families

Clinical Pearls

- Bronchiolitis treatment is primarily supportive.
- Repeated episodes of wheezing with completely asymptomatic periods between episodes are consistent with an asthma phenotype caused by common cold viruses.
- Persistent wheezing responsive to corticosteroids suggests the potential for inhalant allergy.
- Cough is as much a symptom of asthma as wheezing.

Chapter 44

Allergic Bronchopulmonary Aspergillosis

Erin Walker MacKintosh, MD, FAAP, and Margaret Rosenfeld, MD, MPH

Introduction/Etiology/Epidemiology

- Allergic bronchopulmonary aspergillosis (ABPA) is an immunologic pulmonary disorder caused by immunoglobulin E (IgE)–mediated hypersensitivity to the fungus *Aspergillus fumigatus*, primarily in patients with asthma or cystic fibrosis.
- *A fumigatus* is a ubiquitous environmental fungus; it cannot be transmitted person to person.
  - It is typically found in dust, soil, or decaying organic matter, such as compost.
- Risk for ABPA is multifactorial and includes genetic predisposition and environmental exposures.
- ABPA typically manifests as poorly controlled asthma with productive cough and recurrent pulmonary infiltrates; it can progress to bronchiectasis and pulmonary fibrosis.
- More than 4 million patients are affected worldwide; the disorder is widely underdiagnosed.
  - Prevalence of ABPA ranges from 1% to 3.5% in people with asthma.
  - Regional differences exist in the United States, due in part to different diagnostic criteria and frequency of screening of asymptomatic patients.

Pathophysiology

- *A fumigatus,* a common environmental fungus, is inhaled into the lung.
- In healthy, normal lungs, inhaled spores are cleared from the airway. The spores are immunologically inert and do not lead to sensitization.
- Defective clearance (seen in asthma and cystic fibrosis) of inhaled spores allows *A fumigatus* to germinate into hyphae.
- The hyphal form is proinflammatory, activating innate and adaptive type 2 T helper (Th2) cell immune response.
  - Type 1 T helper (Th1) cells primarily promote cell-mediated immunity, and Th2 cells more typically promote allergic responses.
  - Macrophages recognize surface antigens on the hyphal forms and secrete proinflammatory cytokines.

  - — *Aspergillus* proteases can be directly toxic to pulmonary epithelium and lead to exposure of lymph tissue to antigens and further inflammation.
  - — While a normal lung would elicit a Th1 response, leading to *Aspergillus*-specific T cells, a lung susceptible to ABPA (due to genetic risk factors) is more likely to respond with Th2 response. This creates inflammation and leads to IgE synthesis and influx of eosinophils and other inflammatory cells.
- Typically, hyphal forms would be cleared by neutrophils, but defects in innate and adaptive immunity (genetic risk factors, poor mucociliary clearance) can lead to persistence of hyphal forms in the airway.
  - — Genetic mutations and polymorphisms associated with ABPA have been identified in multiple genes (including *HLA*, surfactant protein A2, *TLR9*, mannose-binding lectin, *IL4Rα*, *IL10*, *TGBβ*, *CFTR*, and *CHIT1*); the clinical significance of these findings is not yet clear.
- Patients develop *Aspergillus* sensitization, identified by either positive skin test results or increased *Aspergillus*-specific IgE.
- Prolonged positive reinforcement of antigen-mediated inflammatory cascade via persistent exposure to *Aspergillus* antigen leads to progressive parenchymal and airway damage.

Clinical Features

- Poorly controlled asthma
- Airflow obstruction, wheezing
- Recurrent pulmonary infiltrates
- Bronchiectasis
- Hemoptysis
- Productive cough, sometimes producing brown or black mucus plugs
- Can include low-grade fevers, weight loss, malaise, and fatigue with acute exacerbations
- Can be asymptomatic except for declining forced expiratory volume in 1 second values
- With prolonged and poorly managed disease, can develop clubbing, pulmonary hypertension, and cor pulmonale

Differential Diagnosis

- Poorly controlled asthma
- Pneumonia: viral, bacterial, eosinophilic
- Hypersensitivity pneumonitis
- Retained foreign body
- Pulmonary tuberculosis
- Chronic pulmonary aspergillosis
  - — Pulmonary aspergilloma
  - — Chronic cavitary pulmonary aspergillosis
  - — Chronic fibrosing pulmonary aspergillosis

- *Aspergillus* sensitization is the first pathogenetic step in developing ABPA and is associated with higher rates of bronchiectasis and severe asthma.
- Severe asthma with fungal sensitization is similar to ABPA, but without bronchiectasis and mucus plugging, with an IgE level <1,000 IU/mL (<2.4 mg/L).
- Allergic *Aspergillus* sinusitis is mucoid impaction of the sinuses with a mechanism similar to ABPA.
- Allergic bronchopulmonary mycosis is an ABPA-like syndrome caused by fungi other than *Aspergillus*, with <150 cases reported.

Diagnostic Considerations

- ABPA is typically diagnosed and managed by a pediatric pulmonologist or allergist. Thus, when a patient is not responding adequately to the usual treatment of asthma, or if there is suspected or confirmed ABPA, the child should be referred.
- There are varying diagnostic criteria in use. The International Society for Human and Animal Mycology working group is trying to create a unified diagnostic paradigm (see Box 44-1).
- Additional studies frequently used, but not required for diagnosis, are as follows.
  - — Sputum cultures for *A fumigatus* are neither sensitive nor specific but can be useful in terms of susceptibilities if positive.
  - — Pulmonary function tests can be used to trend response to treatment, but in some cases can have normal findings in confirmed ABPA.
  - — Chest computed tomographic findings may include
    - Bronchiectasis: a complication, not diagnostic criteria; usually central, can be peripheral
    - Mucus impaction, classically described as "finger in glove" owing to mucus filling the airways
    - Mosaic attenuation (air trapping)
    - Centrilobular nodules
    - Tree-in-bud opacities
    - Pleuropulmonary fibrosis
    - Rarely: effusions, pulmonary masses, miliary nodular opacities, perihilar opacities simulating hilar adenopathy

Treatment

- Goals of treatment include control of symptoms, prevention and/or treatment of acute exacerbations, and arresting development of bronchiectasis and fibrosis.
  - — Consensus exists that patients with ABPA and mucoid impaction or changes to lung function or symptomatic patients should be treated.
  - — There is not consensus on treating asymptomatic patients.
- The target of treatment is Th2 cell–mediated immune response.

Box 44-1. Diagnostic Criteria Proposed by the International Society for Human and Animal Mycology Working Group

Obligatory Criteria

- Underlying diagnosis of asthma
- Positive *A fumigatus*–specific IgE or *Aspergillus*-specific skin test result
  - —Skin test is 90% sensitive, but ≤40% of asthmatics without ABPA may also have a positive result.
- Total IgE level >1,000 IU/mL (>2.4 mg/L) or >2,400 ng/mL
  - —Consensus has not been achieved on this cutoff, and ABPA may be diagnosed with a lower IgE level if other diagnostic criteria are fulfilled.
  - —Levels may decrease spontaneously or with treatment, so the first or highest level available should be used.
  - —Increasing levels may be seen in exacerbations.

Other Criteria (must have 2 out of 3)

- Positive precipitating or IgG antibodies against *A fumigatus*
- Radiographic pulmonary opacities consistent with ABPA
- Total eosinophil count >500 cells/μL (0.5×10^9/L) in patients who have not yet received steroids (may be historical)

ABPA, allergic bronchopulmonary aspergillosis; IgE, immunoglobulin E; IgG, immunoglobulin G.

From Agarwal R, Chakrabarti A, Shah A, et al. Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria. *Clin Exp Allergy.* 2013;43(8):850–873. © 2013 John Wiley & Sons Ltd.

- Standard treatments
  - — The mainstay of treatment is systemic corticosteroids to suppress immune activity.
    - There are inadequate studies to guide dose or duration; many different protocols are in use.
    - A typical initial treatment regimen is prednisone 0.5 mg/kg/d for 1–2 weeks, then tapering over 8–10 weeks.
    - Half of patients relapse when steroids are tapered.
    - Ten percent to 45% of patients become steroid dependent.
  - — If the patient relapses or if the response to steroids is inadequate, antifungal medication is used to decrease fungal load as a steroid-sparing therapy.
    - Therapy is generally continued for minimum of 3–6 months.
    - Evidence supports the use of antifungals in chronic ABPA but not for treatment of acute exacerbations.
    - No evidence exists for antifungals as monotherapy (ie, without systemic corticosteroids), although clinical trials are underway.

  - Itraconazole is the standard first-line antifungal. Newer antifungal agents (eg, voriconazole, posaconazole) can be tried with itraconazole failure or intolerance and are increasingly being used in some centers as first-line agents.
  - Drug level monitoring is required to reduce the risk of toxicity and assess the risk of azole resistance and reduced effectiveness if levels are too low.
- Monitoring response to treatment includes total IgE level (unlikely to normalize but should decrease), symptom assessment, and pulmonary function tests.
- Other treatments have insufficient evidence but may be considered in refractory cases or those with absolute contraindications to systemic corticosteroids and/or itraconazole.
  - Omalizumab is a monoclonal antibody to IgE. There is mounting but still insufficient evidence for use as mainstay therapy, and it may be cost prohibitive.
  - Inhaled corticosteroids do not appear sufficient for treatment of ABPA. If used for control of underlying asthma, consider that effects increase when used concurrently with itraconazole (there is a risk for cushingoid effects and adrenal insufficiency).
  - Inhaled amphotericin: There are case reports of use in cystic fibrosis–associated ABPA, but there is not strong evidence.
  - Pulse doses of intravenous methylprednisolone: There is insufficient evidence to recommend it.
  - Avoidance of activities that provide a high burden of spore inhalation (farming, gardening, composting, building renovations, cleaning dusty environments) may reduce risk, but the evidence is insufficient.

Prognosis

- Minimal data are available for the prognostication of treated ABPA.
  - Patients can have prolonged remissions, but this does not imply cure.
  - ABPA requires lifelong monitoring.
  - If untreated, ABPA can progress to severe bronchiectasis, respiratory failure, and cor pulmonale.
- Complications
  - Recurrent exacerbations may be caused by airway inflammation or mucus plugging.
    - Prevent exacerbations with judicious use of steroids and azoles; treat acutely with steroid bursts.
  - Large airway collapse due to mucus plugging can occur in acute hypoxemic respiratory failure, necessitating therapeutic bronchoscopy.
  - Bronchiectasis can eventually develop. It is irreversible and a prognostic indicator for recurrence of exacerbations.

Resource for Families

- What Is Allergic Bronchopulmonary Aspergillosis? (American Thoracic Society). www.thoracic.org/patients/patient-resources/resources/allergic-bronchopulm-aspergillosis.pdf

Clinical Pearl

- When a patient is not responding adequately to the usual treatment of asthma, or if there is suspected or confirmed ABPA, the child should be referred to a pediatric pulmonologist or allergist.

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Part IV. Infections of the Respiratory Tract

Associate Editor: Kristin Van Hook, MD, MPH, FAAP

SECTION 1. AIRWAY INFECTIONS

SECTION 2. PARENCHYMAL INFECTIONS

Section 1. Airway Infections

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Chapter 45

Upper Respiratory Infections

Fernando Urrego, MD

Introduction

- Upper respiratory tract infections are the most common illness to affect children worldwide.
- Most children experience 1 or more acute respiratory infections per year; the mean is 6–8 per year.
- The frequency of infections varies with the season and the child's age.
- Infections are more common in autumn and winter in temperate regions and in the rainy season in tropical regions.
- The mode of transmission varies between viruses.
- Infections are usually mild and self-limiting but can occasionally lead to complications.
- The decision to investigate is based on clinical judgment and experience.
- Factors to consider when deciding on treatment are persistence of symptoms, time to cure, and complications arising from progressive disease.
- Most children who present with recurrent upper-airway infections are otherwise healthy.
- Antibiotics should not be commonly prescribed, because there is limited evidence of effectiveness.
- Upper respiratory tract infections cause substantial absenteeism of children from school and parents from work.

Rhinosinusitis (Common Cold)

- The nasal part of the respiratory mucosa is predominantly affected.
- Common viral causes include rhinovirus, coronavirus, respiratory syncytial virus, and metapneumovirus.
- The median number of viral colds is 5 per year, but it is not uncommon for a child to experience as many as 10 episodes in a year.
- The mean duration of symptoms is 8 days, but the normal range extends beyond 2 weeks.
- Symptoms include nasal congestion, rhinorrhea, cough, sore throat, and fever.
- Attendance in child care increases the risks of developing viral colds.
- Rhinosinusitis is usually a self-limiting illness that does not require treatment.

- In the absence of any other worrying features identified in the history and physical examination, isolated, recurrent viral colds do not require further investigations unless the frequency is >15 episodes a year and the duration is >15 days per episode.
- In 0.5%–5.0% of cases, common colds become complicated by the development of acute sinusitis (see the next section).
- Most children improve spontaneously within 14 days (see Figure 45-1).

Sinusitis

- *Sinusitis* is defined as an upper respiratory tract infection that affects predominantly the nasal part of the respiratory mucosa.
- It can be acute (signs and symptoms <30 days) or chronic (lasting >30 days).
- It usually manifests as a complication of the common cold.
- The most common causative organisms are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.

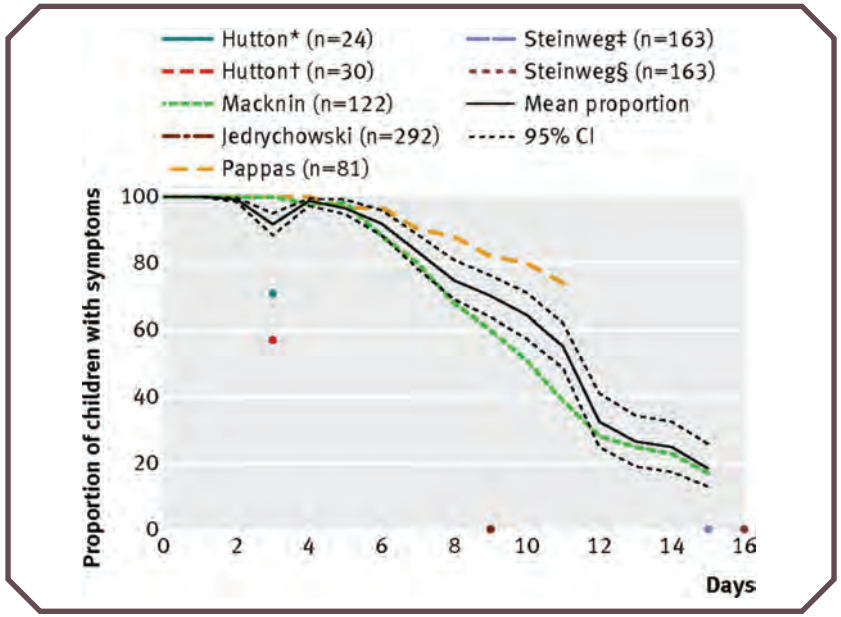

Figure 45-1. Mean duration of cold symptoms according to percentage of children with symptoms. Symptom duration before study onset was not reported in 5 studies (Hutton, Macknin, Gruber, Pappas, Steinweg), Jedrychowski et al reported duration <48 hours. CI = confidence interval, * = placebo arm, † = no treatment arm, ‡ = children with clear rhinorrhoea; § = children with purulent rhinorrhea. From Thompson M, Cohen HD, Vodicka TA, et al. Duration of symptoms of respiratory tract infections in children: systematic review. *BMJ.* 2013(347):f7027.

- The diagnosis is usually established on the basis of clinical grounds and should be considered when there is nasal drainage (of any quality) or cough persisting beyond 10 days without improvement, worsening disease course, or severe onset with concurrent fever and purulent discharge for ≥3 consecutive days.
- Plain sinus radiographs obtained to distinguish acute bacterial sinusitis from viral upper respiratory infections are not useful, because findings are nonspecific.
- Computed tomography of the paranasal sinuses and/or contrast-enhanced magnetic resonance imaging should be considered when complications are suspected or when surgery is being contemplated (Figure 45-2).
- The goal of treatment is to alleviate symptoms.
- Analgesics are helpful to control pain and fever.
- Antibiotics should not be started if symptoms are improving.
- Antibiotics are an option for children who have purulent nasal discharge but provide only modest benefit.
- Amoxicillin with or without clavulanate is the first-line treatment.
- Complications are rare but include meningitis, cavernous venous thrombosis, and orbital cellulitis.

Pharyngitis

- Pharyngitis is an acute upper respiratory tract infection that affects the respiratory mucosa of the throat.
- Children of any age can develop pharyngitis and tonsillitis.
- The etiologic origin may be either viral or bacterial, and it is difficult to distinguish between the two.
- A throat swab is necessary to determine the presence of *Streptococcus pyogenes*.

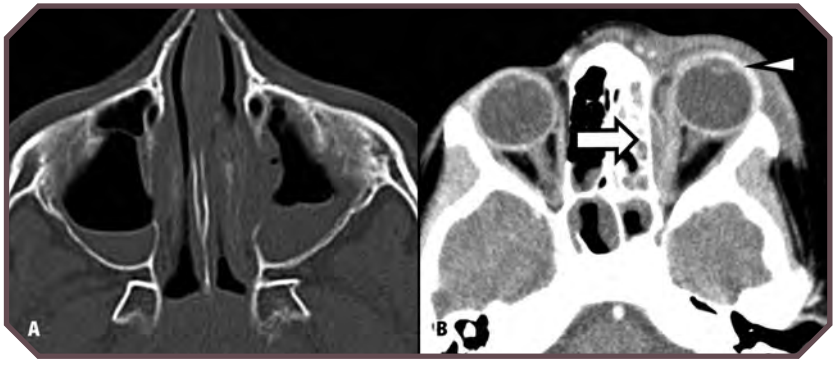

Figure 45-2. Maxillary and ethmoid sinusitis complicated by orbital abscess. A. Axial computed tomographic (CT) bone window image shows bilateral maxiallary sinus fluid levels. B. Axial contrast-enhanced CT soft-tissue window image demonstrates left ethmoid and sphenoid partial opacification in addition to left preseptal swelling (arrowhead), indicating cellulitis, proptosis, and a subperiosteal abscess (arrow).

- Pharyngeal exudate, tender cervical lymphadenopathy, and recent exposure to streptococcal infection are helpful in identifying bacterial infection.
- Symptoms can include pain, headache, fever, and general malaise.
- Analgesics are beneficial for pain, and antibiotics are effective if a bacterial process is confirmed to prevent complications.
- Penicillin remains the recommended treatment by the American Academy of Pediatrics for *S pyogenes* pharyngitis.
- Most children with viral etiologic origins will improve spontaneously within 14 days.
- Complications are uncommon but include peritonsillar abscess, acute otitis media, acute sinusitis, rheumatic fever, and acute glomerulonephritis.

Otitis Media

- Otitis media is an acute upper respiratory tract infection that affects the respiratory mucosa of the middle ear.
- It is common in young children.
- Peak incidence of infection occurs between 6 and 12 months of age.
- The etiologic origin may be either viral or bacterial.
- Diagnosis should not be assigned unless there is bulging or fullness of the tympanic membrane associated with a middle ear effusion and the tympanic membrane is opaque.
- Redness of the tympanic membrane is not a valuable diagnostic sign.
- High-dose amoxicillin is the treatment of choice.
- Amoxicillin-clavulanate is an option for children who were recently treated with amoxicillin.
- When the diagnosis is uncertain, observation can be considered.
- Duration of treatment depends on age and severity.
- Most children improve spontaneously within 14 days.
- Complications are uncommon.

Croup

- Croup causes swelling and inflammation of the larynx and trachea.
- Viral croup is the most common etiologic origin; bacterial croup is now rare.
- Peak age of incidence is 6 months to 5 years of age.
- Parainfluenza viruses are the most common cause of croup.
- Viral croup typically manifests with sudden onset of barky cough, stridor, and respiratory distress in the setting of coryzal illness.
- Investigations are seldom necessary in uncomplicated viral croup. However, radiographs may be useful in atypical presentation and in the case of recurrent episodes (Figure 45-3).
- Treatment depends on severity of illness and may include oral corticosteroids and racemic epinephrine.
- See Chapter 48, Croup, for detailed information.

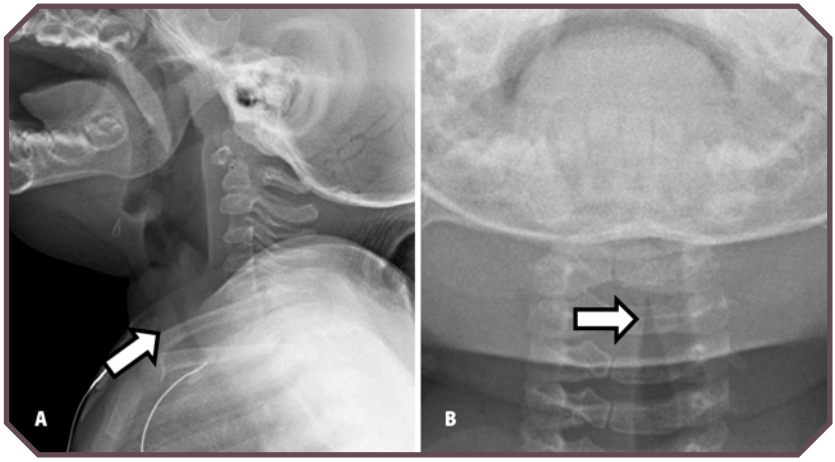

Figure 45-3. Croup in a 1-month-old female infant with stridor. A. Lateral and B. frontal radiographs demonstrate hyperinflation of the hypopharynx, subglottic narrowing, and the steeple sign, which are typical of croup (arrows).

Epiglottitis

- Epiglottitis is a very serious infection of the epiglottis and supraglottic structures that results in acute airway obstruction and high risk for death if left untreated.
- It is rare since the *H influenzae* type b, or Hib, vaccine came into widespread use.
- Onset is typically abrupt, with sore throat, difficulty swallowing, respiratory distress, drooling, choking sensation, irritability, restlessness, and anxiety.
- Diagnosis is confirmed via direct visualization by an experienced airway team (otolaryngologist and anesthesiologist).
- Airway examination should be considered only after the airway is secure.
- Broad-spectrum antibiotics (eg, ceftriaxone or cefotaxime) should be initiated if there is strong clinical suspicion of epiglottitis.

Bacterial Tracheitis

- Bacterial tracheitis causes infection and inflammation of the trachea.
- It is uncommon but potentially life-threatening.
- It is characterized by thick, membranous tracheal secretions that can occlude the airway and cause death.
- Similar to viral croup, the age group most affected is 6 months to 5 years, with a median age of 4 years.
- *Staphylococcus aureus* is the most common causative organism.
- Prodromal upper respiratory tract symptoms usually precede the progression of severe upper airway obstruction.

- Definite diagnosis is assigned via bronchoscopy.
- Most children will need to be intubated and started on broad-coverage antibiotics.
- See Chapter 51, Bacterial Tracheitis, for detailed information.

Resources for Families

- Croup (Mayo Clinic). www.mayoclinic.org/diseases-conditions/croup/home/ovc-20166699
- Croup and Your Young Child (American Academy of Pediatrics). patiented.solutions.aap.org/handout.aspx?gbosid=156422
- The Difference Between Sinusitis and a Cold (American Academy of Pediatrics). www.healthychildren.org/English/health-issues/conditions/ear-nose-throat/Pages/The-Difference-Between-Sinusitis-and-a-Cold.aspx
- AAP Issues Guideline on Treating Bacterial Sinusitis in Children (American Academy of Pediatrics). www.healthychildren.org/English/news/Pages/AAP-Issues-Guideline-on-Treating-Acute-Bacterial-Sinusitis-in-Children.aspx

Chapter 46

Laryngitis

Girish D. Sharma, MD, FCCP

Introduction/Etiology/Epidemiology

- Laryngitis is an inflammation of the larynx and vocal folds from a variety of causes, including infection, irritants, and vocal strain (overuse) (Box 46-1).

Box 46-1. Causes of Laryngitis

Viral

Common: Rhinovirus, influenza, parainfluenza, adenovirus, respiratory syncytial virus

Less common: Measles, mumps, varicella zoster, human immunodeficiency virus, coxsackievirus

Bacterial

Haemophilus influenzae type b, *Streptococcus pneumoniae, Staphylococcus aureus,* β-hemolytic streptococci, *Moraxella catarrhalis, Klebsiella pneumoniae*

Rarely diphtheria (in unimmunized subjects), mycobacteria

Fungal

Laryngeal candidiasis (thrush), *Aspergillus*

Systemic disorders

Rheumatoid arthritis, Wegener granulomatosis, sarcoidosis

Vocal trauma and strain

Prolonged yelling, screaming, forceful singing or speaking, persistent coughing, habitual throat clearing, and prolonged use of abnormal loudness or pitch in speech

Miscellaneous and environmental

Laryngopharyngeal reflux associated with gastroesophageal reflux and prolonged exposure to irritants, allergens, pollutants, toxins, dust, and smoke

Trauma, surgery and/or intubation, corrosive ingestion

- Acute laryngitis is usually infectious in origin, most commonly viral.
- Inflammation and edema of the larynx impair vibration of the vocal folds, resulting in symptoms suggestive of laryngitis.
- Symptoms that last for >3 weeks are suggestive of chronic laryngitis.
- Analysis of the 2012 National Health Interview Survey pediatric voice and language module showed the prevalence of voice and swallow problems to be approximately 1%. Of these, approximately 16% of children had laryngitis.

Clinical Features

- The principal symptoms of laryngitis are dysphonia, hoarseness of voice with breathiness due to excessive loss of air through the incomplete closure of glottis), and aphonia.
- Associated symptoms may include dysphagia, odynophagia, odynophonia, dyspnea, upper respiratory infection symptoms, or gastroesophageal reflux (GER) symptoms.
- Additional findings may be caused by associated conditions, such as upper respiratory infection and thrush.

Diagnostic Considerations

- History of dysphonia with history consistent with or suggestive of possible associated conditions (eg, upper respiratory infection, vocal strain, GER) will help laryngitis to be diagnosed clinically.
- Duration of symptoms will help differentiate acute and chronic laryngitis.
- Findings of a laryngoscopic examination (typically performed by an otolaryngologist) can help to establish the definitive diagnosis.
  - — Erythema and mucosal edema of the vocal folds and other laryngeal structures
  - — Secretions, exudate, and irregular and erythematous laryngeal mucosa
  - — Findings caused by associated conditions, such as upper respiratory infection, irritant exposure, GER, and thrush

Management

- Acute laryngitis, which is mostly caused by viral infections, is usually self-limiting and may resolve spontaneously.
- Control or avoidance of suspected irritants, such as smoke, pollutants, dust, or chemical fumes, will help expedite recovery.
- Adequate hydration, humidification, and voice rest should be maintained.
- Voice rest is especially important if the laryngitis was caused or exacerbated by overuse or vocal strain (prolonged yelling, screaming, forceful singing, speaking, or singing with abnormal loudness or pitch).
- Analgesics and antipyretics may be used to alleviate pain or fever.
- Gargles, mouthwash, and throat lozenges may help with throat pain.
- There are reports of successful use of inhaled budesonide in acute laryngitis.

- Antibiotics may be prescribed if bacterial infection is suspected or confirmed.
- The treatment of chronic laryngitis depends on the underlying etiologic origins and may involve avoidance of environmental irritants and allergens, treatment of allergic rhinitis, treatment of sinusitis, humidification, increased hydration, and correction of any underlying systemic or metabolic disorders.

Prognosis

- Acute laryngitis is self-limiting and tends to last for approximately 1 week.
- Symptoms lasting for >3 weeks suggest chronic laryngitis and warrant further investigations and therapy (see the "When to Refer" section).

When to Refer

- Symptoms persisting for >3 weeks warrant referral to an otolaryngologist for laryngoscopic examination.
- Presence of stridor, respiratory distress, dehydration, hypoxia, or weight loss warrants an urgent referral to the emergency department and evaluation by an otolaryngologist.
- A patient with a recent history of endotracheal intubation, irritant exposure, or trauma should be referred for laryngoscopic examination.
- The presence of specific signs, symptoms, or other indicators that are suggestive of a systemic disorder warrants a referral to an appropriate specialist.

Resources for Families

- Laryngitis (Mayo Clinic). www.mayoclinic.org/diseases-conditions/laryngitis/basics/definition/con-20021565
- Laryngitis (MedicineNet). www.medicinenet.com/laryngitis/article.htm

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Chapter 47

Epiglottitis

Girish D. Sharma, MD, FCCP

Introduction/Etiology/Epidemiology

- Acute epiglottitis is a potentially life-threatening infection of the supraglottic structures that can lead to sudden fatal airway obstruction if treatment is delayed.
- In a classic case, there is cellulitis of supraglottic structures, particularly the lingual surface of the epiglottis and the aryepiglottic folds. The subglottic space and trachea are usually spared.
- *Haemophilus influenzae* type b (Hib) is the most commonly cultured organism in children with epiglottitis.
- After the introduction of the Hib vaccine, the incidence of Hib disease among children <5 years of age decreased by 70%, from 37 children per 100,000 in 1989 to 11 children per 100,000 in 1991. By 2000, the annual incidence of invasive Hib in children <5 years decreased by 97% to <1 case per 100,000, with a concomitant dramatic decline in the incidence of acute epiglottitis in children.
- With the decline of Hib disease, epiglottitis is seen more often to be caused by organisms other than Hib, such as *Streptococcus pneumoniae* and other *Streptococcus* species, *Staphylococcus aureus*, *Moraxella catarrhalis*, *Pseudomonas* species, *Candida albicans*, *Klebsiella pneumoniae*, *Pasteurella multocida*, and *Neisseria* species.
- Bacterial superinfection of the viral infections also occurs, particularly with herpes simplex, parainfluenza, varicella zoster, and Epstein-Barr virus infections.
- Epiglottitis tends to occur throughout the year; however, in the northern hemisphere, most reported cases occur between December and May.
- Epiglottis tends to occur in children between the ages of 2 and 6 years, although more recently, disease has been reported in much older patients and should be considered at any age.

Clinical Features

- Onset is usually abrupt.
- In some cases, acute symptoms are preceded by minor upper respiratory infection.
- Acute symptoms include abrupt high-grade fever and sore throat; dysphagia may develop over a few hours and is associated with drooling, muffled voice, and respiratory distress.

- The patient may be anxious and irritable and may prefer to sit upright with the chin up, bracing himself forward onto his hands (hyperextension of the neck helps maintain airway patency).
- Stridor is a late finding.
- Breathing becomes noisy, and voice and cry are muffled as swelling of the aryepiglottic folds and supralaryngeal mucosa obstructs the glottic inlet.
- Complete airway obstruction may occur at any time, without preceding deterioration in clinical signs.

Diagnostic Considerations

- A very high index of suspicion should be maintained, and epiglottitis should be considered in every child who presents with apparent acute airway obstruction, high fever, sore throat pain, muffled voice, dysphagia, and drooling that develops over a few hours.
- A barking cough typical of croup is rare in children with epiglottitis.
- Avoid performing procedures that might further aggravate an already tenuous airway.
- In general, chest radiography has no role in the management of a critically ill child with acute stridor suspected to be caused by epiglottitis.
- A lateral neck radiograph can be helpful, though it only should be attempted if the patient is stable and the diagnosis is in doubt (Figure 47-1).
- Therapeutic trials of inhaled medicines, such as corticosteroids and racemic epinephrine, may delay specific treatment and irritate the child, leading to complete obstruction of the airway.
- Direct visualization of the epiglottis should not be undertaken until the child is undergoing tracheal intubation.
- Epiglottitis must be differentiated from other causes of acute airway obstruction, including viral croup, bacterial tracheitis, spasmodic croup, and foreign-body aspiration.

Management

- Avoid disturbance; allow the child to sit up and stay in her parent's arms to avoid agitation.
- Provide 100% humidified oxygen via blow-by administration.
- Notify and assemble the epiglottitis team (pediatric intensivist, anesthesiologist, and otolaryngologist).
- Once the diagnosis is established, there should be no delay in establishing an artificial airway.
- If there is time, the child should be intubated in the operating room, with general anesthesia, by personnel who can perform emergency tracheostomy in case intubation fails.
- Provide sedation after intubation and critical care if tracheostomy is required.

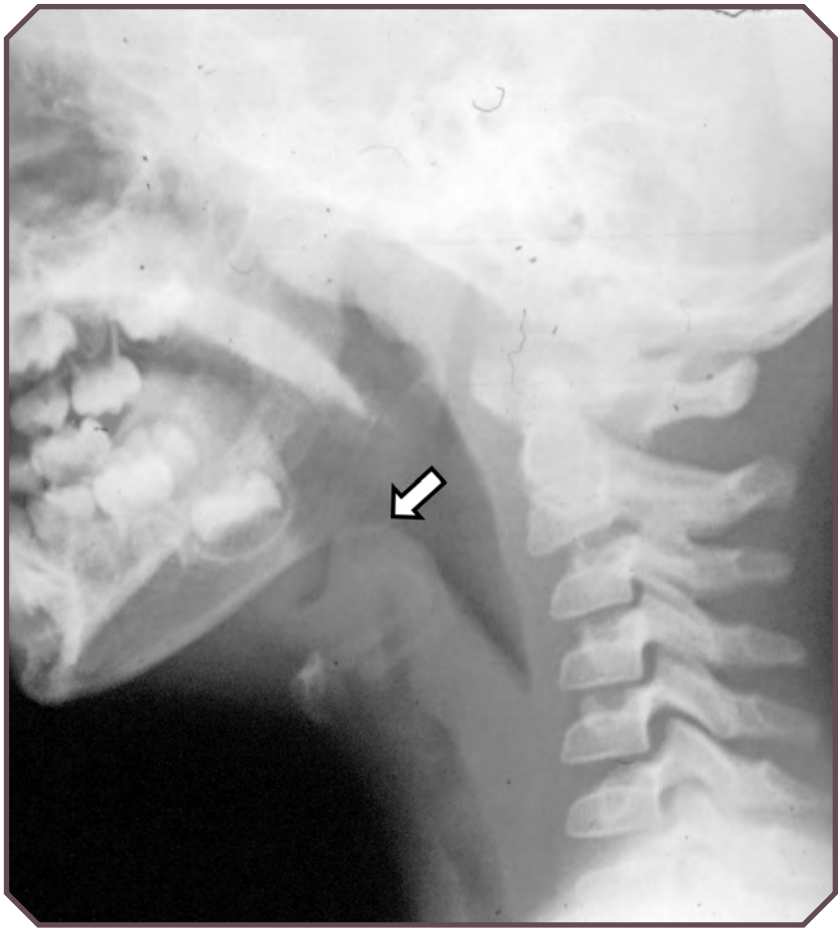

Figure 47-1. Epiglottitis in a 2-year-old boy with fever and stridor. Lateral soft-tissue neck radiograph demonstrates a markedly enlarged epiglottis (arrow).

- Intravenous antibiotics may be used to effectively control inflammation and infection. A third-generation cephalosporin (eg, ceftriaxone or cefotaxime) is usually given and may be changed when antibiotic sensitivities are available. There is some empirical evidence that corticosteroids may help; however, racemic epinephrine has not been shown to be of benefit.
- Blood cultures are usually obtained to detect organisms suspected in the workup for epiglottitis, even though *H influenzae* (which has a recovery rate of 80%–100% from the blood) is now an uncommon cause.

Prognosis

- Approximately 10%–25% of cases may be managed with observation, although these are older patients, with larger airways and less severe symptoms.
- Epiglottitis can lead to acute airway obstruction and death.

When to Refer

- As soon as epiglottitis is suspected, the child should be referred to the nearest pediatric emergency department that has surgical and anesthesia expertise available.
- All children suspected of having epiglottitis should be admitted to the hospital for intensive care monitoring and intravenous antibiotic treatment.
- Medical and surgical teams should be ready to emergently place an endotracheal tube and should also be ready to conduct emergency tracheostomy.

Resources for Families

- Epiglottitis (Mayo Clinic). www.mayoclinic.org/diseases-conditions/epiglottitis/basics/definition/con-20027854
- Epiglottitis (American Academy of Pediatrics). www.healthychildren.org/English/health-issues/conditions/ear-nose-throat/Pages/Epiglottitis.aspx

Chapter 48

Croup

Girish D. Sharma, MD, FCCP

Introduction/Etiology/Epidemiology

- Croup, or acute laryngotracheobronchitis, is a viral syndrome characterized by acute upper airway obstruction due to swelling of the subglottic area that results in the sudden onset of barky cough, inspiratory stridor, hoarse voice, and respiratory distress.
- Croup is the most common cause of infective upper-airway obstruction in the pediatric age group.
- Croup is usually seen in the preschool age group, with a peak incidence between 18 and 24 months (age range, 6 months to 6 years).
- A male predominance is seen in younger children.
- Viral croup is most commonly caused by parainfluenza virus (PIV) type 1, although PIV types 2 and 3 are responsible for sporadic cases.
- Other viruses implicated in the etiologic origin are influenza A and B, adenovirus, respiratory syncytial virus, rhinovirus, measles, human metapneumovirus, coronavirus, and enteroviruses.
- Epidemics in the fall and winter are commonly caused by PIV type 1; other viruses (eg, PIV type 2) are responsible for sporadic cases.
- Spasmodic croup is a recurrent condition with clinical manifestations similar to viral croup but without prodromal upper respiratory infection symptoms.

Clinical Features

- Frequently, there is a history of mild respiratory infection in the form of coryza, pharyngitis, and low-grade fever prior to the onset of croup.
- There is abrupt onset of characteristic barky cough, respiratory distress, stridor, and hoarse voice.
- Respiratory distress and inspiratory stridor, in a mild case, are usually absent at rest but present when the child is agitated.
- Usually, the onset of symptoms occurs during the early hours of the morning; these symptoms are worse during the evening or at night.
- The symptoms are usually short lived, and most children have resolution of barky cough within 48 hours.
- Symptoms of spasmodic croup are more transient than those of viral croup, they respond differently to therapeutic interventions, and they improve after exposure to cold night air. Warm, humid air, such as that in the shower, may also alleviate the symptoms.

- In a mild case, there is a barky cough and a hoarse voice or cry. The patient may have stridor on exertion, but signs of respiratory distress are absent.
- A moderate case may feature frequent barking cough, stridor that is audible at rest, respiratory distress in the form of tachypnea, intercostal and suprasternal retractions, and little agitation, if any. However, the patient remains interactive and able to take adequate liquids.
- There may be diminished breath sounds, rhonchi, and scattered crackles in moderate to severe cases.
- In a severe case, there is increasing respiratory distress. The child may be anxious and tired and may develop dehydration because incoordination between breathing and swallowing renders him unable to drink liquids. Tripod positioning is often seen in severe cases, as the child instinctively tries to line up the airways and use the accessory muscles of ventilation most effectively.
- Presence of restlessness, agitation, pallor, cyanosis, or decreased level of consciousness suggests marked airway obstruction.

Diagnostic Considerations

- Diagnosis of croup is clinical; ancillary testing is rarely needed.
- Presence of stridor with or without intercostal retractions is essential for the diagnosis of clinically important croup.
- Clinical features, such as presence and frequency of barking cough, stridor, retractions, and agitation, are used to classify the severity of croup (Table 48-1).
- Radiographs are not usually indicated. Agitation associated with obtaining a radiograph or performing an aggressive physical examination may significantly worsen the condition.
- In the event of an atypical clinical picture and uncertain diagnosis, an anteroposterior or lateral tissue neck radiograph shows bilateral, symmetrical subglottic narrowing, known as the "steeple sign" (Figure 48-1).

Table 48-1. Classification of the Severity of Croup

Clinical Feature	Mild Croup	Moderate Croup	Severe Croup
Cough	Occasional barking cough	Frequent barking cough	Frequent barking cough
Stridor	Nil at rest	Audible stridor at rest	Prominent inspiratory stridor
Retractions	Nil or mild retractions	Suprasternal retractions Sternal retractions at rest	Marked sternal retractions
Agitation	Nil	Nil or little agitation	Substantial agitation with distress

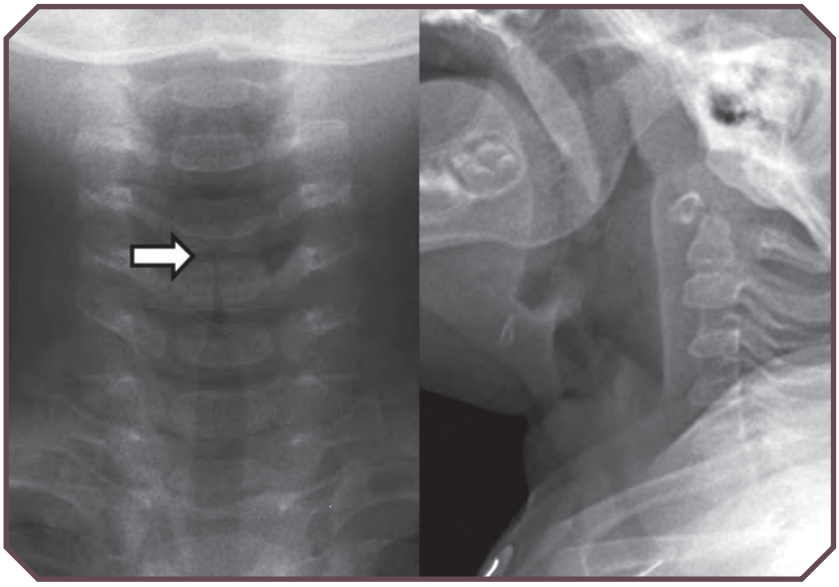

Figure 48-1. Croup. A. Frontal radiograph of the neck shows subglottic narrowing, or the steeple sign (arrow), which is classic for croup. B. Lateral radiograph shows a normal epiglottis and narrowing of the subglottic space. Courtesy of E. M. Comiskey, MD, Rush University Medical Center, Chicago, IL.

Management

- Figure 48-2 shows an algorithm for the management of croup.
- An effort should be made to make the child comfortable and reduce the level of agitation.
- Sitting the child comfortably in the lap of a parent or caregiver is usually the best way to examine the child.
- One oral dose of dexamethasone (0.15, 0.3, or 0.6 mg per kilogram of body weight for mild, moderate, or severe croup, respectively) should be given (see Figure 48-2).
- A parenteral dose of dexamethasone (0.6 mg/kg) can be given for severe croup.
- A single dose of nebulized budesonide (2 mg) is associated with reduction in the intensity of symptoms, frequency of hospitalization, and frequency of return visits and should be considered when the patient is vomiting or unable to take oral medications.
- Epinephrine (0.5 mL of 2.25% racemic epinephrine or 5 mL of 1:1,000 L-epinephrine via nebulizer) improves the symptoms of croup for 1–2 hours; the patient should be monitored for recurrence of symptoms for 2–3 hours.
- If >2 doses of epinephrine are required, the patient should be hospitalized.
- Oxygen supplementation may be used in the unlikely situation of hypoxia.

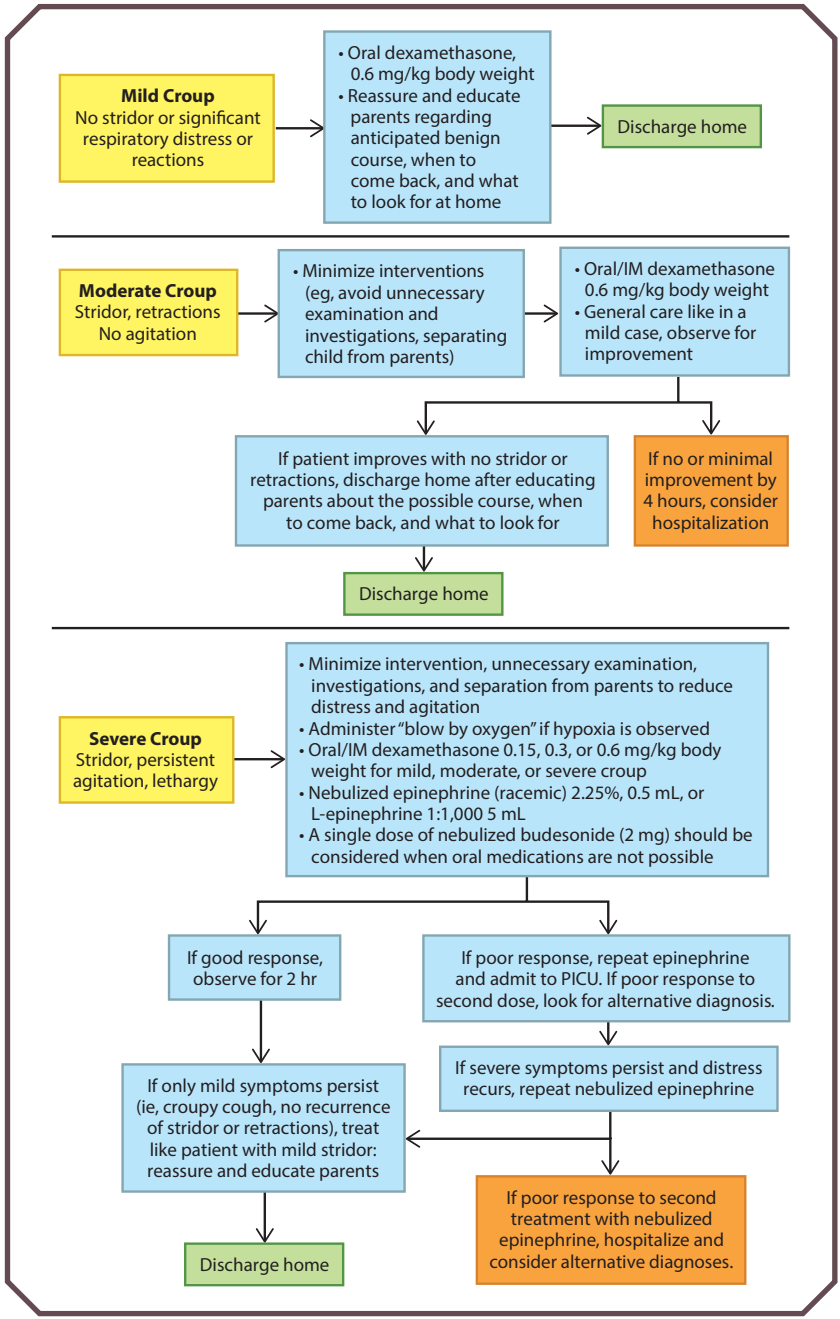

Figure 48-2. Algorithm for the management of croup. IM = intramuscular, PICU = pediatric intensive care unit. From Sharma GD, Conrad C. Croup, epiglottitis, and bacterial tracheitis. In: Light MJ, Blaisdell CJ, Homnick DN, Schechter MS, Weinberger MM, eds. *Pediatric Pulmonology*. Elk Grove Village, IL: American Academy of Pediatrics; 2011: 347–363.

- There is no clear benefit of using humidified air or heliox in patients with croup.
- Other medications, such as short-acting β_2-agonists, antitussives, and analgesics, have no physiological basis for use in croup.
- Sedatives should not be prescribed.

Prognosis

- The symptoms are generally short lived; most children have resolution of barking cough within 48 hours.

When to Refer

- The patient is unable to eat or drink.
- The patient requires ≥2 doses of nebulized epinephrine.
- The patient has croup and excessive tachycardia and tachypea, which may be associated with impending respiratory failure.
- Patients with severe respiratory distress, particularly with hypoxia, should be admitted to the hospital.
- Restlessness, agitation, cyanosis, pallor, and decreased level of consciousness are suggestive of severe airway obstruction and warrant urgent emergency treatment and admission.
- Patients with pre-existing conditions and a compromised airway, such as subglottic stenosis, may experience worse symptoms and may require endotracheal intubation or tracheostomy.
- Refer patients with recurrent croup and a history that may suggest anatomic predisposition, such as history of prior intubation or skin hemangiomas.

Resources for Families

- Croup (Mayo Clinic). www.mayoclinic.org/diseases-conditions/croup/home/ovc-20166699
- Croup and Your Young Child (American Academy of Pediatrics). patiented.solutions.aap.org/handout.aspx?gbosid=156422

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Chapter 49

Papillomatosis

Derek Pepiak, MD, FCCP, FAAP

Introduction/Etiology/Epidemiology

- Papillomatosis is a rare disease characterized by the growth of tumors in the respiratory tract that are caused by human papillomavirus (HPV).
- It is also referred to as *recurrent respiratory papillomatosis.*
- It may occur in children or adults.
- When diagnosed in children, the disease is referred to as *juvenile-onset recurrent respiratory papillomatosis (JORRP).*
- JORRP is the most common benign laryngeal tumor in children.
- Most children receive diagnoses by age 5, with a mean age of 3.8 years at diagnosis.
- A younger age at diagnosis is frequently associated with a more aggressive disease process.
- Male and female patients are affected equally.
- Laryngeal papillomatosis is most commonly caused by HPV-6 and HPV-11, although HPV-16 and HPV-18 have been observed, as well.
- Disease caused by HPV-11 is more severe.
- Incidence is estimated at 4.3 per 100,000 children in the United States.

Pathophysiology

- HPV infection is acquired during passage through the birth canal of an infected mother.
- Risk factors
  - — Firstborn child
  - — Vaginal delivery
  - — Infants born to mothers <20 years of age
- More than 95% of papillomas occur in the larynx, although they may be found anywhere along the respiratory tract.
- Consider a potential history of sexual abuse in children >5 years of age who develop JORRP.

Clinical Features

- History
  - — Hoarseness, the most common symptom
  - — Voice changes (dysphonia or aphonia)
  - — Weak cry
  - — Choking episodes

  - Shortness of breath
  - Chronic cough
- Physical examination
  - Often nonspecific findings
  - Inspiratory stridor
  - Wheezing
  - Vocal changes (weak cry, hoarse voice)
  - Multiple verrucose, polypoid growths overlying the true vocal cords, false vocal cords, subglottic region, and/or trachea at visualization (Figure 49-1)

Differential Diagnosis

- Benign laryngeal or tracheal tumors
- Foreign-body aspiration
- Gastroesophageal reflux disease
- Laryngeal infection
- Laryngomalacia
- Malignant laryngeal or tracheal tumors
- Subglottic stenosis
- Tracheomalacia
- Vocal cord dysfunction
- Vocal cord paralysis

Diagnostic Considerations

- Diagnosed by means of visualization of the larynx, usually by an otolaryngologist.
- Visualization is performed via laryngoscopy and/or bronchoscopy.
- Direct rigid laryngoscopy and/or bronchoscopy is most commonly performed because it allows for both diagnosis and treatment to occur while the patient is under anesthesia.
- Biopsy specimens should be obtained for histologic confirmation and viral typing and to rule out malignant transformation.

Management

- Surgical microdebridement of the lesions is the most common treatment.
- Most children require multiple surgical debulking procedures.
- Adjunctive therapies may increase the intervals between needed resection procedures.
  - Cidofovir injected into the lesions after resection
  - Interferon
  - Carbinol
  - Photodynamic therapy

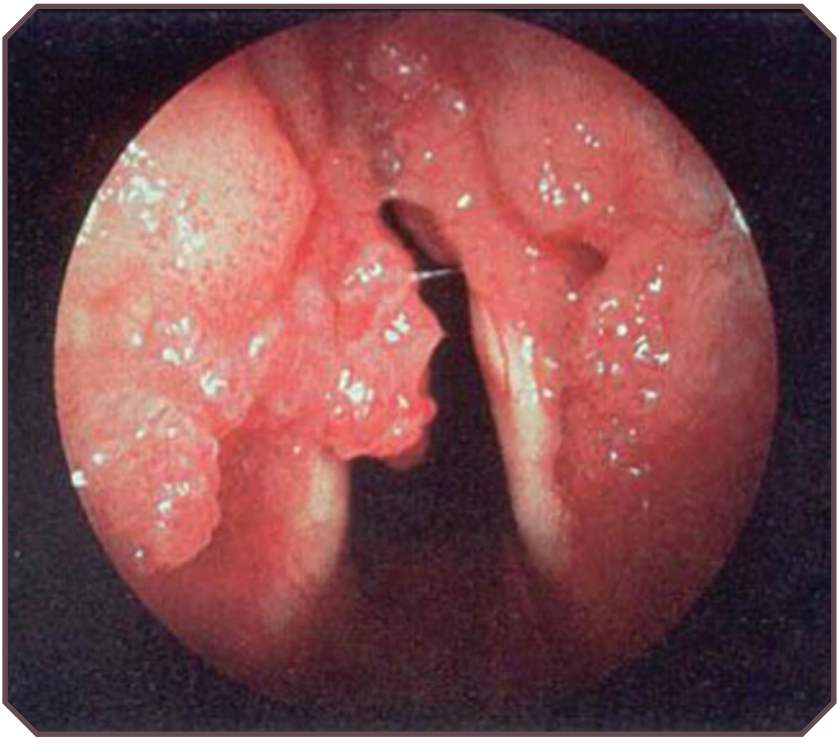

Figure 49-1. Direct laryngoscopic image demonstrates extensive papillomatosis in a patient with stridor and hoarseness. From http://emedicine.medscape.com/article/302648-overview, courtesy of Sat Sharma, MD, and L. Garber, MD.

- Children with aggressive lesions may require tracheostomy tube placement.
  - — Ten percent to 15% of children with aggressive lesions will require a tracheostomy tube, although many can later be decannulated.
  - — Placement of a tracheostomy tube can be associated with increased risk of papillomatosis recurrence or development of lower-airway papillomas.
- Management should include comprehensive education for families about the condition, as well as information on support groups.

Expected Outcomes/Prognosis

- The mean number of surgical procedures required is 4.4 per child per year; the mean number of procedures required in a child's lifetime can be >20.
- Remission is common after several years and usually occurs around puberty.
- Complications include airway obstruction and malignant transformation.
- Development of squamous cell carcinoma occurs in 3%–5% of patients.

When to Refer

- Consider referral to an otolaryngologist for patients with persistent vocal changes (hoarse voice and/or weak cry), stridor, and shortness of breath that seems unlikely to be attributed to croup or asthma.

When to Admit

- Consider admission for a patient who presents with respiratory distress and/or cyanosis with persistent vocal changes (hoarse voice and/or weak cry), stridor, and shortness of breath that seems unlikely to be attributed to croup or asthma.

Prevention

- Advising adolescents and young adults to get HPV vaccinations, thereby reducing the occurrence of genital and oropharyngeal lesions, could significantly decrease the incidence of HPV airway disease in young children born to these individuals.
- Consider delivery via cesarean section if a mother is giving birth to her first child and has visible condylomata.

Resources for Families

- Recurrent Respiratory Papillomatosis Foundation. www.rrpf.org
- Recurrent Respiratory Papillomatosis (National Organization for Rare Disorders). rarediseases.org/rare-diseases/recurrent-respiratory-papillomatosis

Clinical Pearls

- Papillomatosis is most commonly caused by HPV-6 and HPV-11.
- Hoarseness is the most common presenting symptom.
- Papillomatosis is diagnosed by visualizing the larynx.
- Surgical debridement is the most common treatment.
- Advising adolescents and young adults to get HPV vaccinations could significantly decrease the incidence of HPV airway disease in young children born to these individuals.

Chapter 50

Pertussis

Kenan Haver, MD, FAAP

Introduction/Etiology/Epidemiology

- Pertussis, or whooping cough, is an acute infectious disease caused by the bacterium *Bordetella pertussis*.
- The first observation of pertussis occurred in France in 1414, and the first epidemic was noted in Paris in 1578; *B pertussis* was first isolated in 1906.
- Pertussis remains a major health problem among children in developing countries, with 195,000 deaths resulting from the disease reported in 2008. Even in the United States, pertussis remains a public health problem. In 2012, 48,277 cases of pertussis were reported to the U.S. Centers for Disease Control and Prevention (CDC), including 20 pertussis-related deaths.
- Transmission occurs via aerosolized droplets of respiratory secretions.
  - — Adolescents and adults are an important reservoir for *B pertussis* and are often the source of infection for infants.
  - — No animal or insect source or vector is known to exist.

Pathophysiology

- *B pertussis* is an aerobic gram-negative rod.
- The bacteria attach to the cilia of the respiratory epithelial cells, produce toxins that paralyze the cilia, and cause inflammation of the respiratory tract, which interferes with the clearing of pulmonary secretions. Pertussis antigens appear to allow the organism to evade host defenses. An immune response to 1 or more antigens produces immunity after infection.
- Pertussis is highly communicable, as evidenced by secondary attack rates of 70%–100% among susceptible household contacts. Persons with pertussis are most infectious during the catarrhal period and the first 2 weeks after cough onset (ie, approximately 21 days).

Clinical Features

- Disease progression is shown in Figure 50-1.
- The incubation period lasts 7–10 days (range, 4–21 days).
  - — It has insidious onset, similar to the common cold, with nonspecific cough.

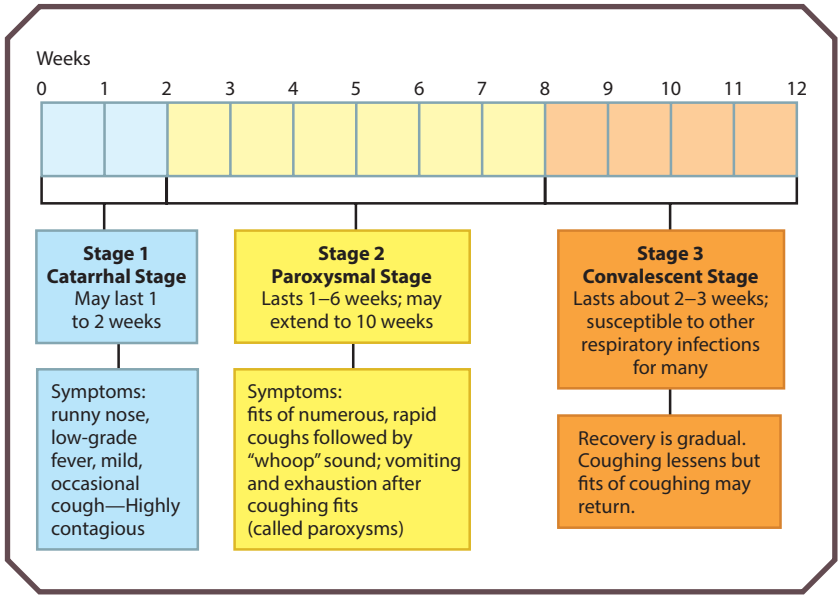

Figure 50-1. Disease progression in pertussis. From https://www.cdc.gov/pertussis/about/signs-symptoms.html.

- Fever is usually minimal throughout the course of illness.
- The catarrhal stage (maximum communicability) lasts 1–2 weeks.
  - — Coryza
  - — Low-grade fever
  - — Occasional cough
- The paroxysmal cough stage lasts 1–6 weeks.
  - — Minimal fever
  - — There are paroxysms of numerous, rapid coughs, apparently due to difficulty in expelling thick mucus from the tracheobronchial tree. At the end of the paroxysm, a long inspiratory effort is usually accompanied by a characteristic, high-pitched whoop.
    - ▪ For audio of the characteristic sound of a child with pertussis, see www.pkids.org/diseases/pertussis.html
  - — Vomiting and exhaustion often follow these episodes.
- Convalescence and intermittent cough last weeks to months (sometimes referred to as the "100-day cough").
  - — Recovery is gradual.
  - — Pertussis may recur with subsequent respiratory infections.

Presentation in Infants

- Cough (98%)
- Respiratory distress (95%)
- Cyanosis (72%)
- Apnea (67%)
- "Whoop" (42%)
- Seizures (9%)
- Altered mental status (20%)

Differential Diagnosis

- Acute infection with cough
- Sinusitis
- Gastroesophageal reflux disease
- Habit cough

Diagnostic Considerations

- The diagnosis of pertussis is based on a characteristic clinical history (cough for more than 2 weeks with whoop, paroxysms, or posttussive vomiting).
- In the absence of a more likely diagnosis, the clinical case definition is a cough illness lasting ≥2 weeks, with 1 of the following symptoms:
  - Paroxysms of coughing
  - Inspiratory "whoop"
  - Posttussive vomiting
  - Apnea (with or without cyanosis) for infants <1 year of age only
- Culture is considered the standard of reference for diagnosis.
  - The organism is fastidious and requires special media for isolation.
  - Use polyethylene terephthalate or calcium alginate swabs (not cotton swabs) in the posterior nasopharynx.
  - Isolation rates are highest during the first 2 weeks of illness.
- Polymerase chain reaction (PCR) has excellent sensitivity.
  - PCR is best when a specimen is obtained 0–3 weeks after cough onset.
  - It may provide accurate results for ≤4 weeks of cough in infants or unvaccinated persons.
  - It is unlikely to be useful if antimicrobial therapy has been given for >5 days.
  - PCR lacks sensitivity in previously immunized people but is still more sensitive than culture.
- Fluorescent antibody is not recommended by the CDC.
- Optimal timing for specimen collection for serologic testing is 2–8 weeks after cough onset, when the antibody titers are at their highest; however, serologic analysis may be performed on specimens collected ≤12 weeks after cough onset (see Figure 50-2).
- State health departments should report all cases of probable and confirmed pertussis.

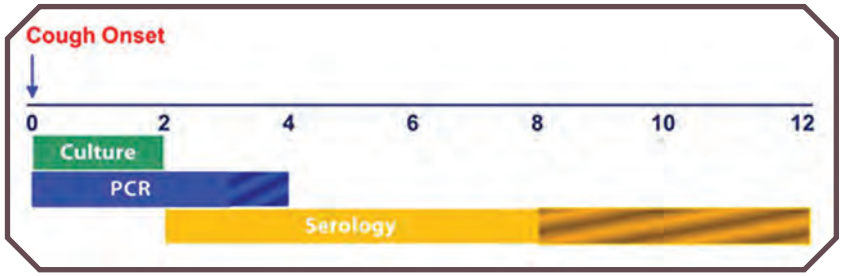

Figure 50-2. Optimal timing for diagnostic testing (in weeks). PCR = polymerase chain reaction. From https://www.cdc.gov/pertussis/clinical/diagnostic-testing/diagnosis-confirmation.html

Importance of Rapid Case Identification

- Early diagnosis and treatment of pertussis might limit its spread to other susceptible people.
- Identification and prophylaxis to prevent transmission to household and other close contacts at high risk should proceed without waiting for laboratory confirmation.
- Prophylaxis to prevent transmission to pregnant women and infants, as well as their household contacts, should not be delayed.

Management

- The medical management of pertussis cases is primarily supportive.
- Antibiotics eradicate the organism from secretions, thereby decreasing communicability.
- Per the CDC, recommended antibiotics are azithromycin, clarithromycin, and erythromycin. Trimethoprim-sulfamethoxasole can also be used.

Expected Outcomes/Prognosis

- Complete recovery

When to Refer

Infants and Children

- Pertussis can cause serious and potentially life-threatening complications in infants and young children who are not fully vaccinated. An infant or child who develops apnea, pneumonia, seizures, dehydration, pneumothorax, hypoxia, or chest pain should be referred for further evaluation and hospital admission.

Adolescents and Adults

- Adolescents and adults can also develop complications from pertussis, but they are usually less severe in this older age group, especially in those who have been vaccinated. Adolescents and adults with severe complications should be referred for further evaluation and hospital admission.

When to Admit

- Respiratory distress
- Cyanosis
- Apnea
- Seizures
- Altered mental status

Prevention

- Immunization with DTaP (diphtheria, tetanus, and pertussis), Td (tetanus and diphtheria), and Tdap (tetanus, diphtheria, and pertussis) vaccines
- DTaP contraindications
  - Severe allergic reaction to a vaccine component or a reaction after a prior dose
  - Encephalopathy not attributable to another identifiable cause occurring within 7 days after vaccination

Resources for Families

- Whooping Cough (Centers for Disease Control and Prevention). www.cdc.gov/pertussis

Clinical Pearls

- Culture is considered the standard of reference for diagnosis, but PCR has excellent sensitivity and more readily available results.
- Antibiotics eradicate the organism from secretions, thereby decreasing communicability, but do not reduce symptoms.
- Cough may last weeks to months.

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Chapter 51

Bacterial Tracheitis

Girish D. Sharma, MD, FCCP

Introduction/Etiology/Epidemiology

- Bacterial tracheitis—also referred to as *membranous croup* or *laryngotracheobronchitis (LTB)*, *bacterial croup, pseudomembranous croup,* and *nondiphtheritic laryngitis with marked exudate*—is a serious and potentially life-threatening cause of upper-airway obstruction.
- The most common causative pathogen is *Staphylococcus aureus*; other organisms implicated are pneumococcus, *Moraxella catarrhalis*, and, occasionally, gram-negative enteric organisms and *Pseudomonas aeruginosa.*
- Since the decline in the incidence of epiglottitis and viral croup (associated with the use of the *Haemophilus influenzae* type b, or Hib, vaccine and nebulized and systemic corticosteroids, respectively), bacterial tracheitis has become a more common cause of upper-airway obstruction in children >2 years of age. However, bacterial tracheitis is still a rare disease.
- Reported incidence in children with an artificial airway is 0.67 (95% confidence interval, 0.59–0.81) and 5%–14% in patients with upper-airway obstruction who require intensive care.
- Bacterial tracheitis generally affects children between 4 weeks and 13 years of age, with a mean age of 5 years.
- Although it may be a primary bacterial infection, bacterial tracheitis is considered secondary to viral LTB.
- Tracheal mucosal injury caused by viral infection and impaired local immunity predisposes a child to bacterial superinfection.
- Bacterial tracheitis is characterized by marked subglottic edema, with ulceration, erythema, pseudomembranous formation on the tracheal surface, and thick, mucopurulent tracheal secretions.
- There is no seasonal variation.

Clinical Features

- Children with bacterial tracheitis tend to be older (preschoolers) than those with viral croup (toddlers).
- Onset of symptoms ranges from a few hours to 5 days and includes the following:
  - Toxic appearance and high fever
  - Inspiratory and possibly expiratory stridor

  - Seal-like brassy cough
  - Hoarseness
  - Dyspnea, retractions, and nasal flaring
  - Cyanosis
- Other symptoms may include choking episodes, orthopnea, dysphagia, and choking episodes.
- Progression is usually slow; however, the patient may progress rapidly to airway obstruction and respiratory failure.

Diagnostic Considerations

- Clinical features described for epiglottitis, viral croup, and bacterial tracheitis in Table 51-1 will help differentiate bacterial tracheitis from other conditions.
- Anteroposterior and lateral neck radiographs will show an irregular or "shaggy" subglottic narrowing versus the symmetrical tapering typically seen in croup.

Table 51-1. Comparison of Epiglottitis, Viral Croup, and Bacterial Tracheitis

Factor	Epiglottitis	Viral Croup	Bacterial Tracheitis
Age	2 to 6 y	3 mo to 3 y	6 mo to 6 y
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 Drooling Dysphagia Muffled voice	Child lying down Nontoxic Barking cough Hoarseness	Toxic Barking cough
Onset prodrome	Rapid, over a few hours	Variable, a few hours to 4 d	Variable, a few hours to 5 d
Stridor	Less common	Common	Common
Fever	High	Low grade	High
Chest retractions	Less common	Common	Common
Lateral neck radiographic finding	Swollen epiglottis	Subglottic narrowing	Pseudomembrane
Progression	Rapid	Usually slow	Usually slow
Recurrence	Rare	Common	Rare

From Sharma GD, Conrad C. Croup, epiglottitis, and bacterial tracheitis. In: Light MJ, Blaisdell CJ, Homnick DN, Schechter MS, Weinberger MM, eds. *Pediatric Pulmonology*. Elk Grove Village, IL: American Academy of Pediatrics; 2011.

- Direct visualization with a laryngoscope will show thick, mucopurulent tracheal secretions or pseudomembrane.
- Pertinent negative findings are lack of drooling and ability to lie supine without increased respiratory distress.
- Bacterial culture and Gram stain of bacterial culture will help confirm the causative organism.

Management

- The patient should be monitored very closely.
- Tracheal intubation and ventilation are often necessary in the event of respiratory collapse and failure to remove secretions effectively.
- Diagnostic endoscopy, which should be performed under general anesthesia, is also therapeutic because it reduces airway obstruction caused by the removal of secretions and sloughed tissue from the tracheal lumen.
- Rigid endoscopy may be necessary; sometimes, a repeat procedure is needed.
- Intravenous broad-spectrum antibiotics are started and later refined once the tracheal culture results are available.
- Corticosteroids may be administered before extubation.
- Frequent suctioning and humidification of the inspired air will prevent mucus plugging of the endotracheal tube.

Prognosis

- Complications include toxic shock syndrome, septic shock, acute respiratory distress syndrome, subglottic stenosis, and postintubation pulmonary edema.
- Most children recover with appropriate antimicrobial agents and aggressive supportive treatment, allowing extubation within 72–96 hours and median length of stay in the hospital of <1 week.
- With current management strategies, mortality is now uncommon.

When to Refer

- If bacterial tracheitis is suspected, immediately refer the patient to the emergency department for otolaryngology or pulmonology consult and emergent endoscopy.
- Sudden deterioration or worsening of airway obstruction may be caused by movement of the membrane and may warrant emergency interventions.

Resource for Families

- Croup (Patient). patient.info/doctor/croup-pro

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Chapter 52

Bronchitis

Kenan Haver, MD, FAAP

Introduction/Etiology/Epidemiology

- *Bronchitis* is defined as inflammation of the bronchus or bronchi, triggered by infection or irritation from noxious stimuli (eg, cigarette smoke, pollution).
- It is a common feature of many acute and chronic pulmonary diseases.
- It overlaps with many common disorders (eg, asthma, allergies with postnasal drip, gastroesophageal reflux).
- Treatment without identifying the underlying cause is rarely effective.
- There are 4 types of bronchitis: acute, chronic, protracted bacterial, and (rarely) plastic bronchitis.

Acute Bronchitis

- Acute bronchitis is usually caused by a respiratory infection that manifests with cough, with or without phlegm production that lasts for ≤3 weeks.
- Initially, the cough is dry but can become productive; dyspnea may be present.
- Acute bronchitis is usually accompanied by a nasal discharge that is watery at first; then, after several days, it may become thicker and colored or opaque. Change in consistency and/or color, by itself, does not indicate bacterial infection.

Chronic Bronchitis

- Bronchitis is considered chronic when it lasts for more than 3 or 4 weeks.
- Chronic bronchitis is often associated with underlying disease (eg, cystic fibrosis, primary ciliary dyskinesia, chronic aspiration).

Protracted Bacterial Bronchitis

- Protracted bacterial bronchitis (PBB) consists of cough associated with high colony counts of potentially pathogenic bacteria and neutrophils in the airway.
- It is seen more commonly in children with airway malacia; this is thought to be due to dynamic collapse that results in retention of bacteria and associated inflammation.
- Children with PBB may be at risk for chronic airway damage, including bronchiectasis.

Plastic Bronchitis

- Plastic bronchitis is a rare condition seen most often in patients with congenital heart disease who have undergone a Fontan procedure, but it has been reported in children with asthma and sickle cell disease.
- Arborizing, thick, tenacious casts of the tracheobronchial tree produce airway obstruction that may be expectorated or require retrieval with bronchoscopy.
- Selective lymphatic duct embolization has been effective in selected cases of recurrent plastic bronchitis associated with heart disease.

Pathophysiology

- Cough is a normal response to irritation (eg, mechanical, chemical, or inflammatory) of the tracheobronchial tree, mediated by neural reflexes from the brainstem. Cough receptors are in the nose, sinuses, larynx, pharynx, trachea, large airways, ear canals, pleura, pericardium, and diaphragm.
- Resulting inflammation leads to edema and mucus production.
- Resolution typically occurs in 2 weeks.
- Acute bronchitis is most commonly associated with viral respiratory infections.
  - Respiratory syncytial virus
  - Adenovirus
  - Influenza viruses
  - Parainfluenza
- Bacterial infections and other pathogens are much less common, including
  - *Bordetella pertussis*
  - *Mycoplasma pneumoniae*
  - *Chlamydophila pneumoniae*

Clinical Features

- Cough
- Shortness of breath
- Chest tightness or pain while coughing
- Expectoration of mucous plugs, which may be blood streaked

Differential Diagnosis

- There is broad overlap with disorders that manifest with persistent cough.
- The top 3 are
  - Asthma
  - Reflux
  - Allergies with postnasal drip

- Others include
  - Acute sinusitis
  - Aspiration
  - Bacterial tracheitis
  - Inhalation injury
  - Bronchiectasis
  - Pneumonia
  - Tracheomalacia
  - Tuberculosis
  - Habit cough

Diagnostic Considerations

- Diagnosis is primarily clinical. Other causes for acute cough, such as pneumonia, asthma, or postnasal drip, should be ruled out if suspected.
- A thorough patient history will help guide diagnosis.
- Chest examination findings may be normal or may manifest with findings of consolidation, crackles, or unequal breath sounds.
- Evaluation should focus on excluding other illnesses, particularly pneumonia.

Clinical Assessment for Pneumonia

- The *presence of ≥2 of the following signs* is associated with a high risk of pneumonia:
  - Fever ≥38°C (≥100.4°F)
  - Tachypnea
    - Age <2 months: >60 breaths per minute
    - Age 2–12 months: >50 breaths per minute
    - Age 1–5 years: >40 breaths per minute
  - Oxygen saturation ≤94%
    - Sensitivity of 26%
    - Specificity of 93%
- The *absence of all 3 of these signs* makes a diagnosis of pneumonia unlikely.
- Tests for the rapid diagnosis of influenza virus and other respiratory viruses should be used.
- A positive influenza test result may decrease both the need for additional diagnostic studies and antibiotic use, while guiding the appropriate use of antiviral agents.
  - In children, respiratory syncytial virus, rhinovirus, human metapneumovirus, human bocavirus, and parainfluenza viruses are the agents identified most frequently in both developed and developing countries. Dual viral infections are common, and one-third of children have evidence of viral-bacterial coinfection.

Chest Radiography

- Chest radiography is not necessary for patients well enough to be treated in the outpatient setting after evaluation in the office, clinic, or emergency department.
- It should be performed in patients with hypoxemia or clinically significant respiratory distress and those with failed initial antibiotic therapy. When obtained, radiographic findings are often normal. However, findings may include hyperinflation or a fine reticulated pattern bilaterally.
- It is both sensitive (75%) and specific (42%–100%) in the detection of pneumonia.

Pulmonary Function Testing

- Pulmonary function tests are not indicated but may help exclude other disorders—in particular, the reversible obstruction that is characteristic of asthma.

Bronchoscopy

- Flexible fiberoptic bronchoscopy is not indicated in acute bronchitis.
- Bronchoalveolar lavage can be helpful in the diagnosis of protracted bacterial or cast bronchitis and may help exclude other disorders, including tracheomalacia.

Management

- Treatment is aimed at symptom reduction until infection and inflammation resolve.
- Pulse oximetry should be performed in all children with pneumonia and suspected hypoxemia.
  - The presence of hypoxemia should guide decision-making regarding site of care and further diagnostic testing.
- Empirical antibiotic treatment is not indicated for acute bronchitis.
- If influenza is considered, confirm the diagnosis and initiate treatment within 48 hours of symptom onset for clinical benefit.
  - Neuraminidase inhibitors, such as oseltamivir or zanamivir, have activity against influenza A and B viruses.
  - Antiviral therapy reduces symptom duration by approximately 1 day.
- If pertussis is suspected, empirical therapy may be initiated while performing a diagnostic test for confirmation.
  - Antibiotic treatment decreases transmission but has little effect on symptom resolution.
- Published data show no effectiveness for most ingredients in over-the-counter cough suppressants when compared to placebo.
- Antitussives and expectorants have not been demonstrated to be useful.
- Effectiveness for the cough suppression properties of dextromethorphan and codeine has not been established in children.

Expected Outcomes/Prognosis

- Acute bronchitis is almost always self-limited in the otherwise healthy child.
- Chronic bronchitis is manageable with avoidance of triggers and management of underlying disease.
- Persistent bacterial bronchitis typically responds to antibiotic treatment.
- Patients with plastic bronchitis should be referred to a provider familiar with this disorder.

When to Refer

- Recurrent bronchitis
- Chronic bronchitis
- Chronic illness is suspected
- Airway abnormality is suspected

When to Admit

- Respiratory distress (grunting, retractions, nasal flaring)
- Hypoxemia
- Patient unable to maintain adequate hydration

Prevention

- Good handwashing is one of the best ways to avoid getting viruses and other respiratory infections.
- Advise getting influenza immunizations.
- Advise getting pertussis immunizations.
- Contact with another person with bronchitis or other acute respiratory illnesses should be avoided.
- Reduce exposure to secondhand smoke, chemicals, dust, and air pollution.

Resource for Families

- Bronchitis (Chest Cold) (Centers for Disease Control and Prevention). www.cdc.gov/getsmart/community/for-patients/common-illnesses/bronchitis.html

Clinical Pearls

- *Bronchitis* is defined as inflammation of the bronchus or bronchi.
- It is a common feature of many acute and chronic pulmonary diseases.
- It overlaps with many common disorders (eg, asthma, allergies with postnasal drip, gastroesophageal reflux).

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Chapter 53

Bronchiolitis

Girish D. Sharma, MD, FCCP

Introduction/Etiology/Epidemiology

- Bronchiolitis is a lower respiratory tract viral infection in infants, characterized by acute inflammation, edema, necrosis of the epithelial lining of the small airways, and mucus production.
- Bronchiolitis is the most common cause of hospital admission among infants during the first 12 months of life.
- In the United States, 2%–3% of infants younger than 12 months are hospitalized with a diagnosis of bronchiolitis.
- Bronchiolitis is most commonly caused by respiratory syncytial virus (RSV) (50%–80%), followed by human rhinovirus (5%–25%), parainfluenza, human metapneumovirus, coronavirus, adenovirus, influenza, and enterovirus.
- Bronchiolitis occurs most commonly from November to March in the United States, with some regional variation; human rhinovirus RSV occurs most commonly in the spring and fall.
- Ninety percent of children are infected with RSV in the first 2 years of life; ≤40% have signs and symptoms of lower respiratory tract infection during the initial infection.

Clinical Features

- In a typical case, after an incubation period of 4–6 days (range, 2–8 days), upper respiratory infection symptoms develop with irritability and poor feeding.
- Bronchiolitis typically begins as an upper respiratory infection with rhinorrhea, congestion, and cough, which may progress to tachypnea, grunting, wheeze, inspiratory crackles, rales, use of accessory muscles with retractions, and nasal flaring.
- Patients with more severe disease and respiratory distress may develop feeding with interruptions, reduced oral intake, dehydration, apnea, and respiratory failure.
- Risk factors include age <12 weeks, history of prematurity, underlying cardiopulmonary disease, immunodeficiency, and low concentration of maternal antibodies.
- Babies with low ex vivo interferon-γ responses in early life are more likely to have frequent viral respiratory infections, including those associated with wheeze.

- The disease course is variable and dynamic, ranging from transient events, such as apnea, to prolonged respiratory distress and respiratory failure.
- Bronchiolitis is likely to be more severe in the presence of chronic lung disease of prematurity, in infants born before 29 weeks, and in the presence of certain types of hemodynamically important congenital heart disease with pulmonary hypertension or congestive heart failure. Other factors include chronic lung disease caused by cystic fibrosis and Down syndrome and perinatal environmental smoke exposure.
- Twenty-five percent to 50% of patients who receive a diagnosis of bronchiolitis have similar recurrent symptoms, in the form of viral infection–associated wheeze.
- RSV bronchiolitis has been correlated with subsequent development of wheeze and asthma, and recent findings from the "COAST" (Childhood Origins of Asthma) study suggest that early rhinovirus illnesses are a more robust predictor of subsequent development of asthma in high-risk children.

Diagnostic Considerations

- American Academy of Pediatrics (AAP) clinical practice guidelines indicate that physicians should diagnose bronchiolitis and assess the disease severity on the basis of history and physical examination findings.
- The guidelines do not advocate the use of radiographic or laboratory studies routinely.
- Antigen testing of nasal washings, respiratory viral panel, and viral cultures is not routinely recommended.

Management

- Supportive management consists of oxygen supplementation when oxygen saturation at pulse oximetry (Spo_2) is <90%, with intravenous or nasogastric fluids administered to children with inadequate oral intake.
- AAP clinical practice guidelines do not recommend the administration of nebulized hypertonic saline in the emergency department or the administration of albuterol, epinephrine, or systemic steroids.
- Use of continuous pulse oximetry, chest physical therapy, and antibiotics (unless there is concomitant bacterial infection or strong suspicion) is not recommended by AAP guidelines.
- The physician may choose not to administer oxygen supplementation if the oxyhemoglobin saturation exceeds 90%.

Prevention

- Palivizumab should be given during the first year of life to infants with hemodynamically significant heart disease, chronic lung disease, or prematurity (preterm infants <32 weeks' gestation who require >21% oxygen for at least the first 28 days after birth).

- Palivizumab prophylaxis may be administered to preterm infants born before 29 weeks' gestation who are <12 months of age at the start of the RSV season.
- A maximum of 5 monthly doses (15 mg/kg per dose) should be given during the RSV season for the infants that qualify for its administration.
- Use alcohol-based disinfectant hand rubs or perform thorough hand-washing with soap and water before and after direct contact with the patient, after contact with inanimate objects in the direct vicinity of the patient, and after removing gloves.
- Counsel parents about the harmful effects of tobacco smoke exposure and advise smoking cessation.
- Encourage breastfeeding.
- Educate medical personnel and family members on appropriate evidence-based diagnosis, treatment, and prevention of bronchiolitis.

Prognosis

- The prognosis is usually self-limited, with a high degree of morbidity and a low mortality rate.
- Up to 60% of patients may develop acute otitis media.
- The presence of apnea, respiratory distress, respiratory failure, poor oral intake and resultant dehydration, and inability of the caretaker to monitor the infant may warrant hospitalization.
- Reported rare complications include myocarditis, arrhythmia, complete heart block, sepsis-like syndrome, seizures, focal neurological deficits, and hepatitis.
- Some patients develop asthma subsequent to human rhinovirus bronchiolitis.
- The mortality rate is ≤2.0 per 100,000 live births, with most deaths occurring in the 1–3-month-old age group; risk factors are low birth weight, increasing birth order, low 5-minute Apgar score, young maternal age, unmarried mother, and tobacco use during pregnancy.
- For patients with RSV bronchiolitis who are admitted to the pediatric intensive care unit, a mortality rate of 2%–7% has been reported.
- Reported long-term sequelae after severe bronchiolitis include bronchiolitis obliterans, allergic sensitization, wheeze, and asthma.

When to Refer

- Poor oral intake; dehydration; low oxyhemoglobin saturation (Spo_2 <90%); inability of the caretaker to monitor the patient; presence of complications, such as marked respiratory distress and apnea; and signs of respiratory failure are indications for referral.
- The presence of risk factors for severe disease, such as age <12 weeks, history of prematurity, underlying cardiopulmonary disease, or immunodeficiency, are indications for referral.

- Uncertain diagnosis, a need for prolonged oxygen supplement, and the need for frequent hospitalizations warrant referral to a pediatric pulmonologist.

Resources for Families

- Bronchiolitis (American Academy of Pediatrics). www.healthychildren.org/English/health-issues/conditions/chest-lungs/Pages/Bronchiolitis.aspx
- Bronchiolitis and Your Child (American Academy of Family Physicians). www.aafp.org/afp/2001/0215/p767.html
- Bronchiolitis – Discharge (Medline Plus). medlineplus.gov/ency/patientinstructions/000007.htm

Section 2. Parenchymal Infections

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Chapter 54

Bacterial Pneumonia

Paul C. Stillwell, MD, FAAP

Introduction/Etiology/Epidemiology

- Pneumonia in children is categorized in the following ways to help differentiate the potential infecting organisms, treatment strategies, and expected outcomes:
  - — Community-acquired pneumonia (CAP) in an otherwise healthy child
  - — Health care–related pneumonia or hospital-acquired pneumonia
  - — Pneumonia in an immunocompromised patient
  - — Pneumonia with complications (effusion, empyema, abscess)
- The incidence of CAP is highest in children <4 years of age—approximately 35–40 per 1,000, compared to only 20 per 1,000 school-aged children and 10 per 1,000 teenagers and adolescents.
- Pneumonia is a common cause of death in children who reside in underserved countries.
- The prevalence of bacterial pneumonia in CAP in children is ≤10% overall; it is less frequent in younger children and more common in teenagers and adolescents.
- *Mycoplasma* is emerging as the most common bacterial cause of CAP in hospitalized children. In a study of hospitalized children with CAP in 3 U.S. cities, *Mycoplasma* was identified in 2% of the children <2 years of age and 23% of the adolescents.
- *Streptococcus pneumoniae* accounts for 3%–4% of cases, and *Staphylococcus aureus* accounts for about 1% of cases across all age groups. These organisms may account for a higher percentage of pneumonias in developing countries.
- The spectrum of bacterial agents that causes pneumonia in children with incomplete immune function includes not just streptococci and staphylococci, but also *Pseudomonas aeruginosa, Klebsiella* species, *Legionella, Enterobacter, Acinetobacter, Stenotrophomonas maltophilia, Burkholderia cepacia,* and anaerobes.
- Viral, fungal, and mycobacterial infections should also be considered as etiologic origins in the immunocompromised child.

Clinical Features

- The most common symptoms of bacterial pneumonia are cough, fever, and shortness of breath.
- Other constitutional symptoms may include nausea, loss of appetite, and fatigue.
- The most common signs of bacterial pneumonia are tachypnea, crackles and/or wheezes, retractions, and perhaps reduced intensity breath sounds.
- If an area of consolidated lung is present, tactile fremitus or vocal egophony may be evident.
- If an effusion is present, there may be dullness at percussion.

Diagnostic Considerations

- Although most young children with bacterial pneumonia either do not have much sputum or have trouble with expectoration, a good sputum sample, if available, may be used to identify the infecting bacteria.
- Blood culture results are positive in an estimated ≤10% of bacterial pneumonia, but this increases to almost 25% if a parapneumonic effusion or empyema is present.
- Bacterial antigen and antibody tests are of low yield and are nonspecific.
- Polymerase chain reaction (PCR) assessment of *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* are components of most multiplex respiratory pathogen panels. (Currently, there is only 1 Food and Drug Administration–approved multiplex PCR test.)
- A chest radiograph may not be needed to establish a clinical diagnosis of pneumonia.
  - If obtained, a chest radiograph offers poor discrimination between viral and bacterial pneumonia.
  - Focal lobar consolidation coupled with high fever, increased white blood cell (WBC) count, and a left-shifted differential WBC count is concerning for bacterial pneumonia (Figure 54-1) and is commonly treated as bacterial, even if microbiological confirmation is lacking.

Treatment

- For a child with mild illness from CAP, supportive therapy might be all that is needed.
- Empirical antibiotic therapy for presumed bacterial pneumonia should be administered with high-dose (eg, 90 mg/kg/d) amoxicillin as an outpatient or perhaps intravenous ampicillin if an inpatient (although oral penicillin therapy as an inpatient might be acceptable).
- The antibiotic agent and dose should be selected according to local bacterial and resistance profiles.

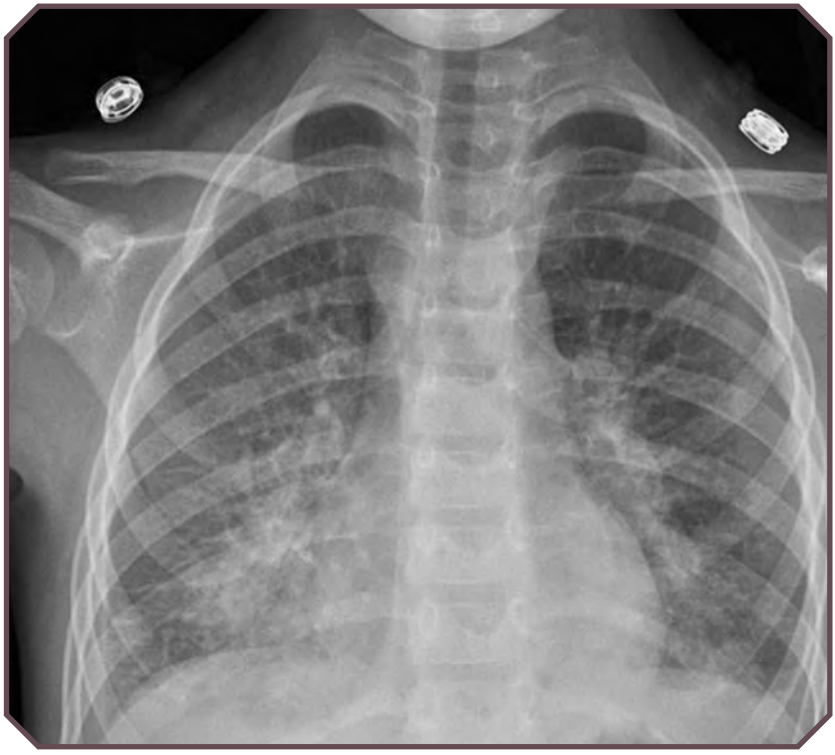

Figure 54-1. *Streptococcus pneumoniae* in a 7-year-old child with high fever, increased white blood cell count, and a positive blood culture finding. Frontal chest radiograph shows bilateral disease with perihilar markings and lobar opacity in the right middle lobe. Note: This child had not been immunized.

- Per the 2015 American Academy of Pediatrics *Red Book*, "Macrolides, including azithromycin, clarithromycin, and erythromycin, are the preferred antimicrobial agents for treatment of pneumonia in school-aged children who have moderate to severe infection and those with underlying conditions, such as sickle cell disease."

Prognosis

- Most children in advantaged countries recover completely with antibiotic therapy and have no long-term sequelae.
- Bronchiectasis may occur with severe bacterial pneumonia, even with appropriate antibiotic therapy.
- In less advantaged countries, pneumonia is a common cause of death in children.

When to Refer

- Refer the patient if there is prolonged illness or fevers, lethargy and dehydration, or deteriorating physical examination findings suggestive of more serious disease and perhaps pneumonia complicated by an abscess, bronchopleural fistula, or necrosis (Figure 54-2).

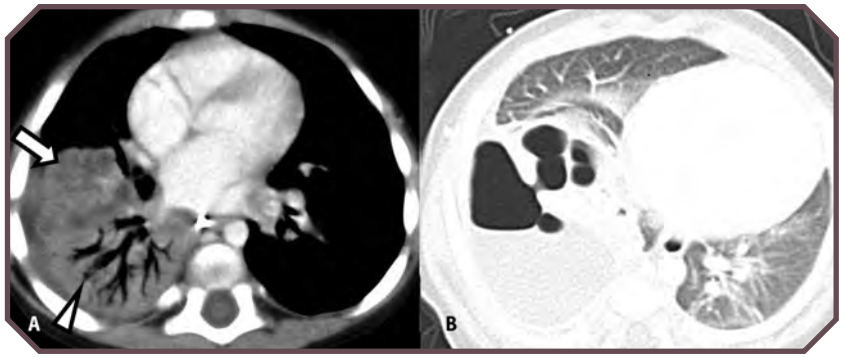

Figure 54-2: Complicated pneumonia in a 6-year-old child. A. Axial contrast-enhanced computed tomographic (CT) image demonstrates right lower lobe airspace attenuation. Note the region of patchy, poor perfusion (arrow) anterior to the region of extensive air bronchograms (arrowhead). B. Follow-up axial CT image obtained 13 days later demonstrates right lower lobe cystic necrosis. A chest radiograph obtained 2 years later, at 8 years of age, demonstrated normal findings (not shown).

Resources for Families

- Pneumonia (American Lung Association). www.lung.org/lung-health-and-diseases/lung-disease-lookup/pneumonia
- Pneumonia (American Academy of Pediatrics). www.healthychildren.org/English/health-issues/conditions/chest-lungs/Pages/Pneumonia.aspx

Clinical Pearl

- Most CAPs in otherwise healthy, immunized children are caused by viruses or atypical bacteria, especially *Mycoplasma*. A small percentage is caused by bacteria, usually *S pneumoniae*.

Chapter 55

Viral Pneumonia

Paul C. Stillwell, MD, FAAP

Introduction/Etiology/Epidemiology

- Pneumonia in children is categorized in the following ways to help differentiate the potential infecting organisms, treatment strategies, and expected outcomes:
  - Community-acquired pneumonia (CAP) in an otherwise healthy child
  - Health care–related pneumonia or hospital-acquired pneumonia
  - Pneumonia in an immunocompromised patient
  - Pneumonia with complications (effusion, empyema, abscess)
- The incidence of CAP is highest in children <4 years of age—approximately 35–40 per 1,000, compared to only 20 per 1,000 school-aged children and 10 per 1,000 teenagers and adolescents.
- Pneumonia is a common cause of death in children who reside in regions poor in health resources.
- Viral lower respiratory tract infections are the most common etiologic origin of CAP and account for approximately 65% of infections in all children and approximately 80% in children <2 years of age.
- Viral coinfections occur 15%–20% of the time, and viral-bacterial infections occur about 5% of the time. In particular, viral-bacterial coinfections have been well documented between influenza virus and *Streptococcus pneumoniae*, *Staphylococcus aureus*, and group A *Streptococcus*.
- The most common viruses identified as causing pneumonia are
  - Respiratory syncytial virus
  - Human rhinovirus
  - Human metapneumovirus
  - Adenovirus
  - Parainfluenza virus types 1–3
  - Influenza virus A and B
  - Coronaviruses
- Other viruses can cause problematic pneumonia in the immunocompromised host, and the viruses listed here can cause life-threatening pneumonia in children with chronic lung conditions or those with abnormal host defenses.
- *Varicella* pneumonia occurs rarely in older children and young adults; the frequency has declined since the *Varicella* vaccine became available.

Clinical Features

- The most common symptoms of pneumonia are cough, fever, and shortness of breath.
- Other constitutional symptoms may include nausea, loss of appetite, and fatigue.
- The most common signs are tachypnea, crackles and/or wheezes, retractions, and perhaps reduced-intensity breath sounds.
- Wheezing tends to be more commonly associated with viral or *Mycoplasma* pneumonia than with "typical" bacterial pneumonia.

Diagnostic Considerations

- Differentiating viral from bacterial pneumonia is challenging without identification of a specific organism.
  - — While chest radiographic findings in viral pneumonia tend to be diffuse and bilateral (Figure 55-1), the findings are nonspecific.

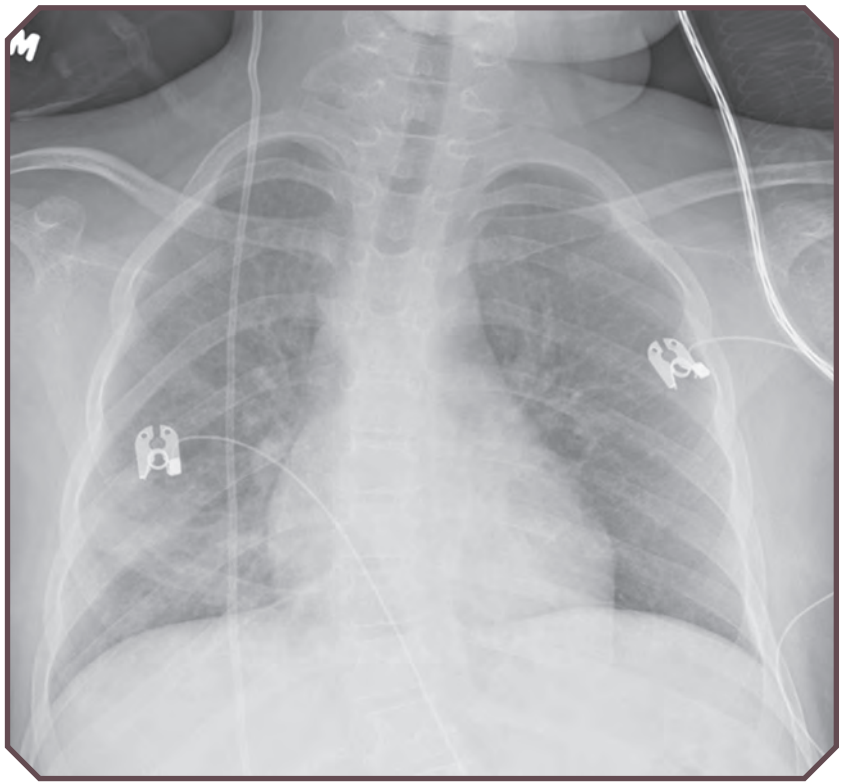

Figure 55-1. Adenovirus pneumonia in an 8-year-old hospitalized child. Frontal chest radiograph demonstrates diffuse, bilateral, fine perihilar opacities with no focal air space disease or effusions. Also note ventriculoperitoneal shunt tubing vertically oriented over the right hemithorax.

  - The total white blood cell (WBC) count, WBC differential, C-reactive protein level, and procalcitonin level are marginally helpful in differentiating viral from bacterial pneumonia.
- There is controversy whether chest radiography is necessary for the diagnosis of pneumonia in children.
  - Some guidelines indicate that the diagnosis can be established on the basis of clinical grounds alone.
  - Other guidelines base the diagnosis of pneumonia on an abnormal chest radiographic finding. The main utility for radiographs is to search for focal opacities when there is unresolved concern for bacterial infection.
  - For mildly ill children in the outpatient setting, obtaining a chest radiograph is not likely to affect management or outcome. For children ill enough to be admitted to the hospital, obtaining a chest radiograph is suggested.
- The currently available polymerase chain reaction (PCR) panels are used to test for a multitude of viruses, as well as *Mycoplasma* and *Chlamydophila,* with a rapid turnaround time.
- The currently available rapid influenza tests are less sensitive than PCR but may be acceptable for use in the outpatient setting.
- Serial serologic testing and viral cultures are too slow to be of clinical usefulness.
- Direct fluorescent stains have largely been replaced by PCR technology.

Treatment

- Children with mild CAP with either suspected or proven viral etiologic origins require only supportive care.
- The decision to hospitalize the child depends on the severity of the respiratory disease, as well as the resources and ability of the child's family to provide safe care at home. Hospitalization should be considered for all infants <6 months of age.
- The antivirals oseltamivir and zanamivir are effective therapies for influenza pneumonia if started early in the course of illness. Treatment for influenza should be considered in severe or complicated pneumonia due to influenza, regardless of whether onset of illness has been >48 hours before admission.
- Other antiviral antibiotics, such as cidofovir, acyclovir, famciclovir, and valacyclovir, are most often used for immunocompromised children with severe infections, usually in conjunction with assistance from pediatric infectious disease specialists.

Prognosis

- Most children recover in a few days to 2 weeks.
- Some patients may develop an asthma-like condition afterward that can be managed like asthma to try to minimize the respiratory impact of subsequent viral infections.
- Rarely, bronchiolitis obliterans can develop, particularly after adenovirus infection; this complication is more prevalent in indigenous children.

When to Refer

- Refer the patient if there is a recurrence of fever after initial improvement, which is concerning for sequential bacterial pneumonia, particularly after influenza pneumonia.
- Refer the patient if there is prolonged illness or recurrent cough and wheeze after viral infection, which may be indicators of asthma.

When to Admit

- Rapidly deteriorating respiratory status, impending respiratory failure, hypoxemia, and inability to stay well hydrated are all indications for hospitalization.

Prevention

- Infections with influenza can be limited by appropriate vaccine strategies: All people >6 months of age should receive annual influenza immunizations.
- Oseltamivir and zanamivir can be used prophylactically in children exposed to an infected individual.

Resources for Families

- Pneumonia (American Lung Association). www.lung.org/lung-health-and-diseases/lung-disease-lookup/pneumonia
- Pneumonia (American Academy of Pediatrics). www.healthychildren.org/English/health-issues/conditions/chest-lungs/Pages/Pneumonia.aspx

Clinical Pearl

- Most CAP in otherwise healthy pediatric hosts is caused by viruses and probably does not require treatment with antibiotics.

Chapter 56

Mycoplasma Pneumonia

Oren Kupfer, MD, and Paul C. Stillwell, MD, FAAP

Introduction/Etiology/Epidemiology

- *Mycoplasma pneumoniae* is considered an "atypical" bacterial organism because it lacks a cell wall; the other organisms that commonly cause atypical pneumonia are *Chlamydophila pneumoniae* and *Legionella*; *Bordetella pertussis, Bordetella parapertussis,* and *Chlamydia psittaci* are other atypical bacteria that may be associated with pneumonia.
- Infection with *M pneumoniae* is a common cause of community-acquired pneumonia (CAP) in children that accounts for 16% of the pneumonias in hospitalized children aged 5–9 years and 23% in children aged 10–17 years. It can occur in clusters related to schools or smaller communities.
- *M pneumoniae* is the most common single infecting agent that causes CAP in adolescents.
- *Mycoplasma* can also be an etiologic origin of otitis media and acute tracheobronchitis.
- Mucocutaneous lesions are unusual. Other extrapulmonary (particularly neurological) problems have been associated with *Mycoplasma* infections.

Clinical Features

- The infection usually begins with pharyngitis and nonproductive cough, followed by chest pain and dyspnea. Subsequently, the cough may become productive.
- The degree of fever is highly variable.
- Constitutional symptoms are common, including headache and malaise.
- Inspiratory crackles with or without expiratory wheezing are common.
- Upper respiratory tract symptoms of nasal congestion or mucoid rhinorrhea are not common.

Diagnostic Considerations

- The diagnosis is commonly established by using polymerase chain reaction testing on respiratory secretions. This method is increasingly replacing other tests when available. However, serologic testing (immunoglobulin M and G antibody testing) is still used in some circumstances. *Mycoplasma* is difficult to culture and requires special media.

- Cold agglutinins, which are present in about 50% of children with an acute *Mycoplasma* infection, are nonspecific.
- Chest radiographic findings can be variable but most commonly show patchy, streaky opacities that are not distinguishable from pneumonias caused by other organisms, both typical and atypical (Figure 56-1).

Treatment

- Treatment with a macrolide antibiotic is usually offered, although there is controversy regarding the benefit of antibiotic therapy.
- Other supportive measures, such as hydration, adequate oxygenation, and nutrition, should be assessed.

Prognosis

- The prognosis for full recovery is excellent.
- Cough may linger for a month or so after resolution of the acute infection.
- There is a small risk of prolonged airway injury, such as bronchiectasis, air trapping, or mosaic attenuation, that is suggestive of bronchiolitis obliterans at computed tomography.
- Rarely, acute *Mycoplasma* pneumonia progresses to acute respiratory distress syndrome or necrotizing pneumonia.

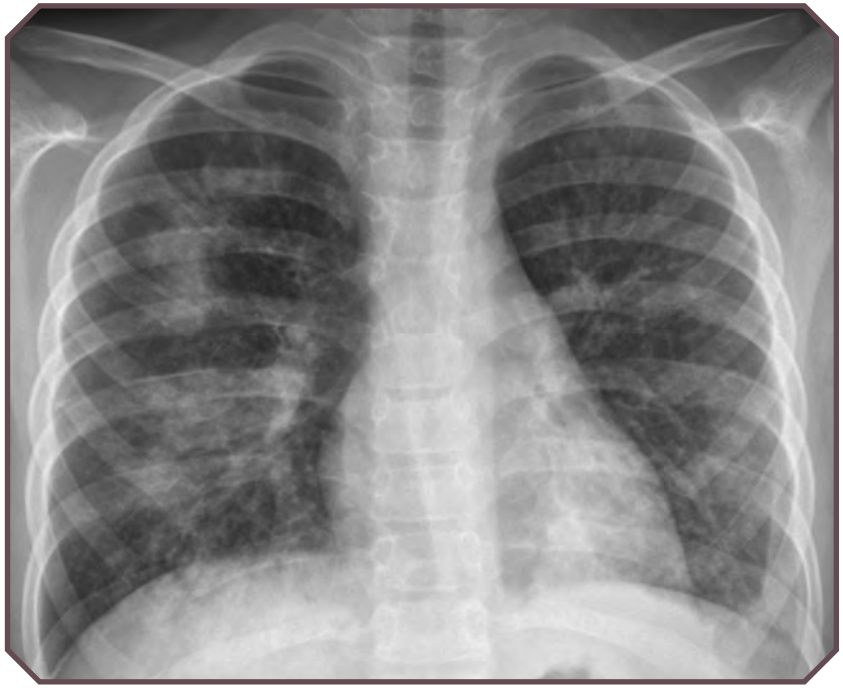

Figure 56-1. *Mycoplasma* pneumonia in a previously healthy 9-year-old boy. Frontal chest radiograph shows nonspecific bilateral upper and lower lobe patchy opacities.

- More severe *Mycoplasma* infections can occur in children with sickle cell disease, Down syndrome, immunodeficiencies, and chronic cardiorespiratory disease.
- Severe *Mycoplasma* pneumonia can cause obliterative bronchiolitis and residual airway obstruction.
- There may be an association between *Mycoplasma* and incident asthma.
- Outbreaks of *Mycoplasma*-associated Stevens-Johnson syndrome have been reported.

When to Admit

- Admit children with progressive respiratory illness or impending respiratory failure.

Resources for Families

- *Mycoplasma pneumoniae* Infections (American Academy of Pediatrics). www.healthychildren.org/English/health-issues/conditions/chest-lungs/Pages/Mycoplasma-pneumoniae-Infections.aspx
- *Mycoplasma pneumoniae* Infection (U.S. Centers for Disease Control and Prevention). www.cdc.gov/pneumonia/atypical/mycoplasma/index.html

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Chapter 57

Chlamydial Pneumonia

Paul C. Stillwell, MD, FAAP

Introduction/Etiology/Epidemiology

- There are 3 members of the *Chlamydia* family that can cause pneumonia in children: *Chlamydophila pneumoniae, Chlamydia psittaci,* and *Chlamydia trachomatis*.
- *C pneumoniae* accounts for <1% of the organisms identified in children hospitalized with community-acquired pneumonia (CAP).
  - *C pneumoniae* is considered one of the "atypical pneumonias," along with *Mycoplasma pneumoniae* and *Legionella,* which are challenging to differentiate from one another and from other organisms without positive identification of the infecting agent.
  - Children with sickle cell disease may be exceptionally prone to pneumonia with *Chlamydophila,* causing acute chest syndrome and potentially fatal outcome.
- Psittacosis is rare and is usually contracted from household pet birds.
- *C trachomatis* is usually acquired from the birth canal and accounts for many cases of "afebrile pneumonia of infancy" in the first few months after birth.
  - Eye prophylaxis in the delivery room does not protect the infant from respiratory infection by *C trachomatis.*

Clinical Features

- The signs and symptoms of *C pneumoniae* are similar to the other CAPs: cough, wheeze, fever, dyspnea, fatigue, and reduced oral intake.
- Wheezing may be more prominent with *Chlamydophila* infections; there is concern for an association between *Chlamydophila* and childhood asthma.
- A prolonged staccato cough with apparent bronchitis may accompany or precede pneumonia caused by *Chlamydophila*.

Diagnostic Considerations

- *C pneumoniae* can be identified by means of polymerase chain reaction (PCR) testing on samples obtained from the nasopharynx.
- Serologic testing can be used if PCR technology is not available.
- *C pneumoniae* is difficult to culture and requires a special medium.
- Chest radiographs of pneumonia caused by *Chlamydophila* are of little diagnostic value. However, when obtained, radiographs demonstrate patchy airspace disease that may be multilobar.

Treatment

- A macrolide antibiotic (eg, erythromycin, clarithromycin, or azithromycin) is the treatment of choice for *C pneumoniae* lower respiratory tract infection.
- The response to antibiotic therapy may be slow; this slow response may support the diagnosis.

Prognosis

- The prognosis for full recovery is excellent.
- The pneumonia may relapse, particularly if the course of antibiotics is not completed as recommended.
- In children with sickle cell disease, *C pneumonia*e may cause fatal acute chest syndrome.

When to Refer

- Any child with sickle cell disease suspected of having *C pneumoniae* pneumonia should be referred for specialized care.
- A child with presumed CAP who is deteriorating despite receiving empirical therapy should be further evaluated as to the etiologic origin of the infection and the potential management of complex pneumonia.

Resources for Families

- Chlamydia pneumoniae Infection (U.S. Centers for Disease Control and Prevention). www.cdc.gov/pneumonia/atypical/cpneumoniae
- Psittacosis (U.S. Centers for Disease Control and Prevention). www.cdc.gov/pneumonia/atypical/psittacosis.html

Clinical Pearl

- Pneumonia caused by *C pneumoniae* occurs infrequently in childhood CAP. Many current PCR multiplex respiratory panels can be used to test for this organism.

Chapter 58

Tuberculosis

Carol Conrad, MD

Introduction

- Tuberculosis (TB) is typically caused by *Mycobacterium tuberculosis* and occasionally by *Mycobacterium bovis.*
- The lungs are the major site of *M tuberculosis* infection.
- *M bovis* infection results primarily from ingestion of unpasteurized milk or dairy products. Infection by *M bovis* represents about 1%–2% of TB cases and occurs most often in developing countries.

Epidemiology

- Worldwide, TB remains one of the leading causes of death from infectious disease. In 2015, there were an estimated 10.4 million new (incident) TB cases worldwide.
- Diagnosis of TB had previously been difficult, with the standard testing relying on sputum testing with acid-fast bacilli stain and culture of the primary organism, which can take <6 weeks. More effective diagnostic methods and treatments are in use today. Globally, the treatment success rate for people with newly diagnosed TB was 86% in 2013, which has been sustained since 2005.
- Multidrug-resistant (MDR; resistant to both isoniazid and rifampin) and extensively drug-resistant (resistant to isoniazid, rifampin, fluoroquinolones, and at least 1 second-line injectable agent, such as amikacin, kanamycin, or capreomycin) TB pose the greatest threat to elimination of TB, particularly in Sub-Saharan southern Africa, China, India, and the former Soviet Union.
- Almost all cases of TB are acquired through person-to-person contact via droplet nuclei formed by sneezing, coughing, or phonating.

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, a cellular response is elicited by macrophage activation.
- At the slow rate of replication by *M tuberculosis,* this process takes about 4–8 weeks.

- A tubercle, or granuloma, is a formation of an epithelioid cluster of macrophages with phagocytosed bacilli and is the primary focus that represents infection.
- The infection spreads through the lymphatic system to the hilar lymph nodes.
- The granuloma will proceed to fibrosis and calcification and produce an isolated calcification at chest radiography. This is termed a *tubercle* or *Ghon focus*.
- A Ghon focus consists of the primary focus, lymphangitis, and regional hilar lymph node inflammation associated with it. This tends to be located in the middle or lower lobes of the lungs.

Dissemination

- Bacilli can escape before a sufficient immune response has been elicited. The bacilli proliferate inside alveolar macrophages and kill the cells. Dying cells release TB bacilli into the surrounding lung parenchyma.
- Bacilli spread by erosion of the caseating lesions into the lung airways, or cavities can form. Infection is spread via droplets produced during cough.
- Bacilli spread hematogenously to other organs and can result in miliary TB.
- Symptomatic hematogenous spread occurs in immunocompromised patients.

Reactivation of Disease

- Reactivation of latent disease occurs in adolescents and adults and results when persistent bacteria in a host suddenly proliferate. Immunosuppression is associated with reactivation of TB (Box 58-1). This reactivated form of TB is the classic upper-lobe, cavitary disease.
- In contrast to primary disease, reactivated TB tends to be localized, and there is little regional lymph node involvement.
- Reactivation of disease may occur in 50%–60% of patients who do not receive appropriate antibiotic therapy.

Clinical Features

Primary Pulmonary Disease

- Latent tuberculous infection is different from active disease. Most initial infections are asymptomatic and controlled by cell-mediated immunity. When infection is present, the child yields a positive tuberculin skin test (TST) result, but there is no clinical evidence of organ involvement.
- Approximately 10% of children who become infected develop disease, with infants and postpubertal adolescents at highest risk.
- Pulmonary disease is the most common presentation of TB in children. Symptoms include fever most commonly, cough, weight loss or poor weight gain, night sweats, and chills.

Box 58-1. Immunosuppressive Conditions Associated With Reactivated Tuberculosis

- HIV infection and AIDS
- Solid organ transplant recipient
- Diabetes mellitus
- Lymphoma
- Corticosteroid use
- Diminution in cell-mediated immunity
- Chronic renal disease
- Treatment with tumor necrosis factor–α inhibitors

- A positive skin test result directs the diagnosis toward TB. However, a negative test result for TB infection (skin test or blood-based test) does not rule out TB, particularly if the child was infected within 12 weeks.
- Radiographs may demonstrate lymphadenopathy, lymphohematogenous spread, and calcified nodules (Ghon foci), often with calcified nodes (Ghon complex). Approximately one-third of patients develop a pleural effusion. Lymphadenopathy can cause bronchial compression with resultant atelectasis (Figure 58-1).
- Infants <1 year of age are at highest risk for developing disseminated TB (10%–20%), as well as pulmonary TB (30%–40%), because they have reduced microbial killing capacity. The risk for dissemination decreases with increasing age, but it increases again in adolescents (Table 58-1).
- The most common sites of extrapulmonary disease in children are the superficial lymph nodes and the central nervous system. Infants have the highest risk of progression of TB disease with meningeal involvement.

Table 58-1. Risk of Pulmonary and Extrapulmonary Disease in Children After Infection With *Mycobacterium tuberculosis*

Age	Risk of Disseminated TB or TB Meningitis	Risk of Pulmonary TB	Risk of 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%

TB, tuberculosis. Adapted with permission from Marais BJ, Gie RP, Schaaf HS, et al. The natural history of childhood intrathoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. *Int J Tuberc Lung Dis.* 2004;8:392–402.

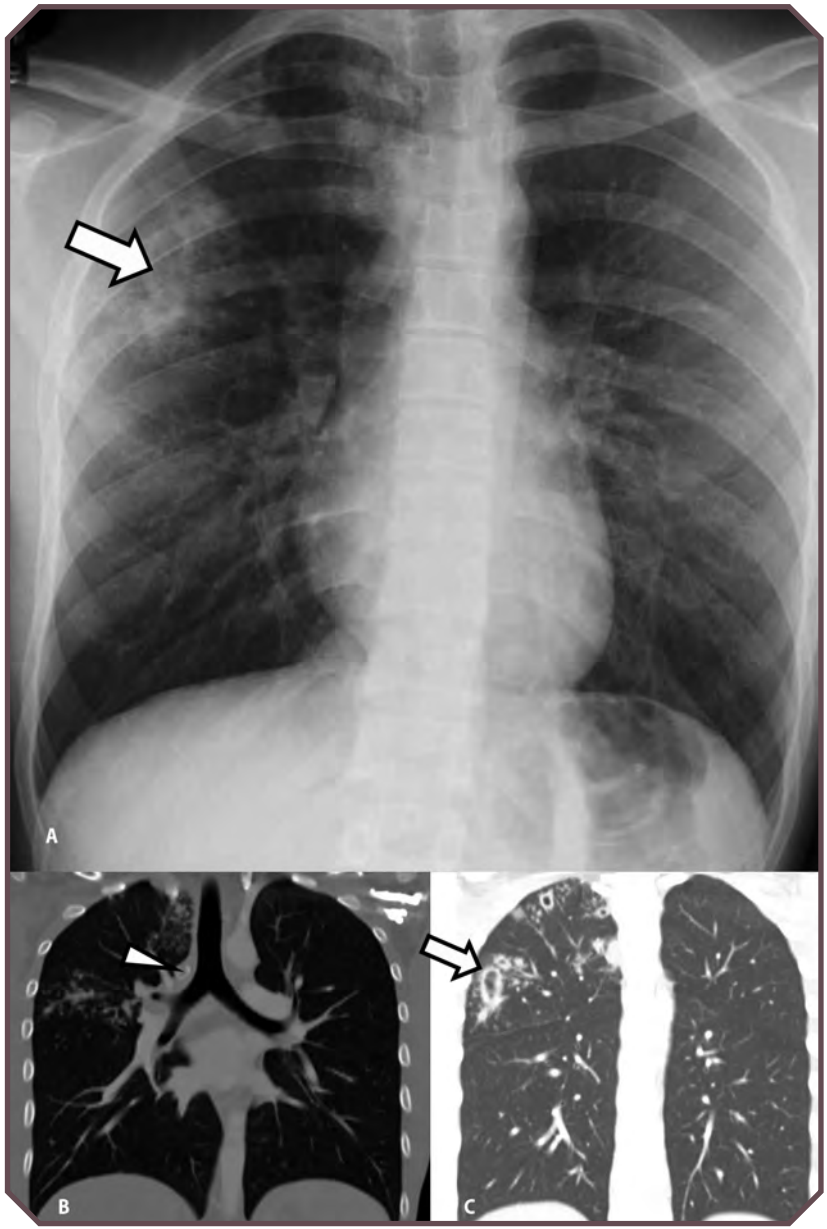

Figure 58-1. Tuberculosis in a 16-year-old girl with chronic cough. A. Frontal chest radiograph shows multiple nodules in the right upper lobe, some of which are cavitary (arrow). Coronal reconstructed images from a contrast-enhanced computed tomographic examination in B. bone and C. soft-tissue windows demonstrate nodules, some with cavitation (arrow on C), in addition to areas of tiny, miliary nodules and a calcified hilar node (arrowhead on B).

Extrapulmonary Disease

- Approximately 15% of patients with active TB also present with TB disease in an extrapulmonary site. The risk is increased in immunocompromised patients, as well as children <2 years of age.
- The most commonly involved sites include, in order of frequency, lymph nodes, pleural space, meninges, pericardium, skin, genitourinary tract, bone and joint sites, and peritoneum–gastrointestinal tract.

Diagnostic Considerations

Skin Testing

- The TST (Figure 58-2) is the primary screening tool used in the United States. The American Academy of Pediatrics (AAP) recommends that a TST be performed to determine latent TB infection if any of the following conditions are true:
  - A patient has had contact with people with confirmed or suspected contagious TB (contact investigation).
  - Children have radiographic or clinical findings suggestive of active TB disease.
  - Children emigrated from countries with endemic infection (eg, Asia, the Middle East, Africa, Latin America, or countries of the former Soviet Union).
  - Children have travel histories to countries with endemic infection and have had substantial contact with people from such countries.
  - Annual skin testing is indicated in children with HIV infection and in incarcerated adolescents.
  - An initial skin test should be performed before initiation of immunosuppressive therapy, including prolonged steroid administration, use of tumor necrosis factor–α antagonists, and other immunosuppressive therapy.
- The preferred skin test is the Mantoux test, the results of which should be interpreted within 48–72 hours of placement. See Box 58-2 for guidelines in interpreting induration in low- and high-risk populations.
- The sensitivity of TST tests ranges from 80% to 96%.
- Causes of false-negative TST findings are listed in Box 58-3.
- For children >5 years of age, interferon-γ release assays (IGRAs) are now available for diagnosis (see the Improving Immunologic Diagnosis section in this chapter).

Interpreting Skin Test Results

Figure 58-3 provides a flowchart for the evaluation of a child exposed to a person with contagious TB.

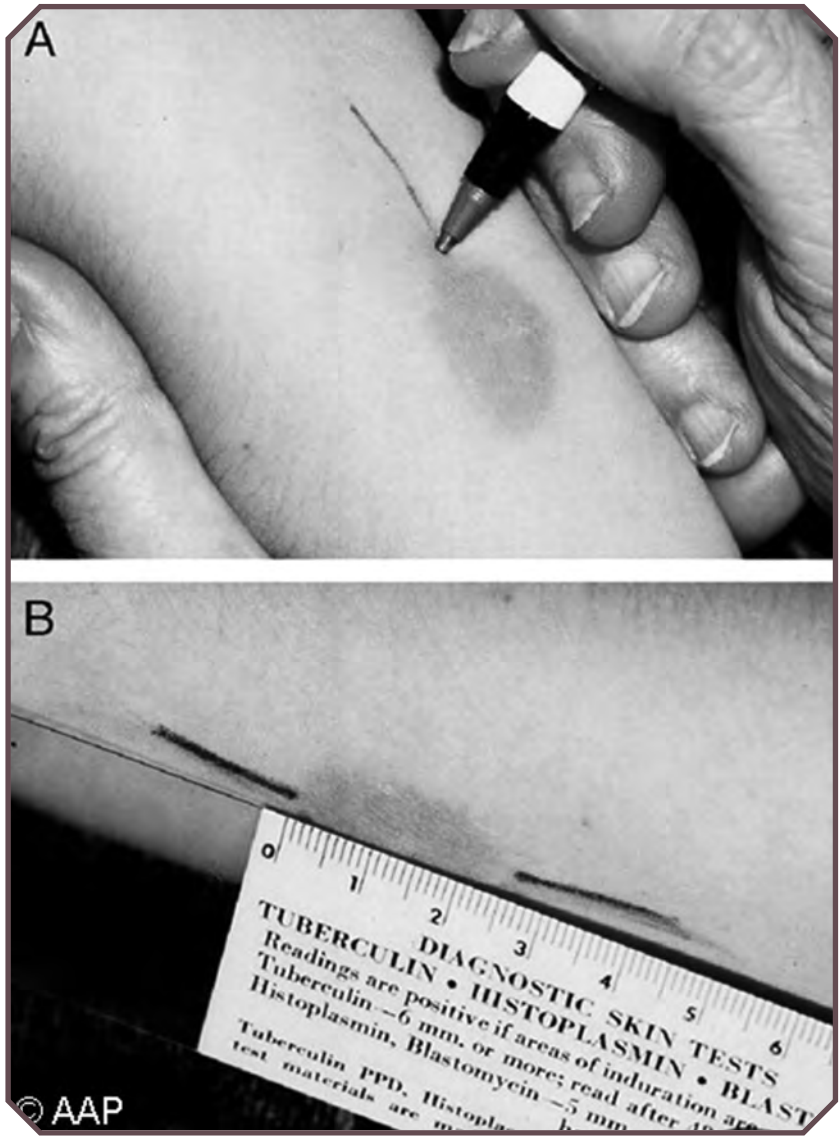

Figure 58-2. A positive skin test result for tuberculosis is shown. A. The edges of the induration are marked prior to measurement. B. The induration is measured.

Effect of BCG Vaccine

- False-positive reactions may occur in children who have received the bacille Calmette-Guérin (BCG) vaccine.
- Nonetheless, receipt of the BCG vaccine is not a contraindication to TST administration, and interpretation of TST results is not affected by receipt of the BCG vaccine.
- Interpretation of the TST results depends on the child's risk factors.

Box 58-2. Definition of Positive Tuberculin Skin Test Results in Infants, Children, and Adolescents

Induration of 5 mm and Larger

Children in close contact with people with active tuberculosis (TB) disease who are known or suspected to be contagious

Children suspected to have active TB disease
- Findings on chest radiographs consistent with active or previously active TB disease
- Clinical evidence of active TB disease[a]
- Children undergoing immunosuppressive therapy[b] or those with immunosuppressive conditions, including HIV infection

Induration of 10 mm and Larger

Children at increased risk of disseminated TB disease
- Children <4 years of age
- Children with other medical conditions, including Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, and malnutrition
- Children with a likelihood of increased exposure to TB disease
- Children born in regions of the world with high TB prevalence
- 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
- Children who travel to regions of the world with high TB prevalence

Induration of 15 mm and Larger

- Children ≥4 years of age without any risk factors

These definitions apply, regardless of previous bacille Calmette-Guérin immunization; erythema alone at the tuberculin skin test site does not indicate a positive test result. Test results should be interpreted 48–72 hours after intradermal antigen placement. From American Academy of Pediatrics. Tuberculosis. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases.* 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:805

[a] Evidence at physical examination or laboratory assessment that would include TB in the working differential diagnosis (eg, meningitis).

[b] Including immunosuppressive doses of corticosteroids.

Sputum Analysis

- It can be difficult to establish a diagnosis of TB in children because they tend to be unable to expectorate, and the bacterial load within the sputum is low.
- In general, for patients with no evidence of cavitary lesions, it is best to select bacteriologic specimens for smear and culture from early-morning gastric aspirate washings obtained from a nasogastric tube after overnight fasting on 3 consecutive days. This is typically completed in a hospital.

Box 58-3. Causes of False-Negative Tuberculin Skin Test Reactions

1. Infections (eg, recent tuberculosis [TB] infection [<12 weeks], active TB, HIV, measles, varicella, typhoid fever, brucellosis, typhus, leprosy, blastomycosis)
2. Live-virus vaccines (can suppress tuberculin reactivity for 4–6 weeks; live-virus vaccines can be administered at the same visit as the TST, but if they are not administered on the same day, they should be separated by at least 6 weeks)
3. Medical conditions (eg, chronic renal failure, malignancies, sarcoidosis, poor nutrition) and glucocorticoid therapy (if initiated before the TST)
4. Technical factors (eg, inadequate dose, improper storage, failure to administer the test intradermally, improperly timed interpretation)

- Even so, the rate of positive confirmation via smear is only 10%–15%, and culture results are positive 30%–40% of the time.

Improving the Analysis of Specimens Obtained

- Sputum obtained via induction with nebulization of hypertonic saline can induce a higher yield.
  - — Sputum can be induced from children as young as 1 month of age.
  - — The microbiological yield from induced sputum is similar to that from 3 gastric aspirates.
  - — Bronchoalveolar lavage may offer advantages in cases of negative smear results.
- The microscopic observation drug susceptibility assay method is a molecular method for the detection of *M tuberculosis* for species identification of isolates from culture by using molecular probes of the genetic sequence of *M tuberculosis* and can be used to identify drug-resistant genes in parallel.
- These methods have been assessed in a pediatric hospital setting and are more sensitive than solid media.
- Polymerase chain reaction techniques are also more sensitive and specific.

Improving Immunologic Diagnosis

- There are 2 available blood-based commercial assays, the T-Spot.TB (Oxford Immunotec, Marlborough, MA) and the Quantiferon-TB Gold (Cellestis, Valencia, CA). T cell assays have proven to be more specific than the TST but do not allow active disease to be distinguished from latent TB infection. Interpretation therefore depends on the clinical context.

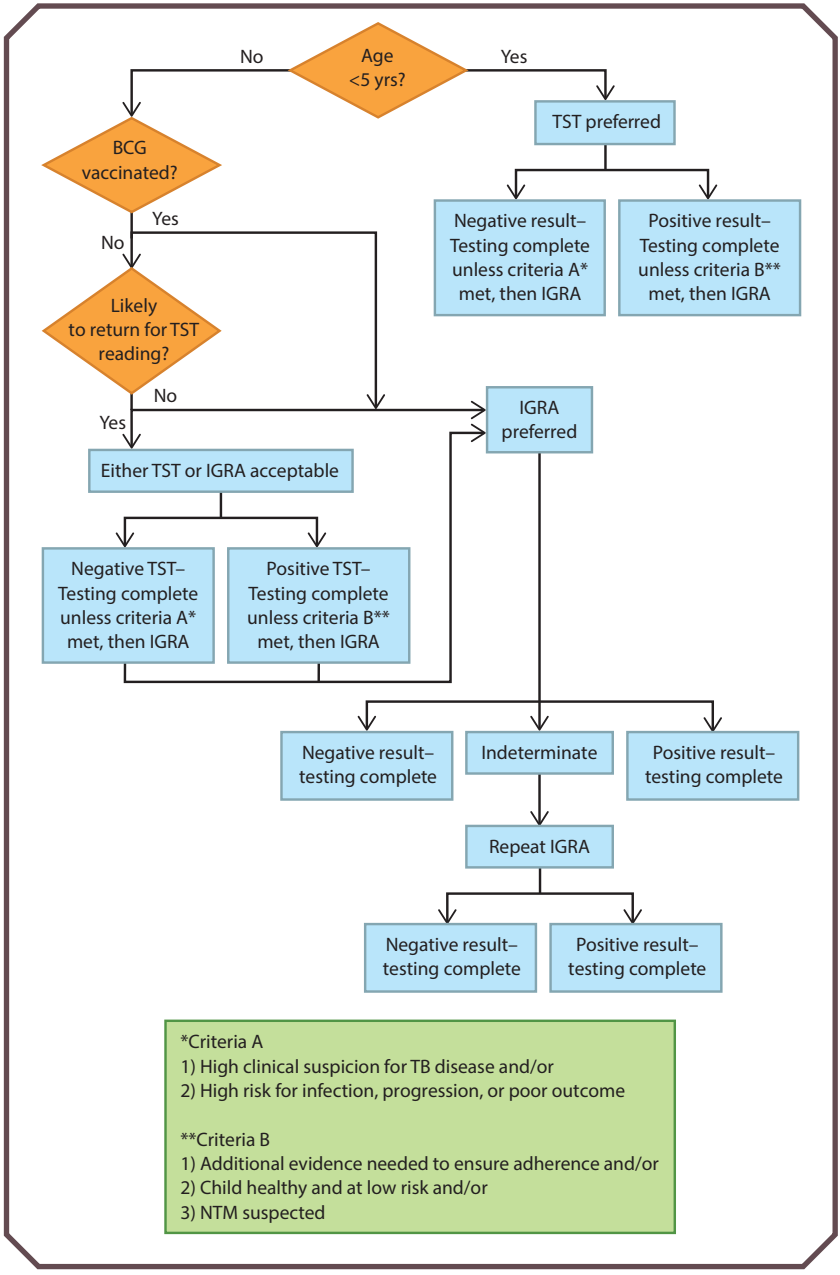

Figure 58-3. Flowchart demonstrates the evaluation of a child exposed to a person with contagious tuberculosis (TB). BCG = bacille Calmette-Guérin, IGRA = interferon-γ release assay, INH = isonicotinylhydrazide (isoniazid), LTBI = latent TB infection, NTM = nontuberculous mycobacteria, TST = tuberculin skin test. From American Academy of Pediatrics. Tuberculosis. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases.* 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:813.

- At this time, neither an IGRA nor the TST can be considered a standard of reference for diagnosis of latent TB infection. Current recommendations in AAP guidelines for use of IGRAs in children are as follows:
  - For immunocompetent children ≥5 years of age, IGRAs can be used in place of a TST to confirm cases of TB or cases of latent TB infection.
  - 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.
  - IGRAs may be useful in children who have received BCG vaccine.
  - Interferon-γ release assays cannot be recommended routinely for use in children <5 years of age or for immunocompromised children of any age.
  - Indeterminate IGRA results do not exclude TB infection.

Treatment after a Positive TST Result and Normal Chest Radiographic Findings (Latent TB)

- In a low-risk patient, evidence of infection with normal chest radiographic findings, which is indicative of no active disease, can be treated with single-drug therapy. Isoniazid is the drug of choice and is prescribed for a minimum of 9 months. For patients who are unable to take isoniazid or who are known to have been exposed to isoniazid-resistant *M tuberculosis,* taking rifampin daily for 4 months is an alternative therapy (Tables 58-2, 58-3).

Treatment of Active TB Disease

- Treatment should be started as soon as the diagnosis is suspected.
- Asymptomatic children with a positive purified protein derivative skin test result and an abnormal chest radiographic finding should undergo combination chemotherapy, usually with isoniazid, rifampin, and pyrazinamide.

Table 58-2. Treatment of Latent Tuberculosis With No Active Disease

Drug	Duration Criteria for Completion
Isoniazid susceptible	Daily treatment for 9 mo If daily treatment is not possible, administer DOT twice weekly for 9 mo
Isoniazid resistant	Rifampin daily for 4 mo If daily treatment is not possible, administer DOT twice weekly for 4 mo

DOT, directly observed therapy. Adapted from American Academy of Pediatrics. Tuberculosis. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases.* 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:805.

Table 58-3. Isoniazid Dosing for Latent Tuberculosis With No Active Disease	
Patient Weight	**Isoniazid Maximum Daily Dose**
<2.5 kg	25 mg
2.5–3.0 kg	30 mg
>3.0 to ≤5.0 kg	50 mg
>5.0 to ≤7.5 kg	75 mg
>7.5 to ≤10 kg	100 mg
>10.0 to ≤15 kg	150 mg
>15 to ≤20 kg	200 mg
>20 kg	300 mg

- All children from a foreign country who did not have known contact with a TB-infected individual should be started on 4-drug therapy with the addition of ethambutol.
- For patients who exhibit drug intolerance or who are infected with minimally resistant organisms, alternative regimens can be substituted. To avoid the development of drug resistance, a 2-drug combination is the minimum recommended by the AAP Committee on Infectious Diseases for treatment of TB disease and is only recommended for patients who absolutely cannot tolerate more. (See Tables 58-4 and 58-5.)
- Isoniazid and rifampin are often associated with liver toxicity, and liver function tests should be performed in the first month of treatment.
  - Routine monitoring of transaminase levels in children taking isoniazid alone is not recommended by the AAP Committee on Infectious Diseases.
  - Rifampin may accelerate the elimination of drugs metabolized by the CYP450 complex in the liver, resulting in the need to alter dosing regimens of those medications.
  - Patients and families should be cautioned that rifampin will turn urine and tears an orange color. Soft contact lenses worn during treatment will be permanently stained.
  - Ethambutol is associated with optic neuritis, in addition to the other typical toxicities listed herein.
- The currently recommended treatment for new cases of drug-susceptible TB by the AAP Committee on Infectious Diseases is a 6-month regimen of 4 first-line drugs: isoniazid, rifampicin, ethambutol, and pyrazinamide. Ethambutol can be discontinued once drug-resistant TB disease is excluded.
- Treatment for rifampicin-resistant TB and MDR TB is longer and requires more drugs.

Table 58-4. Treatment of Active Tuberculosis Disease (Both Suspected and Confirmed Cases)

Drug	Dosage	Daily Dosage Range (mg/kg)	Twice-Weekly Dosage (mg/kg per dose)	Side Effects	Monitoring	Comments
Isoniazid	Children: 10–15 mg/kg ≤300 mg Maximum: Daily, 300 mg Twice weekly, 900 mg	10 (10–15)	20–30	Hepatitis, peripheral neuropathy, mild CNS effects, skin rash, increased phenytoin levels, increased tacrolimus levels	LFTs performed once (to check transaminase levels), more if there is a history of chronic liver disease or other hepatotoxic drugs; not normally needed for children unless signs of hepatitis are seen during therapy	Administer pyridoxine 25–50 mg/d to prevent neuropathy in those with IDDM, nutritional deficiency, pregnancy, HIV, or renal disease; infants breastfed exclusively; and children on meat- and milk-deficient diets
Rifampin	Children: 10–20 mg/kg ≤600 mg. For children <45 kg, use 450 mg Maximum: 600 mg	15 (10–20)	15 (10–20)	Orange discoloration of secretions, cholestatic hepatitis, febrile state (flulike reaction), thrombocytopenia, drug interactions, skin rash	Baseline CBC count; LFTs performed once, more if there is a history of chronic liver disease or other hepatotoxic drugs	Warn patients about orange discoloration of urine and other body secretions, such as tears, since contact lenses will become permanently stained; treatment induces hepatic microsomal enzymes
Ethambutol	Children: 15–25 mg/kg (2.5-g maximum for all ages) Maximum: 2.5 g	20 (15–25)	50	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 assessed at baseline and monthly	Dose adjustment needed for renal disease
Pyrazinamide	Children: 30–40 mg/kg (2-g maximum for all ages) Maximum: 2 g	35 (30–40)	50	Hepatitis, GI upset, hyperuricemia, arthralgia, photosensitive dermatitis	Perform LFTs at baseline and monthly; assess uric acid level if there is renal disease	Dose adjustment needed for renal disease; safety not established in pregnancy

CBC, complete blood cell; CNS, central nervous system; GI, gastrointestinal; IDDM, insulin-dependent diabetes mellitus; LFT, liver function test. Per consult guidelines from the report of the AAP Committee on Infectious Diseases for the treatment of active TB disease for alternative anti-TB regimens.

Table 58-5. Tuberculosis Treatment Regimens		
Regimen	**Treatment Agents**	**Treatment Duration**
Standard regimen for all children in whom INH-susceptible infection is not proven		
Initial phase	INH, RIF, EMB, and PZA	First 2 mo
Continuation phase, if patient is sensitive to all first-line drugs	INH and RIF	Mo 3–6[a]
Standard regimen if culture result is negative and chest radiographic findings are improved		
Initial phase	INH, RIF, EMB, and PZA	First 2 mo
Continuation phase	INH, RIF, and EMB	Mo 3–6
Alternative regimens[b]		
Regimen for INH-resistant patients	RIF, EMB, and PZA	6–9 mo
Regimen for RIF-resistant patients	INH, EMB, and PZA	9–12 mo

EMB, ethambutol; INH, isonicotinylhydrazide (isoniazid); PZA, pyrazinamide; RIF, rifampin. Adapted from Conrad C. Tuberculosis. In: Light MJ, Blaisdell CJ, Homnick DN, Schechter MS, Weinberger MS, eds. *Pediatric Pulmonology*. Elk Grove Village, IL: American Academy of Pediatrics; 2011: 459–482.

[a] A patient with cavitary disease, extensive disease, or positive culture results after 2 months should continue treatment for a total of 9 months, or 6 months beyond the date of culture conversion if culture positivity is prolonged. Expert consultation is recommended.

[b] Alternative regimens should be administered with advice from a tuberculosis specialist.

- The World Health Organization Global TB Report of 2016 recommends a standardized shorter MDR TB regimen of 9–12 months for all patients with pulmonary MDR or rifampicin-resistant TB that is not resistant to second-line drugs.

Directly Observed Therapy

- Directly observed therapy (DOT) should be used for all children with TB.
- Parents should not be relied on to supervise DOT. With DOT, a health care worker is assigned to watch the patient swallow every dose.

Prognosis

- In general, the prognosis for patients infected with TB is good, but mortality rates rise when patients have comorbidities such as malnutrition, disseminated disease, or immunodeficiency (especially HIV) and increase dramatically if patients are infected with MDR TB.

Control of TB

- Most children, particularly those <10 years of age, are not contagious. Exceptions are children with cavitary pulmonary TB, positive sputum acid-fast bacilli smear results, laryngeal involvement, extensive pulmonary infection, or congenital TB who are undergoing oropharyngeal procedures, such as endotracheal intubation.

- The local health department often plays a significant role in the treatment of disease once a TB case is identified.

When to Refer

- All patients suspected of active infection due to TB should be reported to the local health department, according to state statute (within 1 working day).
- An experienced pediatric TB clinician should care for children with active TB disease.

Resources for Families

- Find TB Resources (U.S. Centers for Disease Control and Prevention). findtbresources.cdc.gov
- Tuberculosis Patient Education Materials Series (U.S. Centers for Disease Control and Prevention). www.cdc.gov/tb/publications/culturalmaterials.htm
- Tuberculosis Patient Education (EthnoMed). ethnomed.org/patient-education/tuberculosis

Clinical Pearls

- In the United States, TB disproportionately affects immigrant, Hispanic, and black populations.
- Only children who have a new risk for TB exposure since the last TST or who have features suggestive of active TB disease should undergo testing with the TST or IGRA.
- Interferon-γ assay testing is the recommended first-line testing in patients unlikely to return for skin test result interpretation. However, the IGRA test may be indeterminant and thus not reliable in young children <5 years old.
- All children who receive a diagnosis of latent TB infection should be treated and monitored for adherence and toxicity.
- Active TB disease is diagnosed clinically and radiographically in children, often without the benefit of culture confirmation.

Chapter 59

Nontuberculous Mycobacterial Pulmonary Disease

Stacey Martiniano, MD, and Paul C. Stillwell, MD, FAAP

Introduction/Etiology/Epidemiology

- There are more than 150 identified species of nontuberculous mycobacteria (NTM) that are ubiquitous in the environment; very few exposures result in infection or disease in the general pediatric population.
- In a healthy child, the most common disease due to NTM is lymphadenitis, most typically caused by *Mycobacterium avium* complex (MAC) in the cervical lymph nodes. Pulmonary NTM infection is rare.
- The prevalence of NTM pulmonary infection is highest in the population with cystic fibrosis (CF) and is increasing. In 2015, ≤20% of patients with CF in North America had an isolated NTM species in their sputum.
- Children with HIV infection and children treated with immunomodulating biological agents may also be at risk for pulmonary and disseminated NTM infection.
- The most common NTM organisms isolated in patients in the United States are those of the MAC and *Mycobacterium abscessus* complex, with less frequent isolation of *Mycobacterium kansasii* and *Mycobacterium fortuitum*.
- There is considerable geographic variation in the prevalence and species of NTM across the United States, which may be related to environmental water vapor pressure.
- There may be a risk of person-to-person spread of NTM in patients with CF.

Clinical Features

- Most NTM organisms may produce chronic, indolent symptoms at presentation.
- Pulmonary symptoms include chronic cough, increased sputum production, dyspnea, and hemoptysis.
- Possible constitutional symptoms include fatigue, low-grade fever, and night sweats.
- There may be an associated decrease in pulmonary function.

- There is marked overlap with symptoms and examination findings in patients with CF who have pulmonary exacerbations, such as increased crackles and decreased intensity of breath sounds.

Diagnostic Considerations

- Two or more positive sputum culture findings or 1 bronchoalveolar lavage or lung biopsy culture for NTM are required to establish the diagnosis of NTM pulmonary disease.
  - NTM isolation requires culture on both liquid and solid media, with incubation for at least 6 weeks, to ensure adequate time for isolation of "slow-growing" species, such as MAC.
- In addition to meeting the above microbiological criteria, ≥1 of the following clinical or radiographic features must be present:
  - Pulmonary symptoms, including
    - Unexplained decline in pulmonary function test results
    - Increased cough, sputum, dyspnea, or hemoptysis
  - Progressive radiologic findings, such as cavitary disease, nodules, tree-in-bud opacities, and parenchymal consolidation
- There must also be appropriate exclusion of other diagnoses.
  - In a patient with CF, this would include adequate treatment of underlying CF pulmonary disease and treatment of CF copathogens and comorbidities.
  - If clinical symptoms and findings persist, then the diagnosis of NTM pulmonary disease can be established.
- Skin tests are not available for NTM; polymerase chain reaction testing of sputum is under development.
- Notably, infection with MAC and *Mycobacterium marinum* may cause a false-positive tuberculin skin test finding.
- Typically, pediatric and adult patients with CF are screened for NTM infections with sputum acid-fast bacilli stains and cultures annually if they can expectorate and more frequently if NTM infection is clinically suspected.
- Chest radiographs and computed tomographic images in patients with CF and *M abscessus* complex are shown in Figures 59-1 and 59-2.

Treatment

- Treatment of NTM infections is challenging because of their slow growth and intrinsic resistance to antibiotics.
- Therapeutic regimens typically consist of 3–4 drugs for treatment periods of about 1 year.
- Treatment of MAC typically consists of a prolonged course of 3 oral agents with amikacin (inhaled or intravenous [IV]) added for cavitary or severe disease.
- Treatment of *M abscessus* complex often includes prolonged IV antibiotics for several weeks to months during an intensive phase, followed by a chronic suppressive phase of inhaled and oral medications.

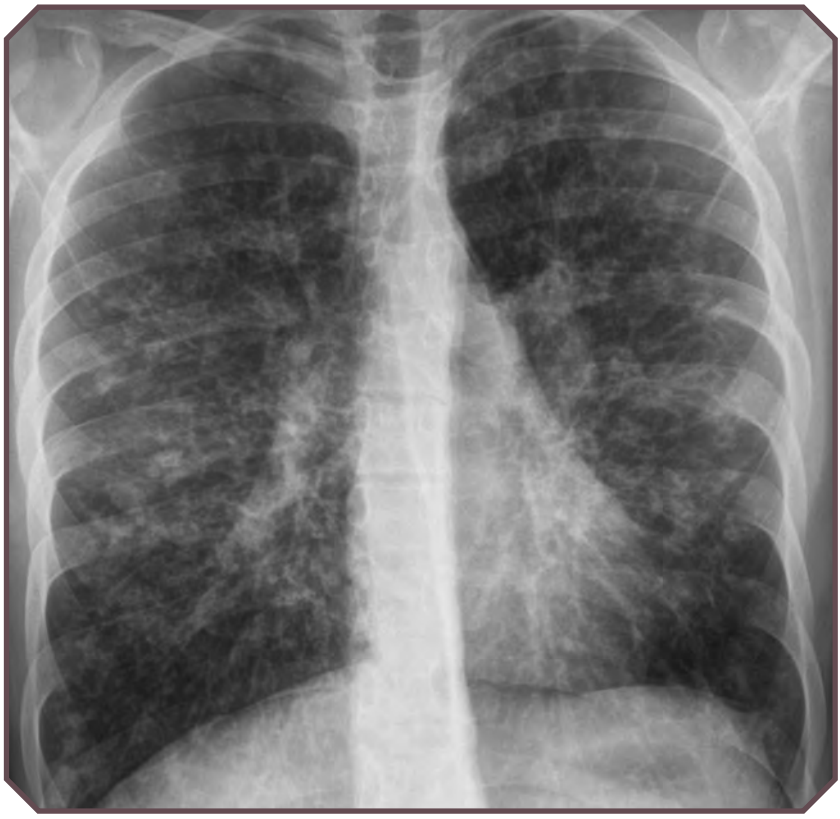

Figure 59-1. *Mycobacterium abscessus* complex in a patient with cystic fibrosis. Frontal chest radiograph shows that the lungs are hyperinflated, and there is extensive peribronchial thickening. Scattered lucencies due to bronchiectasis and nodular foci due to mucous plugging are seen throughout the lungs.

- The antibiotics can be difficult to tolerate because of side effects, and the patient must be monitored diligently, which may include regular assessment of symptoms, laboratory liver and renal function testing, electrocardiograms, audiograms, and visual acuity and color vision testing, depending on the drug regimen.
- The goal of treatment is to obtain 12 months of negative NTM culture findings.
- Potential treatment options are listed in Box 59-1.

Treating Associated Conditions

- In patients with CF, because of marked clinical and radiographic overlap with pulmonary disease caused by typical pathogens like *Staphylococcus aureus* and *Pseudomonas aeruginosa*, it is critical that the patient is adequately assessed for these coinfections and other CF comorbidities and treated accordingly, often with IV antibiotics before and during NTM treatment.

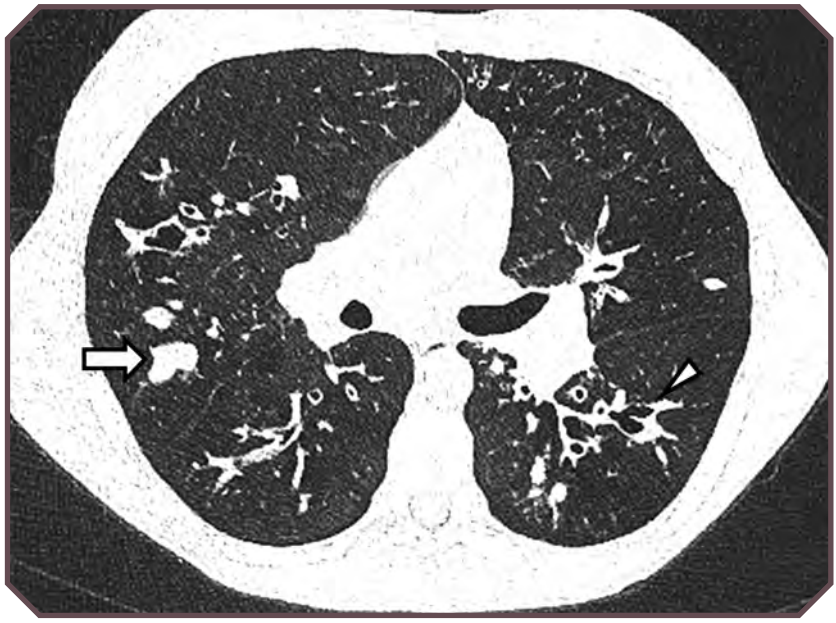

Figure 59-2. *Mycobacterium abscessus* complex infection in a patient with cystic fibrosis. Axial computed tomographic image demonstrates scattered nodules due to mucous plugging (arrow) bronchiectasis, cavity formation, and tree-in-bud opacities (arrowhead).

Prognosis

- There is evidence that NTM pulmonary disease can accelerate disease progression in some patients with CF.
- Treatment can improve clinical and constitutional symptoms and either stabilize or reverse some lost pulmonary function.
- Clearance of the NTM from the sputum is possible but can be difficult, especially in *M abscessus* complex infection.
- Even with clearance of sputum, recurrence of the same NTM infection or infection with a second NTM species is common in CF.

When to Refer

- Refer the patient if NTM is suspected or isolated from the sputum, with or without the presence of CF.
- Refer the patient if the diagnosis is in doubt.
- Bronchoscopy with bronchoalveolar lavage is needed for specimen collection.
- Refer the patient if the response to therapy is suboptimal.
- Refer the patient if the side effects of therapy are limiting treatment.

Box 59-1. Typical Treatment Regimens for NTM Infections

Mycobacterium avium Complex	*Mycobacterium abscessus* Complex
Typically 3 oral agents:	**Intensive phase (typically 3–12 wks of 2–3 IV agents plus 1–2 oral agents):**
Oral azithromycin or clarithromycin	IV amikacin, imipenem, cefoxitin, or tigecycline
Oral rifampin or rifabutin, and oral ethambutol	Oral azithromycin or clarithromycin
	Oral linezolid, moxifloxacin, ciprofloxacin, minocycline, or clofazimine
	Continuation phase (typically 3–4 agents):
Addition of inhaled or IV amikacin for cavitary or more severe disease	Inhaled amikacin
	Oral azithromycin or clarithromycin
	Oral linezolid, moxifloxacin, ciprofloxacin, minocycline, or clofazimine

IV, intravenous.

Resources for Families

- Learn About Nontuberculous Mycobacteria (American Lung Association). www.lung.org/lung-health-and-diseases/lung-disease-lookup/nontuberculosis-mycobacteria/learn-about-ntm.html
- Nontuberculous Mycobacteria (Cystic Fibrosis Foundation). www.cff.org/Living-with-CF/Germs-and-Staying-Healthy/What-Are-Germs/Nontuberculous-Mycobacteria

Clinical Pearls

- Pulmonary NTM infections are relatively common in patients with CF, but they are rare in healthy children.
- NTM pulmonary infections require prolonged, multidrug treatment courses with a prescribed monitoring plan.
- Pulmonary NTM infections should be suspected in a child with respiratory signs and symptoms or radiographic changes that are not responsive to treatment of more typical respiratory pathogens.

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Chapter 60

Fungal Pneumonia

Paul C. Stillwell, MD, FAAP

Introduction/Etiology/Epidemiology

- Endemic fungal pneumonias can occur in otherwise healthy or immunocompromised hosts.
- The endemic fungal pneumonias include
  - Histoplasmosis
  - Coccidioidomycosis
  - Blastomycosis
  - *Cryptococcus gattii* (not *Cryptococcus neoformans*)
- Common characteristics of the endemic fungi are listed in Table 60-1.

Table 60-1. Features of Most Common Endemic Fungal Infections

Fungal Infection	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 dig sites Dust storms Prairie dog habitats	Diffuse or focal opacity	Eosinophilia Ethnic group risks Prolonged fatigue
Blastomycosis	Upper Midwest and Southeast	Rivers and wetlands Wooded areas Buildings with bat droppings	Diffuse or focal opacity	Acute respiratory distress syndrome in 50%–70% (high mortality rate)

- Immunocompromised hosts can get fungal pneumonia from organisms that do not commonly cause invasive infection in normal hosts.
  - *Aspergillus fumigatus* (most common example)
  - *Pneumocystis jirovecii*
  - *Candida albicans* and other *Candida* species

- *C neoformans*
- *Mucormycetes*
- *Rhizopus*
- *Scedosporium*
- *Bipolaris*
- *Curvularia*

Clinical Features

- In the otherwise healthy host, fungal pneumonia manifests similarly to any community-acquired pneumonia (CAP), although the illness may be more protracted or subacute than common bacterial or viral pneumonia.
  - Cough, low-grade fever, dyspnea, malaise, chest pain
  - Localized crackles may be present at examination
- For endemic fungal infections, multiple organ systems may be involved (Table 60-2).

Table 60-2. Common Organ Systems Involved With Endemic Fungal Infections

Organ System	Coccidioidomycosis	Histoplasmosis	Blastomycosis	*Cryptococcus* Infection
Lung	Very common	Very common	Common	Common
Brain and meninges	Common	—	—	Very common
Bone marrow and lymph nodes	—	Very common	Very common	—
Skin, bone, and joints	Common	—	Very common	—

- In the immunocompromised host:
  - Symptoms are often less specific and may include fever, malaise, and cough.
  - Examination findings are often nonspecific, and localizing findings may be absent.
  - Computed tomographic (CT) findings are often suggestive of fungal pneumonia.

Diagnostic Considerations

- A chest radiograph obtained in a patient with an acute endemic fungal infection will have the same findings as CAP caused by other organisms (see Figure 60-1).

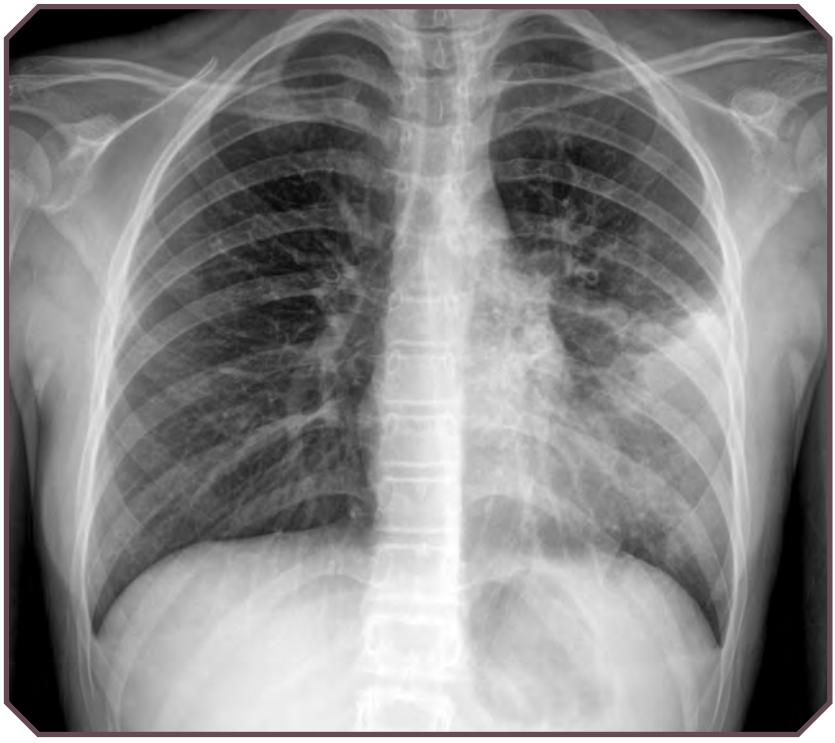

Figure 60-1. Acute fungal pneumonia caused by *Coccidioides.* Frontal chest radiograph demonstrates lingular airspace opacity.

- Chronic pulmonary fungal infections often have nodules or cavities and mediastinal or hilar adenopathy. Similarly, chest CT findings in immunocompromised hosts often demonstrate invasive fungal pneumonia but are not specific for fungal infection (see Figure 60-2).
- The diagnosis of fungal pneumonia often requires several tests and imaging modalities, including radiographs, cultures, tissue stains, and fungal antigens and antibodies, particularly in immunocompromised patients.
- For immunocompromised patients with suspected fungal pneumonia, using a combination of tissue culture, appropriate tissue staining, and antigen detection generally provides the highest chance of establishing the diagnosis, since none of the individual tests are 100% sensitive.
- Antigen tests to detect fungal cell wall components ([1-3]-β-D-glucan and galactomannan) can be helpful in identifying that a fungal infection is present, but they are not specific for a particular fungus.

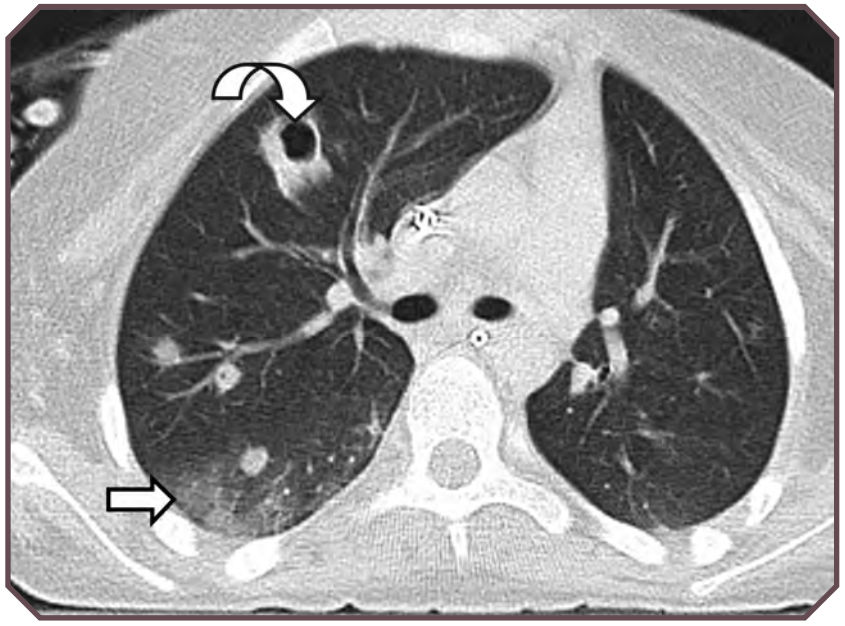

Figure 60-2. Invasive aspergillosis pneumonia in an immunocompromised patient. Axial chest computed tomographic scan demonstrates multiple focal nodules throughout the right lung, a thick-walled cavitary lesion in the middle lobe (curved arrow), and a region of ground-glass opacity in the superior segment of the right lower lobe (straight arrow).

Treatment

- Many individuals with endemic fungal pneumonia have mild disease and need no antifungal treatment.
- Immunocompromised hosts with invasive disease are usually treated, sometimes with more than 1 agent. Even patients who received transplants and have disseminated infections may need only 1 agent (amphotericin followed by posaconazole *or* voriconazole alone or itraconazole alone, depending on the organism). For salvage therapy, 2 agents are sometimes used, but not for standard therapy, even in immunocompromised patients.
- Table 60-3 shows which antifungal antibiotics might be used for each infection.
- Traditionally, itraconazole is used for histoplasmosis and blastomycosis, and fluconazole is used for coccidioidomycosis.
- Therapy is often required for weeks or months, even with acute uncomplicated pneumonia.

Table 60-3. Relative Treatment Success of Antifungal Therapy for the Most Common Fungal Pneumonias

Antifungal Agent	*Aspergillus fumigatus*	*Cryptococcus* species	*Blastomyces dermatitidis*	*Histoplasma capsulatum*	*Coccidioides immitis*
Amphotericin	Success likely	Success likely	Success likely	Success likely	Success likely
Fluconazole	Success unlikely	Success likely	Success likely	Success likely	Success likely
Itraconazole	Success likely	Success likely	Success likely	Success likely	Success likely
Posaconazole	Success likely	Success likely	Success likely	Success uncertain	Success likely
Voriconazole	Success likely	Success uncertain	Success likely	Success uncertain	Success likely
Micafungin[a]	Success uncertain	Success unlikely	Success unlikely	Success unlikely	Success unlikely
Caspofungin[a]	Success uncertain	Success unlikely	Success unlikely	Success unlikely	Success unlikely

Adapted from Thompson GR III, Cadena J, Patterson TF. Overview of antifungal agents. *Clin Chest Med.* 2009;30(2):203–215. Copyright 2009, with permission from Elsevier.

[a] Should not be used as single-agent therapy for *Aspergillus fumigatus*.

Prognosis

- Many patients are asymptomatic and possibly unaware of having been infected with one of the endemic fungi.
- For normal hosts, complete resolution is common, with or without treatment.
- There is a high mortality rate for immunocompromised patients with fungal pneumonia, even with appropriate antifungal therapy and multisystem support.

When to Refer

- Difficulty establishing the correct diagnosis
- Dissemination to brain or meninges
- Progression to chronic or progressive pulmonary disease
- Fungal infections in immunocompromised hosts

Resources for Families

- Infections and Problems From Bacteria, Viruses, Molds and Fungi (American Thoracic Society). www.thoracic.org/patients/patient-resources/topic-specific/infections-and-problems.php
- Types of Fungal Diseases (U.S. Centers for Disease Control and Prevention). www.cdc.gov/fungal/diseases

Clinical Pearls

- If a patient lives in or has recently traveled to an endemic area, think of the appropriate fungus when evaluating CAP, particularly if the condition is not responding to usual antibacterial antibiotics, if there are cavitary lesions, or if hilar adenopathy is present
- For immunocompromised patients with suspected fungal pneumonia, take advantage of all tests and imaging modalities available.

Chapter 61

Histoplasmosis and Other Endemic Fungal Pneumonias

Paul C. Stillwell, MD, FAAP

Introduction/Etiology/Epidemiology

- Histoplasmosis is the most common endemic fungal infection in North America.
- The geographic distribution is primarily the Mississippi and Ohio River Valleys.
- The severity of the infection ranges from mild and often unrecognized to severe and life-threatening; immunocompromised patients are more likely to experience a severe or life-threatening infection with the endemic fungi.
- The organism *Histoplasma capsulatum* is found in the soil (particularly soil rich in bird and bat droppings), caves, old buildings, and chicken coops.
- Once inhaled, the spores are engulfed by macrophages, and the infection is controlled by the cell-mediated immunity.
- Because *H capsulatum* is an intracellular organism, it can persist for years before re-emerging if there is a deterioration of the host's cell-mediated immune system.
- Several different manifestations of thoracic histoplasmosis have been described, with some overlap:
  - Acute pulmonary histoplasmosis
  - Subacute pulmonary histoplasmosis
  - Chronic pulmonary histoplasmosis (uncommon in the pediatric age range)
  - Disseminated histoplasmosis (immunocompromised hosts)
  - Mediastinal granulomas and fibrosis
- All of the endemic fungal pneumonias can occur in normal hosts or immunocompromised hosts. The endemic fungal pneumonias include (see Table 60-1 in Chapter 60, Fungal Pneumonia):
  - Histoplasmosis
  - Coccidioidomycosis
  - Blastomycosis
  - *Cryptococcus gattii* (not *Cryptococcus neoformans*)

Clinical Features

- In patients with mild acute pulmonary endemic mycosis:
  - Symptoms are minimal and may include malaise, low-grade fever, and arthralgias.
  - Cough and chest discomfort may be present.
  - If these symptoms resolve spontaneously, medical care is usually not pursued, and the infection may go undetected.
- With a large inoculum or a compromised immune system:
  - Symptoms may be severe, with respiratory distress, fever, and hypoxemia.
  - Examination findings may be unremarkable or demonstrate poor breath sounds with inspiratory crackles.
- Extrapulmonary findings may include hepatosplenomegaly, adenopathy, and skin manifestations—most commonly nodules, papules, plaques, ulcers, vesicles, and pustules (see Table 60-2 in Chapter 60, Fungal Pneumonia).

Diagnostic Considerations

- The chest radiographic findings in acute *Histoplasma* pneumonia are indistinguishable from any other community-acquired pneumonia (CAP) (Figure 61-1).
- For subacute *Histoplasma* pneumonia, computed tomographic images typically demonstrate nodules (that may be calcified), airspace opacity, and mediastinal and hilar adenopathy (see Figure 61-2). Lymphadenopathy due to histoplasmosis often shows low-attenuation central necrosis (Figure 61-3). Calcifications are more common in old healed histoplasmosis and may persist into adulthood (Figure 61-4). The radiographic appearance of histoplasmosis can be similar to that of postprimary tuberculosis.
- The diagnosis of histoplasmosis is commonly established with a positive antigen testing result in the urine and serum.
- If the infection has been present for a month or more, serum serologic findings are often positive.
- A positive tissue culture result or a positive histopathologic stain finding can also be used to establish the diagnosis.
- The method to establish a diagnosis of the other endemic fungal infections is indicated in Table 61-1.

Treatment

- Many patients recover without treatment.
- If treatment for mild acute or subacute *Histoplasma* pneumonia is warranted by ongoing symptoms, itraconazole is the most commonly used antifungal.
- Itraconazole is also the primary therapy for blastomycosis.

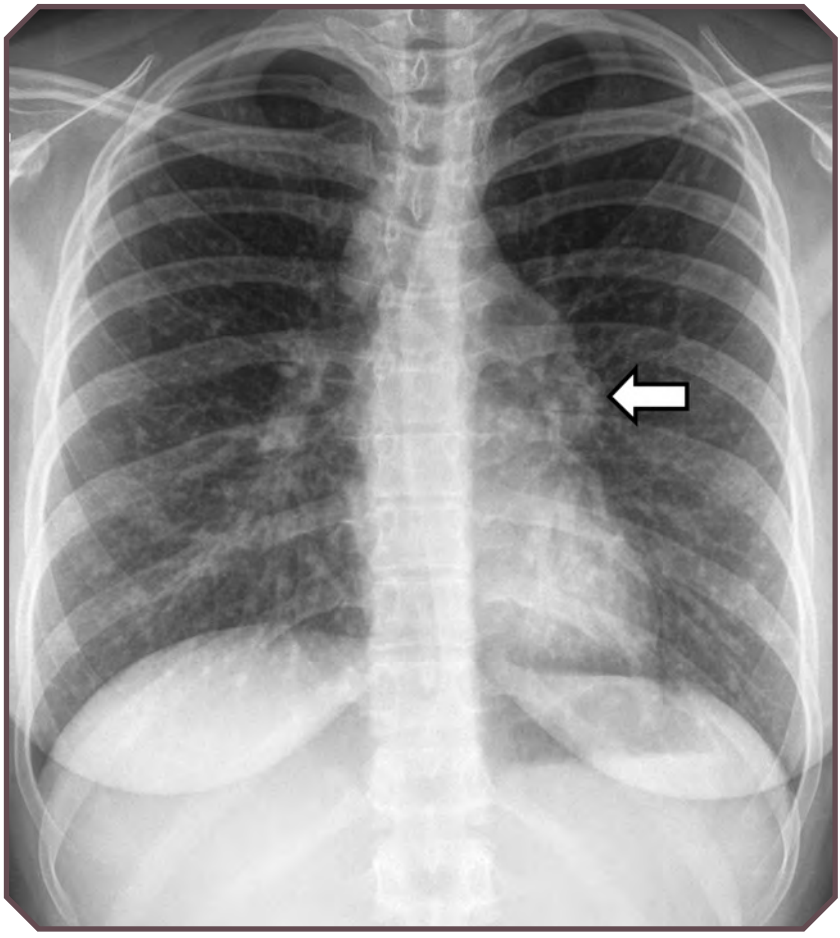

Figure 61-1. *Histoplasma* pneumonia in a 16-year-old girl. Frontal chest radiograph shows diffuse reticulonodular opacities, as well as right paratracheal and left hilar adenopathy (arrow).

- Amphotericin B is used for disseminated histoplasmosis and moderate to severe acute *Histoplasma* pneumonia.
- Fluconazole is the most commonly used antifungal for coccidioidomycosis.
- Table 60-3 in Chapter 60, Fungal Pneumonia, outlines treatment options for various fungal infections.

Prognosis

- Most subacute endemic fungal pneumonia will resolve without complication, with or without antifungal therapy.
- Many patients will recover with persisting nodules seen on chest radiographs that may later be of concern for malignancy, even though that is rarely the case in children.

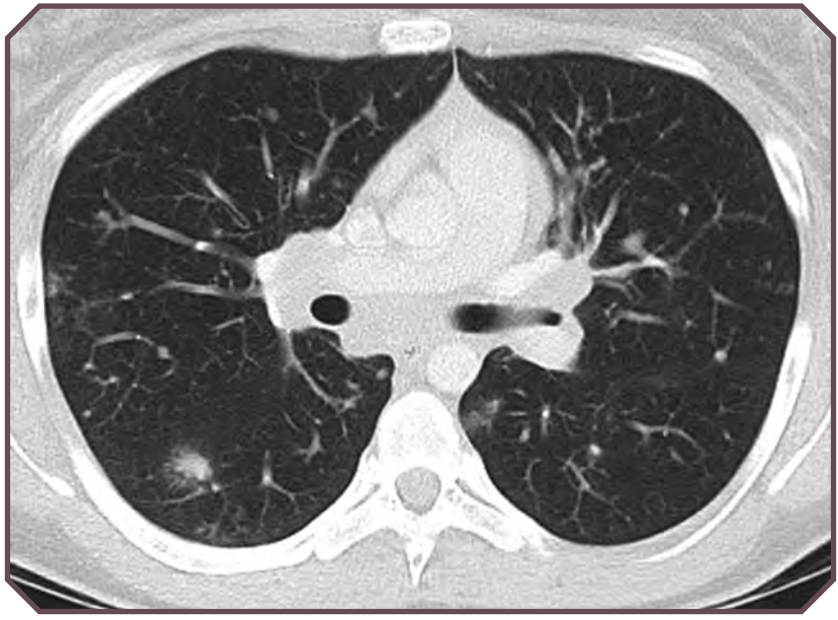

Figure 61-2. *Histoplasma* pneumonia in the same 16-year-old girl as in Figure 61-1. Axial chest computed tomographic image demonstrates multiple nodules of variable size and mediastinal adenopathy.

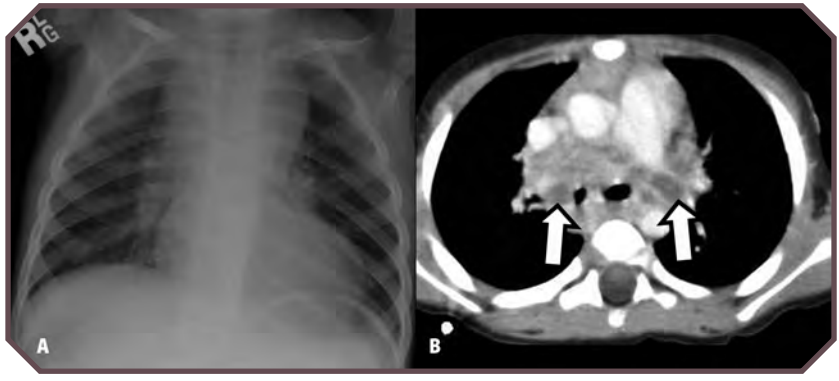

Figure 61-3. Histoplasmosis in a 6-year-old girl. A. Frontal chest radiograph demonstrates mediastinal widening consistent with marked lymphadenopathy. Fine granular opacity is seen bilaterally, which is suggestive of active inflammation. B. Axial contrast-enhanced chest computed tomographic image demonstrates mediastinal nodes, many with central low attenuation surrounding thick, enhancing walls (arrows).

- Disseminated histoplasmosis or fulminant acute histoplasmosis can be fatal, even with antifungal therapy; the same is true of all the endemic fungal infections.

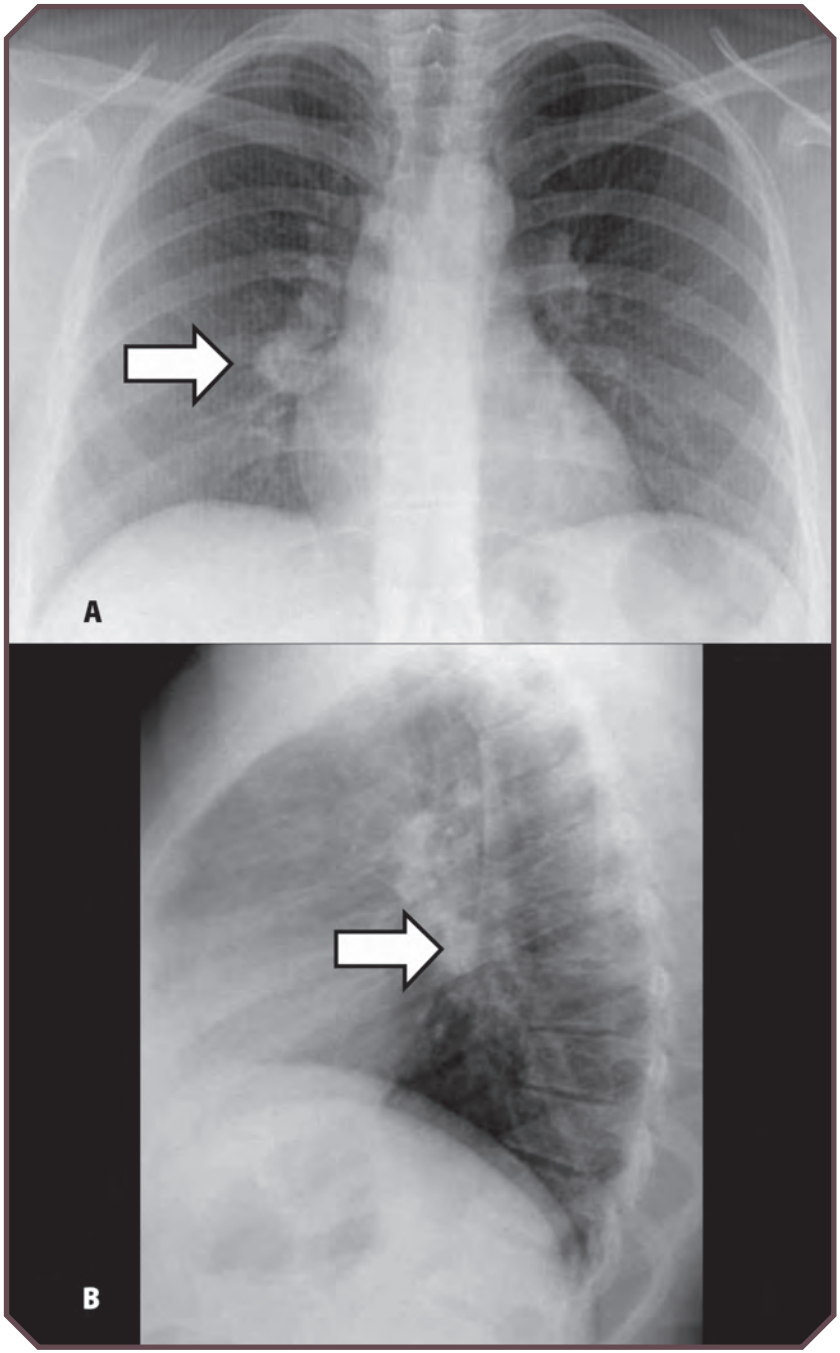

Figure 61-4. Histoplasmosis with calcified lymph nodes in a 14-year-old girl. A. Frontal and B. lateral radiographs show multiple, bilateral calcified hilar nodes (arrows).

Table 61-1. Methods to Establish a Diagnosis of Endemic Fungal Pneumonia

Organism	Culture	Stains	Serologic Analysis	Antigen
Histoplasma capsulatum	Helpful	Occasionally helpful (blood and bone marrow)	Somewhat helpful	Helpful (especially urine)
Coccidioides immitis	Somewhat helpful	Helpful	Helpful	Somewhat helpful (blood test not used often)
Blastomyces dermatitidis	Helpful	Helpful	Somewhat helpful	Helpful (especially urine)
Candida albicans	Helpful	Somewhat helpful	Not yet	Not yet
Cryptococcus neoformans	Helpful	Somewhat helpful	Somewhat helpful	Somewhat helpful
Aspergillus fumigatus (invasive)	Helpful	Somewhat helpful	Occasionally helpful, sometimes unhelpful	Helpful (galactomannan)

When to Refer

- The patient has failed treatment for presumed CAP.
- The pneumonia is progressing despite treatment.
- There is concern for dissemination or clinically significant mediastinal involvement.

Resources for Families

- Infections and Problems From Bacteria, Viruses, Molds and Fungi (American Thoracic Society). www.thoracic.org/patients/patient-resources/topic-specific/infections-and-problems.php
- Types of Fungal Diseases (U.S. Centers for Disease Control and Prevention). www.cdc.gov/fungal/diseases

Clinical Pearl

- The patient may have fungal pneumonia if he or she lives in or has traveled to an endemic area and if treatment for CAP is unsuccessful or there are multiple nodules.

Chapter 62

Complications of Pneumonia: Pleural Effusions

Oren Kupfer, MD, and Paul C. Stillwell, MD, FAAP

Introduction/Etiology/Epidemiology

- Pleural effusion is an abnormal amount of fluid in the pleural space.
- Effusions are often categorized as exudates or transudates, depending on their protein content and chemistry (Table 62-1).
- There are multiple causes of pleural effusion, but in children, the most common is related to an underlying lung infection (Box 62-1).
- The effusions associated with pneumonitis are parapneumonic effusions; the potential infecting organisms are listed in Box 62-2.

Table 62-1. Criteria for Exudates and Transudates in Pleural Effusions

	Exudate	Transudate
Protein level (g/dL)	>3.0	<3.0
Ratio of pleural fluid protein level to serum protein level	>0.5	<0.5
LDH level (U/L)	>250	<250
Ratio of pleural fluid LDH level to serum LDH level	>0.6	<0.6

LDH, lactate dehydrogenase. To convert grams per deciliter to grams per liter, multiply by 10. To convert units per liter to microkatals per liter, multiply by 0.0167.

- The most common pathogens that cause parapneumonic effusions are *Streptococcus* species and *Staphylococcus* species (both methicillin-sensitive and methicillin-resistant *Staphylococcus aureus*).
- In almost half of effusions, no pathogen is found, and patients are treated empirically for streptococcal infection. Coverage for *Staphylococcus* should be considered, depending on the local prevalence of these organisms.
- Parapneumonic effusions are initially thin and fairly clear with a yellow color, and they are freely mobile in the pleural space; this is considered an exudative phase secondary to pleural inflammation and occurs in the initial 2–5 days of illness.

Box 62-1. Causes of Pleural Effusions in Children, Classified According to Exudate and Transudate

Exudative Pleural Effusions	Transudative Pleural Effusions
Parapneumonic effusion	Congestive heart failure
Pulmonary embolism	Nephrotic syndrome
Neoplasm	Cirrhosis or liver failure
Collagen vascular disease	Acute glomerulonephritis
Trauma	Hypoproteinemia
Drug hypersensitivity	Myxedema
Lung transplant rejection	Sarcoidosis
Chylothorax	Peritoneal dialysis
Gastrointestinal diseases	
Lymphatic diseases	
Postcardiac surgery syndrome	
Acute chest syndrome (sickle cell disease)	

Box 62-2. Infections Associated with Parapneumonic Effusions in Children

Bacterial Causes	Nonbacterial Infectious Causes
Aerobic	**Viral**
Streptococcus pneumoniae	Adenovirus
Staphylococcus aureus	Influenza
Streptococcus pyogenes	Parainfluenza viruses
Anaerobic	**Parasitical**
Bacteroides species	*Paragonimus* species
Peptostreptococcus species	*Cysticercus* species
Peptococcus species	*Entamoeba histolytica*
Fusobacterium species	
Atypical	**Fungal**
Mycoplasma pneumoniae	*Coccidioides immitis*
Actinomyces species	
Nocardia species	
Mycobacterium tuberculosis	

- The fibrinopurulent phase occurs 5–10 days after the onset of pneumonia, with fibrin strands that cause loculations in the pleural space, limiting the flow of fluid. This phase is often an empyema with a high white blood cell count or even pus at visual examination during drainage.
- The organizing stage occurs in the second week of illness, with a thick, fibrinous peel that leads to complete healing of the pleural space; rarely, the peel fails to resolve completely, resulting in a trapped lung.

Clinical Features

- Children with parapneumonic effusions caused by common bacteria are usually ill with fever, malaise, and chest pain.
- The breath sound intensity is decreased over the area of the effusion; there may be inspiratory crackles in adjacent areas.
- The percussion note is dull over the effusion.

Diagnostic Considerations

- The chest radiograph commonly shows an area of opacity that represents the pneumonia and increased pleural fluid on the ipsilateral side (Figure 62-1).
- Ultrasonography of the chest can be used to define the degree of infiltrate and the effusion and help identify the presence of loculations in the pleural space (Figure 62-2).
- Chest computed tomography can provide more detailed information about the lung parenchyma and mediastinum if needed clinically (Figure 62-3).
- Once an effusion has been identified, the next consideration should be sampling the fluid by means of either thoracentesis or placement of a chest tube.
- Pleural fluid analysis will help identify the specific etiologic origin and help direct treatment options.
- Novel molecular microbiological techniques, such as polymerase chain reaction, are likely to increase the diagnostic accuracy and help identify more infections.
- Drainage of the pleural space with a chest tube can be both therapeutic and diagnostic.
- Clinicians should ask about exposure to persons with tuberculosis and consider administering a tuberculin skin test or interferon-based test for high-risk populations, such as immigrants (see Chapter 58, Tuberculosis).

Treatment

- With the increasing use of chest tubes and fibrinolytics, the use of video-assisted thoracic surgery has decreased.
  - — Surgical intervention is more common if the effusion is an empyema and fibrinolytics have failed.

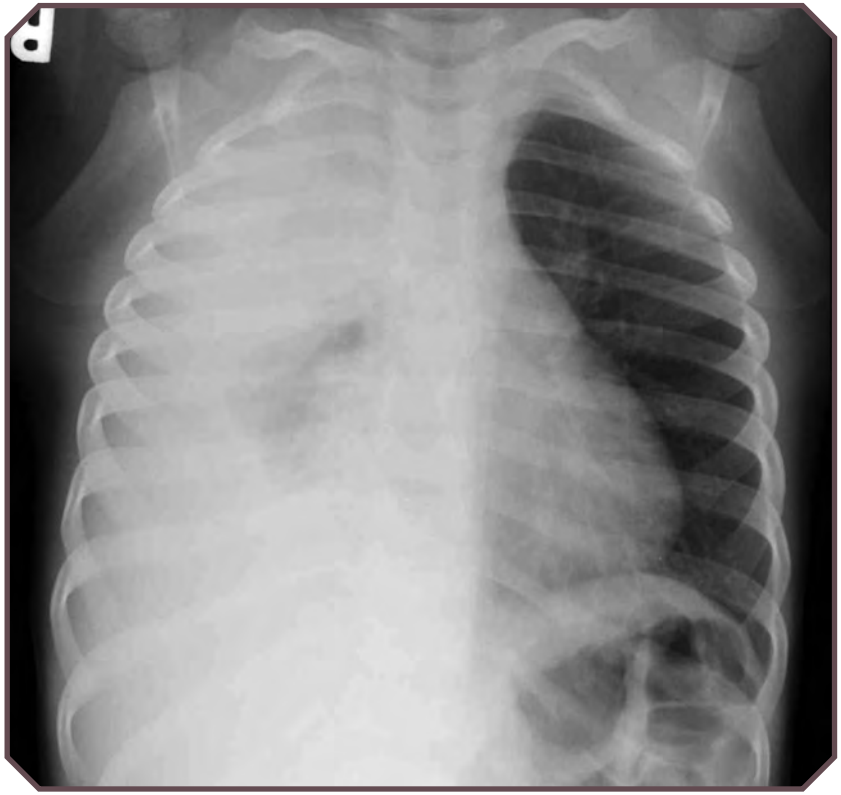

Figure 62-1. Right pleural effusion in a febrile 3-year-old girl with pneumonia. Frontal chest radiograph shows near-complete opacity of the right hemithorax with an effusion tracking up the right chest wall. Note right-to-left mediastinal shift due to large effusion.

  - Surgical intervention is often used as first-line therapy if the effusion has been present for more than 10 days.
- If the infecting organism can be identified, antibiotic therapy is targeted at that infection.
- If no specific infection is found, therapy is usually directed at *Streptococcus* and *Staphylococcus*. Empirical coverage for methicillin-resistant *S aureus* depends on the local prevalence of this organism.
- If the effusion is causing respiratory distress or failure or occupies more than one-half of the ipsilateral chest cavity, chest tube drainage is usually indicated.
- For parapneumonic effusions that are not empyemas or do not have loculations present, fibrinolytics are not usually needed.
- The duration of intravenous and oral antibiotic therapy is not well delineated, but clinical response to therapy guides this decision. Many pediatric infectious disease experts suggest a duration of 7–10 days after defervescence.

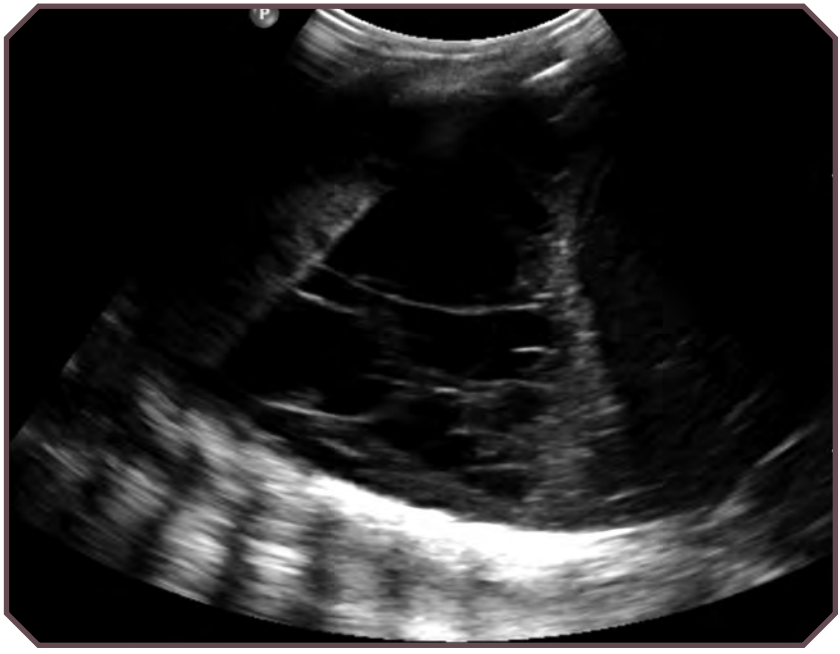

Figure 62-2. Pleural effusion. Longitudinal ultrasonographic image of the right side of the chest demonstrates a septated, mixed echogenicity collection in the right pleural space, indicating complex effusion. Some of the echogenicity is due to opacified lung with pneumonia (Image courtesy of Jason Weinman, MD, Department of Radiology, University of Colorado School of Medicine Anschutz Medical Campus and Children's Hospital Colorado).

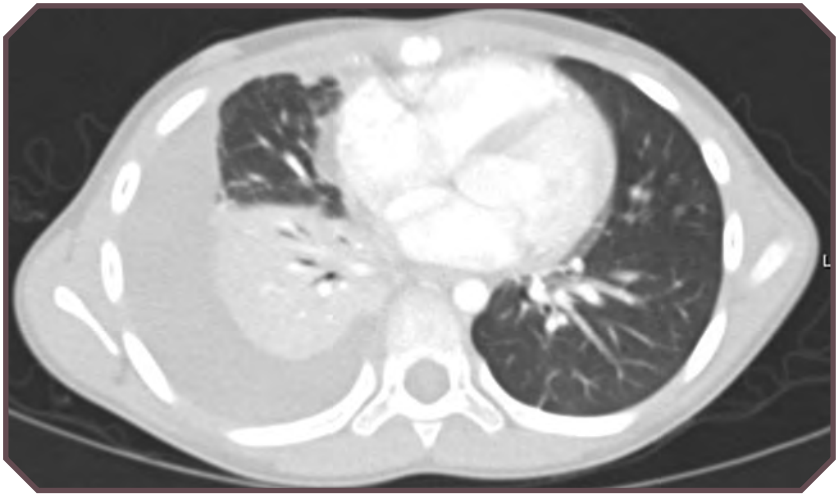

Figure 62-3. Pneumonia complicated by empyema. Axial chest computed tomographic image demonstrates a large right pleural effusion with underlying pneumonia. This empyema was due to methicillin-resistant *Staphylococcus aureus*.

Prognosis

- The prognosis for full recovery is excellent with appropriate antibiotic therapy and drainage, if appropriate, in otherwise healthy children.
- Chest radiographic findings may take several months to completely return to normal.

When to Refer

- A parapneumonic effusion indicates a complicated pneumonia and will likely require complex inpatient management with several specialists, including a pediatric surgeon, interventional radiologist, pulmonologist, and infectious disease consultants.
- Early referral is likely to facilitate prompt therapy.

Resources for Families

- Pneumococcal Disease: Clinical Features (U.S. Centers for Disease Control and Prevention). www.cdc.gov/pneumococcal/clinicians/clinical-features.html
- Empyema (Healthline). www.healthline.com/health/empyema#Overview1

Clinical Pearl

- Parapneumonic effusions are usually associated with a streptococcal or staphylococcal infection, despite the extensive lists of possible infecting agents.

Chapter 63

Pneumonia Complications: Empyema

Oren Kupfer, MD, and Paul C. Stillwell, MD, FAAP

Introduction/Etiology/Epidemiology

- An empyema is a collection of pus in an enclosed part of the body that is normally sterile, which may occur in the pleural space as a complication of pneumonia. Empyemas are by definition exudative pleural effusions.
- Although several different infections can be responsible, the most common are *Streptococcus pneumoniae* and *Staphylococcus aureus* (both methicillin sensitive and methicillin resistant) (Box 63-1).
- The incidence of complex pneumonia and empyema has increased since the 1990s, though the exact cause is unknown.
- An estimated 0.6%–2.0% of pediatric patients hospitalized for pneumonia will have an empyema.

Box 63-1. Organisms That May Be Associated With Infection and Effusion and/or Empyema in the Pleural Space

Bacteria

Streptococcus pneumoniae
Staphylococcus aureus
Haemophilus influenzae type b
Streptococcus pyogenes
Bacteroides species
Peptostreptococcus species
Peptococcus species
Fusobacterium species
Actinomyces species
Tuberculosis
Mycobacterium tuberculosis

Viruses and Atypical Bacteria

Adenovirus
Parainfluenza
Influenza
Mycoplasma pneumoniae
Fungi
Coccidioides immitis
Parasites
Paragonimus species
Cysticercus species
Entamoeba histolytica

Clinical Features

- Most children with an empyema caused by *Streptococcus* or *Staphylococcus* are acutely ill with high fever, ill appearance, chest pain, and respiratory distress.
- If the patient does not appear seriously ill, the etiologic origin is likely a less virulent organism (see Box 63-1).
- At examination, the breath sounds over the empyema will be decreased or absent, and there will be a dull percussion note.
- Adjacent to the empyema, crackles may be heard, reflecting the portion of the lung affected by the underlying pneumonia.

Diagnostic Considerations

- Chest radiographic findings have the characteristic appearance of pneumonia, with a pleural effusion blunting the costophrenic angle and a meniscus sign (Figure 63-1).

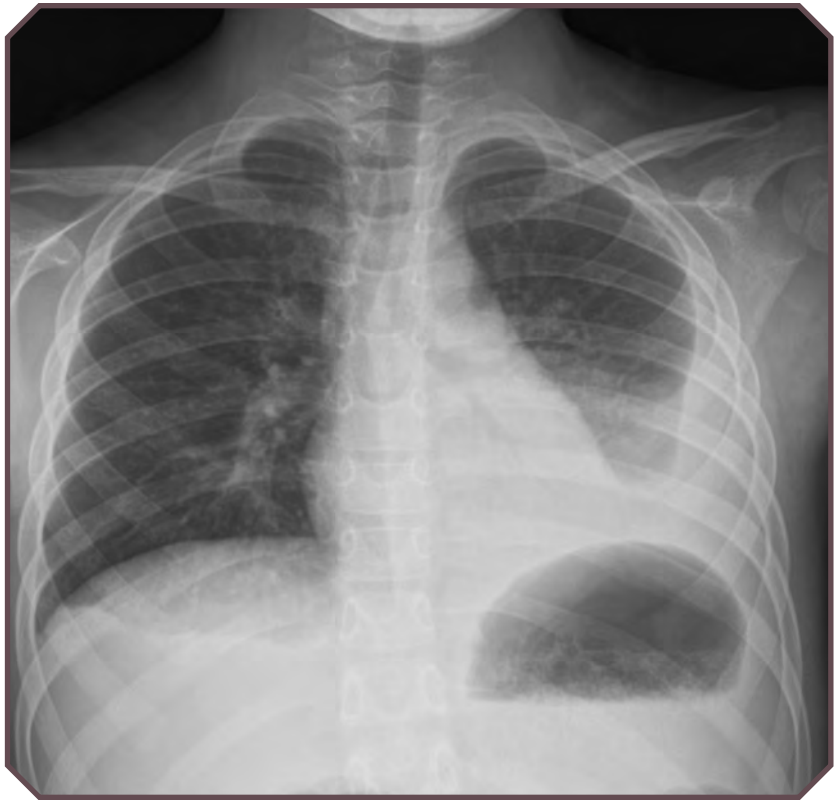

Figure 63-1. Pleural effusion. Frontal chest radiograph shows a left lower-lobe pneumonia with blunting of the costophrenic angle (meniscus sign), indicating pleural fluid, which was proven to be caused by an empyema.

- Clinicians should ask about exposure to persons with tuberculosis and consider administering tuberculin skin test or interferon-based test for high-risk populations, such as immigrants (see Chapter 58, Tuberculosis).
- Ultrasonography (US) can be used to confirm an effusion and identify loculations and septations in the effusion (see Figure 63-2).
- Chest computed tomography (CT) can be used to clarify the degree of effusion and help differentiate parenchymal disease from pleural involvement. (see Figure 62-3 in Chapter 62, Complications of Pneumonia: Pleural Effusions).
- Pleural fluid should be sampled by means of either thoracentesis, when the chest tube is placed, or at the time of video-assisted thoracoscopic surgery (VATS).
- As a parapneumonic effusion progresses from the initial collection of noninfected fluid to the exudative stage, the fluid characteristics change. As the effusion progresses to the fibrinopurulent stage, there is an increase in the cell counts, and septations become evident at US or chest CT. The infection may extend into the pleural space as evidenced by
  - Gross pus at inspection of the fluid
  - White blood cell count >12,000/mm^3 (12×10^9/L)
  - Positive Gram stain finding or culture result

Treatment

- All treatment options include intravenous (IV) antibiotic therapy directed against the infecting organism.
- If no organism is identified, antibiotic therapy is usually directed at *Streptococcus* or *Staphylococcus*.

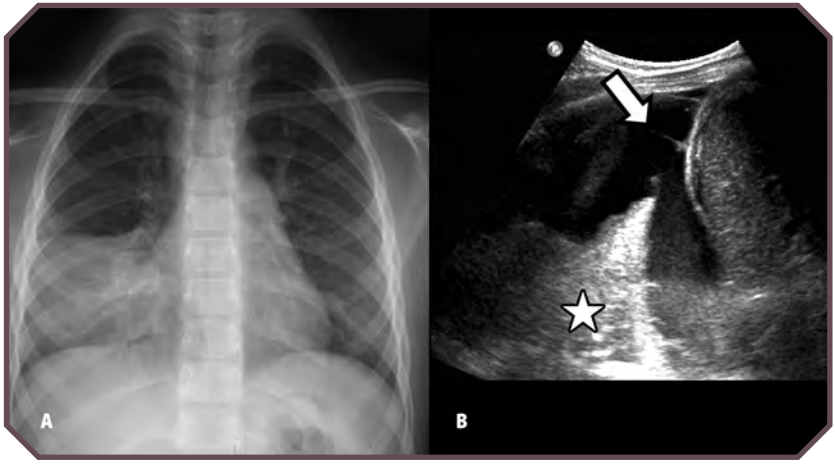

Figure 63-2. Empyema in a 3-year-old girl with fever and lower-lobe pneumonia. A. Frontal chest radiograph shows right lower-lobe opacity. B. Longitudinal ultrasonographic image demonstrates a hypoechoic pleural collection (arrow) surrounding the lower lobe (star).

- The most currently used treatment options include draining the empyema either primarily with a chest tube insertion or with VATS.
- Fibrinolytics, such as tissue plasminogen activator or urokinase, may be injected into the pleural space via the chest tube to resolve loculations in the pleural space.
- The use of fibrinolytics and VATS has similar outcomes in terms of hospital length of stay and duration of symptoms.
- The duration of IV antibiotic therapy, the transition to oral antibiotics, and the duration of total antibiotic therapy have not been clearly established.
- IV antibiotics are commonly administered until clinical improvement occurs; the total antibiotic duration is commonly 3–4 weeks or longer.
- A peripherally inserted central catheter (PICC) can facilitate administration of long-term IV antibiotics inside and outside of the hospital setting. Studies in which IV and oral antibiotics were compared at the time of discharge for children with empyemas and complicated pneumonia have shown similar clinical outcomes. The benefits versus risks of a PICC line as opposed to using oral antibiotics should be considered on an individual basis.

Prognosis

- Despite the extensive radiographic involvement of the lung parenchyma and pleura, the prognosis is excellent for a return to normal, both radiographically and functionally.
- Even with clearing of the infection, there may be prolonged fevers because the inflammation in the pleural space takes some time to resolve.
- The radiographic findings may not return to normal for several months.
- A trapped lung is an uncommon occurrence in children.

When to Refer

- An empyema represents a complex pneumonia with pleural infection that often requires inpatient care with multidisciplinary input from surgery and pulmonology, infectious disease, and perhaps intensive care. Referral should be considered at the earliest suspicion that an empyema is present.

Resources for Families

- Pneumococcal Disease: Clinical Features (U.S. Centers for Disease Control and Prevention). www.cdc.gov/pneumococcal/clinicians/clinical-features.html
- Empyema (Healthline). www.healthline.com/health/empyema#Overview1

Clinical Pearl

- A pleural effusion or empyema should be suspected if treatment for pneumonia fails to produce clinical improvement or if the patient worsens despite treatment.

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Chapter 64

Complications of Pneumonia: Pulmonary Abscess

Oren Kupfer, MD, and Paul C. Stillwell, MD, FAAP

Introduction/Etiology/Epidemiology

- The incidence of pulmonary abscess has decreased with the expansion of available antibiotics to treat respiratory infections.
- Pulmonary abscesses tend to occur in children with altered consciousness, either transiently (eg, anesthesia, intoxication, seizure) or as part of a neurological disability (eg, cerebral palsy, traumatic brain injury).
- The organisms most commonly associated with pulmonary abscesses are listed in Box 64-1; many are anaerobic mouth flora that proliferate after aspiration.

Box 64-1. 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*
α-hemolytic *Streptococcus*	*Bacteroides* spp
Haemophilus influenzae	*Bifidobacterium* spp

From Brook I. Anaerobic pulmonary infections in children. *Pediatr Emerg Care.* 2004;20(9):636–640.

Clinical Features

- Symptoms may be indolent, with low-grade fever, malaise, and fatigue.
- Chest pain and cough are common.
- Symptoms tend to occur a week or more after the aspiration event (if the event can be identified).

- Because the abscess is usually localized and often not very large, examination findings may be limited or minimal.

Diagnostic Considerations

- Obtaining bacterial confirmation of the infection is difficult because communication with the airway is uncommon, and sputum production is infrequent.
- Most often, the diagnosis is established via the following:
  - Chest radiographs or chest computed tomographic findings, including (Figure 64-1) presence of a thick-walled, rounded opacity, with central aeration or an air-fluid level
  - A history that indicates a risk for an abscess
  - Exclusion of causes of similar-appearing lesions, such as tuberculosis, granulomatosis with polyangiitis, pulmonary lymphoma, pneumatocele, and pulmonary embolus
- If an abscess seems to be the most probable etiologic origin, biopsy, resection, or needle aspiration is not required.
- Consideration of immunodeficiency may be relevant, particularly diseases of granulocyte function or hyper–immunoglobulin E syndromes (Job syndrome).
- If there is concern for a retained foreign body as the underlying cause of the abscess, bronchoscopy might be useful.

Treatment

- Oral antibiotics usually suffice.
  - The choice of antibiotics can be clindamycin, ampicillin, or ampicillin plus clavulanate, and the duration of therapy should be ≥2 weeks.
  - If a gram-negative pathogen is suspected, ciprofloxacin may be the appropriate antibiotic.
- Surgical drainage is no longer used as a primary mode of therapy, because it may lead to dissemination of infection.

Prognosis

- The prognosis for full recovery and normal chest radiographic findings is good in an otherwise healthy child, with no ongoing risks for further lung injury.
- It may take several weeks for the chest radiographic findings to normalize.

When to Admit

- Progressive fevers or worsening radiographic appearance suggests the need for more invasive evaluation and perhaps intravenous antibiotic therapy, as well as reassessment of the precise etiologic origin of the abnormal radiographic findings.

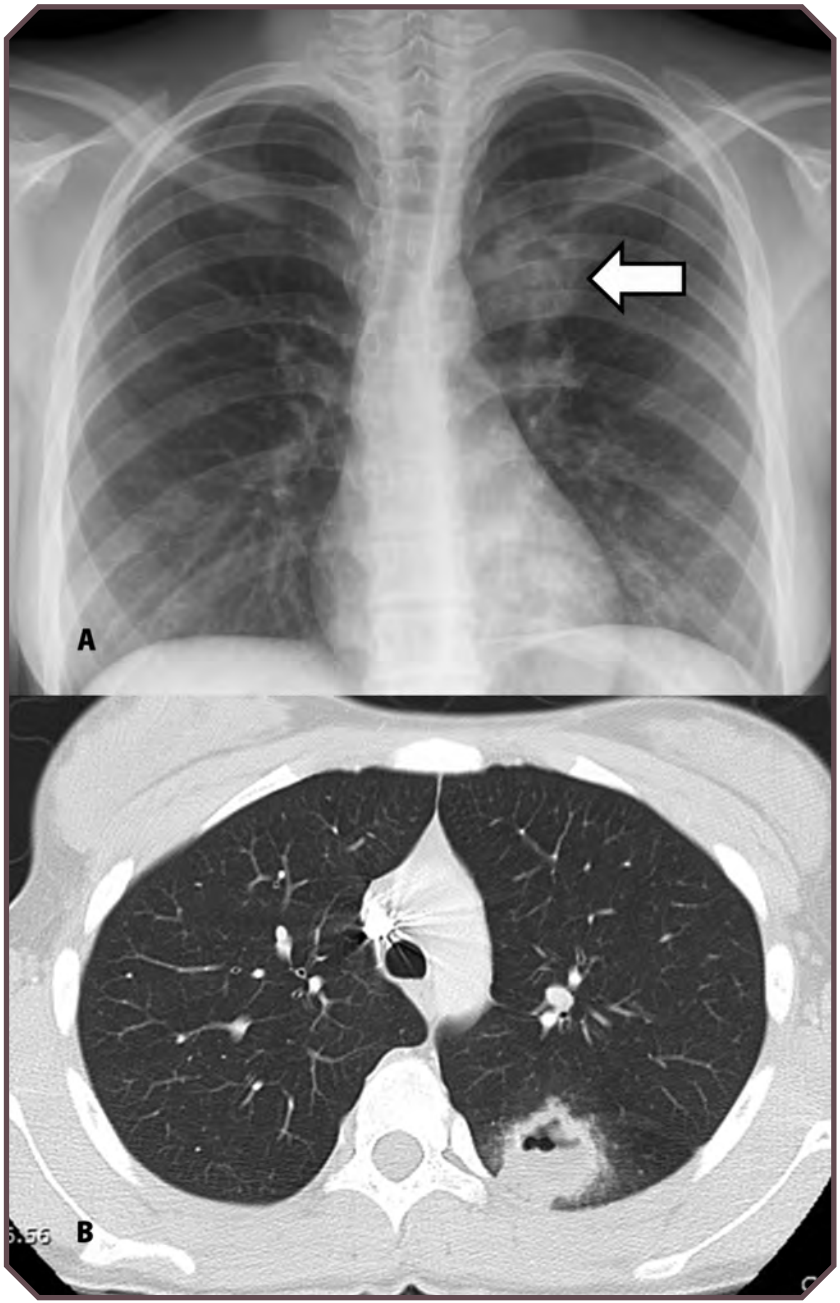

Figure 64-1. Complicated pneumonia with left upper lobe abscess in a teenaged girl. A. Frontal chest radiograph demonstrates a left upper lobe focal opacity with central air (arrow). B. Axial chest computed tomographic image confirms an air-containing opacity in the left upper lobe, with a thick wall and irregular margins, which are typical of focal abscess.

Resources for Families

- Lung Abscess (Healthline). www.healthline.com/health/lung-abscess#Overview1
- Anaerobic Infections (American Academy of Pediatrics). www.healthychildren.org/English/health-issues/conditions/infections/Pages/Anaerobic-Infections.aspx

Clinical Pearl

- Most pulmonary abscesses are caused by oral flora, many of which are anaerobic.

Chapter 65

Complications of Pneumonia: Postinfective Bronchiolitis Obliterans

Paul C. Stillwell, MD, FAAP, and Deborah R. Liptzin, MD, MS, FAAP

Introduction/Etiology/Epidemiology

- Obliterative bronchiolitis, or bronchiolitis obliterans, is obliteration of the small brochiolar airways with fibrinoproliferative material.
- It occurs in a variety of settings (Box 65-1).
  - — In North America, it occurs infrequently after viral infection and more commonly after lung transplantation or hematopoietic stem cell transplantation.
  - — In indigenous populations, it is commonly seen after viral infections (postinfectious bronchiolitis obliterans).

Box 65-1. Underlying Systemic Disease or Trigger for Development of Obliterative Bronchiolitis

Autoimmune disease
Rheumatoid arthritis
Sjogren syndrome
Systemic lupus erythematosus

Inhalational agents
Sulfur mustard
Nitrogen oxides
Mold
Avian antigens
Others

Infections
Adenovirus
Measles
Mycoplasma
Others

Posttransplant causes
Hematopoietic stem cell transplant
Lung transplant

Aspiration

Stevens-Johnson syndrome

Clinical Features

- Signs of obliterative bronchiolitis are inspiratory crackles, barrel chest, hypoxemia, and tachypnea.
- Symptoms of obliterative bronchiolitis are cough, dyspnea, and wheezing.
- Signs and symptoms may be subtle. Dyspnea is often very prominent, even with minimal exertion.

Diagnostic Considerations

- The standard of reference for diagnosis is lung biopsy; however, disease can be patchy and missed at biopsy (particularly transbronchial biopsy).
- The pathologic process causes the airways to be narrowed or completely obliterated; airway fibrosis will be present.
- At pulmonary function testing, obstruction and air trapping will be found, typically with minimal postbronchodilator improvement (Figure 65-1).
- Chest radiographs show variable, nonspecific findings that range from patchy to diffuse air space opacity (Figure 65-2). Computed tomographic (CT) findings are more specific and include air trapping, mosaic perfusion, and vascular attenuation, with or without bronchiectasis (Figure 65-3).
  - Mosaic perfusion appears as areas of decreased attenuation that are darker on CT images, due to decreased perfusion.
  - Vascular attenuation appears as loss of blood vessel visibility in areas of decreased lung perfusion.
- Lung transplant recipients with a clinically significant change in pulmonary function test results (obstruction) without a lung biopsy have bronchiolitis obliterans syndrome.

Treatment

- Treatment is based on expert opinion and on adult trials for bronchiolitis obliterans syndrome.
- Monitor the patient for hypoxemia with exercise and at night, and treat as needed.
- Monitor the patient for pulmonary hypertension, and treat as needed.
- Consult with a pediatric pulmonologist with expertise in children's interstitial and diffuse lung disease.
- Common medication regimens are listed in Table 65-1.
- Adult studies also suggest fluticasone, azithromycin, and montelukast.
- If the patient also has bronchiectasis, airway clearance and early antibiotics should be initiated for a cough.

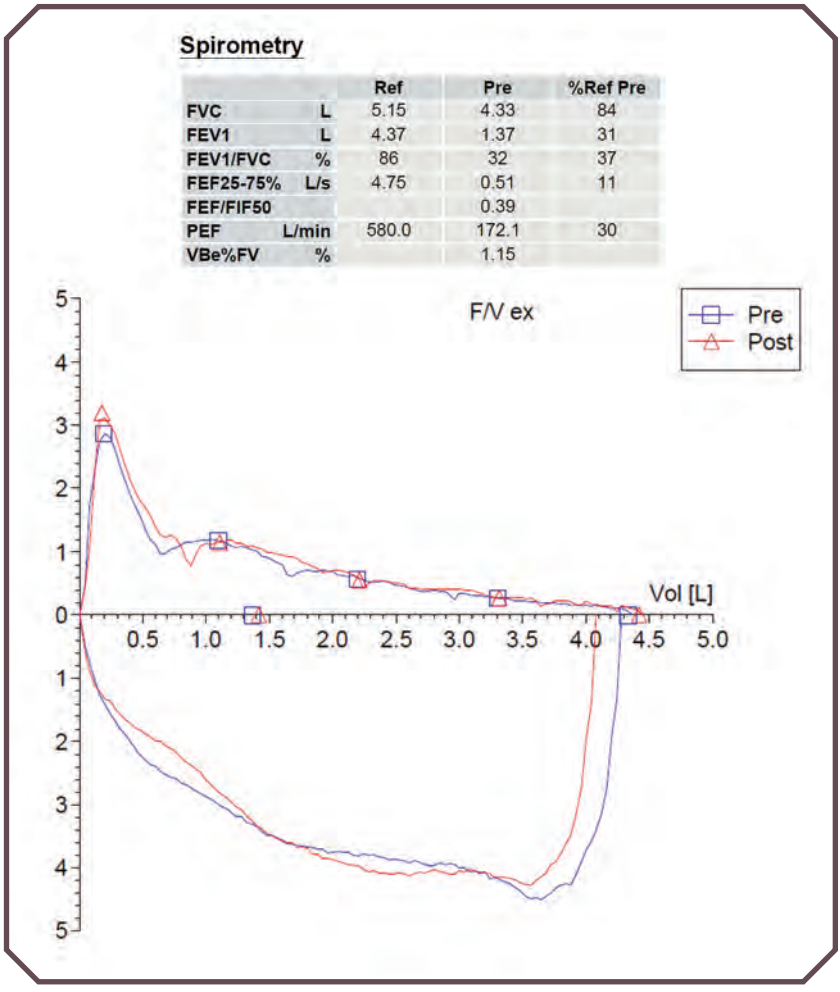

Figure 65-1. Pulmonary function testing demonstrates severe obstruction in obliterative bronchiolitis. ex = expiratory, FEF25%-75% = forced expiratory flow between 25% and 75% of vital capacity, FEV 1 = forced expiratory volume in 1 second, F/V = flow-volume, FVC = forced vital capacity, in = inspiratory, PEF = peak expiratory flow, Ref = reference, VBe = volume backextrapolation, Vol = volume.

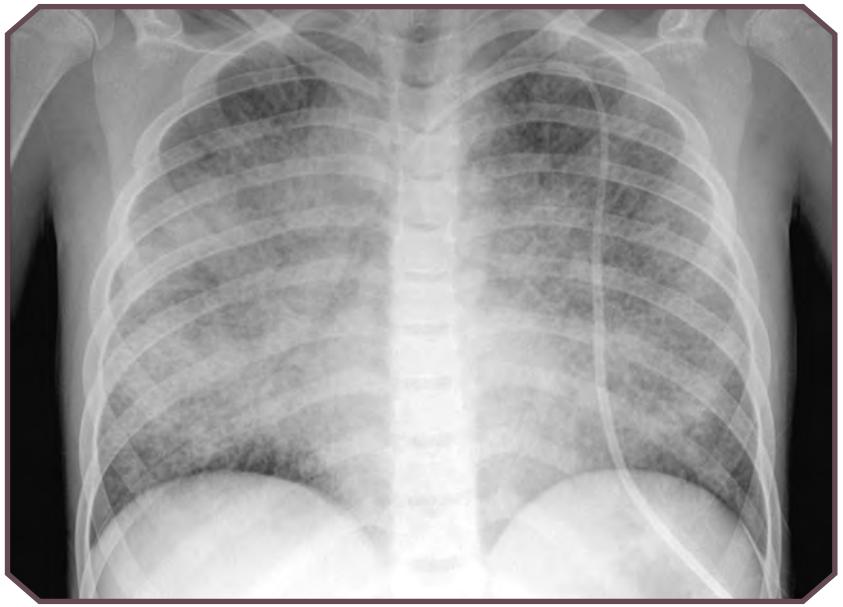

Figure 65-2. Obliterative bronchiolitis in a 10-year-old boy with leukemia. Frontal chest radiograph demonstrates nonspecific bilateral, diffuse air space opacity. Note the central line overlying the left brachiocephalic vein.

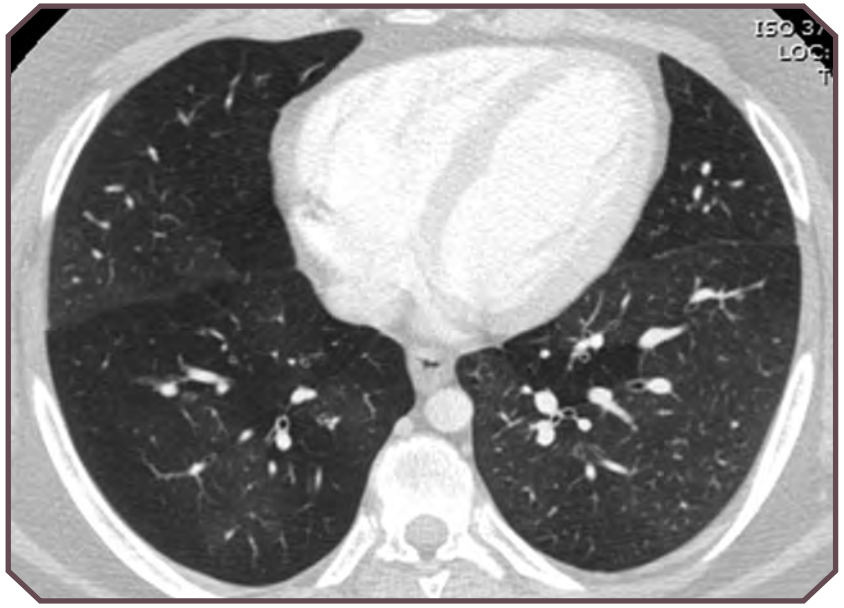

Figure 65-3. Obliterative bronchiolitis in a patient after having Stevens-Johnson syndrome. Axial chest computed tomographic image demonstrates regions of mosaic perfusion (typical of obliterative bronchiolitis) scattered between areas of normal lung. The mosaic perfusion areas can be recognized by the well-defined margins and low attenuation due to decreased visualization of the normal vascular structures.

Table 65-1. Treatment for Obliterative Bronchiolitis		
Treatment	**Dose**	**Interval**
Methylprednisolone	IV 10–30 mg/kg for 3 d	Every month
IV immunoglobulin	IV 2 g/kg for 1 d	Every month
Azithromycin	10 mg/kg by mouth (maximum, 500 mg) Alternate dosing: 18.0–35.9 kg: 250 mg >36.0 kg: 500 mg	3 d a week

IV, intravenous.

Prognosis

- Few outcome data exist in children.
- Some patients, especially those with postinfectious bronchiolitis obliterans, may have stable lung function for years.
- Other patients may have progressive disease despite therapy.
- Once fibrosis has set in, reversal of the disease may be challenging.
- There may be a role for antifibrotic therapy in this population.

When to Refer

- Establishing the correct diagnosis
- Treatment induction and maintenance therapy
- Disease follow-up and management of exacerbations

Resource for Families

- What Is Interstitial Lung Disease in Children? (American Thoracic Society) www.thoracic.org/patients/patient-resources/resources/interstitial-lung-disease-in-children.pdf

Clinical Pearls

- Consider a diagnosis of obliterative bronchiolitis in patients who have new shortness of breath, exercise intolerance, and/or crackles after a hematopoietic stem cell transplant or lung transplant.
- A diagnosis of obliterative bronchiolitis should also be considered in patients with a history of severe pneumonia, particularly with adenovirus, Stevens-Johnson syndrome, or measles, and poorly reversible airway obstruction (“atypical asthma”).

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Part V. Genetic Respiratory Diseases

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Chapter 66

Surfactant Metabolism Disorders, Including Surfactant Protein Deficiencies

Jennifer J Soares, MD, FAAP, and Eugene R. Soares, MD, PhD, FAAP

Introduction/Etiology/Epidemiology

- Pulmonary surfactant is a mixture of lipids and proteins (surfactant protein A, B, C, and D) produced by type II alveolar epithelial cells and packaged and stored in lamellar bodies until secreted into the alveoli.
- Once secreted, surfactant lines the alveoli, reducing the surface tension and preventing end-expiratory atelectasis, thus allowing for optimal gas exchange.
- Metabolism (production, function, degradation, and clearance) of surfactant depends on various proteins: thyroid transcription factor 1 (TTF-1), membrane transporter, member A3 of the adenosine triphosphate–binding cassette family (ABCA3), and granulocyte-macrophage (GM) colony-stimulating factor.
- Defects in the genes encoding the surfactant proteins or the proteins involved in their metabolism result in diffuse lung disease.
- Known surfactant metabolism defects include
  - Surfactant protein B (SP-B) deficiency caused by mutations in *SFTPB*
  - Loss of or reduced function of ABCA3 because of mutations in *ABCA3*
  - Dysfunction of surfactant protein C (SP-C) because of mutations in *SFTPC*
  - Haploinsufficiency of *NKX2.1*, the gene encoding TTF-1
  - GM colony-stimulating factor receptor gene mutations or auto-antibody development
- These disorders are rare, cause substantial morbidity and mortality, and present a large cost burden for their evaluation and treatment.

Clinical Features

- Disorders of surfactant metabolism manifest most commonly in infancy but may also appear later in life, including in adolescents or adults (Table 66-1).
- Presentation in the newborn and infant period resembles respiratory distress syndrome (RDS) clinically and radiographically, except that the patient is usually born full term and lacks risk factors for RDS.
- At birth and in infancy:
  - Signs include tachypnea, grunting, nasal flaring, intercostal and subcostal retractions, cyanosis, and hypoxemia.
  - Symptoms include increased work of breathing, cough, feeding intolerance, and respiratory failure.

Table 66-1. Genetic Surfactant Metabolism Disorders

	SP-B Deficiency	ABCA3 Deficiency	*NKX2.1* Haploinsufficiency	SP-C Dysfunction	GM Colony-Stimulating Factor Abnormalities
Inheritance	AR	AR	Primarily de novo	AD, de novo	AR or autoimmune
Most common mutation	121ins2 accounts for two-thirds of identified mutant alleles	Glu292Val accounts for <10% of identified alleles; >150 mutational variants have been identified to date	Most mutations reported to date are private (unique to a given kindred)	p.Ile73Thr accounts for >25% of mutant alleles	Multiple mutations have been reported, including *CSF2RA* and *CSF2RB*
Onset of pulmonary symptoms	Neonatal period	Primarily neonatal period and infancy	Primarily neonatal period and infancy	Primarily neonatal period and infancy, occasionally later	Primarily adulthood and late childhood
Other findings	—	—	With or without neurological and thyroid abnormalities	—	—
Outcome	Fatal without transplant	Variable	Variable	Variable	Variable

ABCA3, member A3 of the adenosine triphosphate–binding cassette family; AD, autosomal dominant; AR, autosomal recessive; GM, granulocyte-macrophage; NKX2.1, gene encoding thyroid transcription factor 1; SP-B, surfactant protein B; SP-C, surfactant protein C.

- In childhood and later:
  - Signs include tachypnea, digital clubbing, pectus excavatum, crackles, wheeze, failure to thrive, cyanosis, and hypoxemia.
  - Symptoms include increased work of breathing, cough, shortness of breath, and exercise intolerance.
- The severity of disease at presentation can be variable, depending on the etiologic origin and genotype.

Types of Surfactant Metabolism Disorders and Clinical Course

SP-B Deficiency

- Results in absent mature SP-B and secondary changes in surfactant
- Extremely rare (<1 in 1 million live births)
- At birth, the patient presents with severe atelectasis and poor lung compliance, leading to progressive, irreversible respiratory failure and death.
- Some rare *SFTPB* mutations causing only partial SP-B deficiency have been reported to result in milder disease.

ABCA3 Loss of Function or Reduced Function Defects

- Results in decreased surfactant lipids critical for surface tension reduction
- The most common cause of genetic surfactant dysfunction
- Can present at birth or later in childhood and, depending on genotype, may cause severe progressive respiratory failure, stabilize, or improve

NKX2.1 Haploinsufficiency

- Results in decreased amounts of TTF-1, leading to ineffective expression of 1 or all of the following:
  - SP-B
  - SP-C
  - ABCA3
  - Additional proteins
- May manifest as severe respiratory failure early in life or chronic disease characterized by frequent pulmonary infections
- The term *brain-lung-thyroid syndrome* is used when endocrine and/or neurological systems are also affected. Findings include hypothyroidism, hypotonia, ataxia, and chorea.

SP-C Dysfunction

- Results in misfolding of the precursor of SP-C (prosurfactant SP-C), causing lung disease from a gain-of–toxic function mechanism.
- Onset and severity of disease are highly variable, even within family members who carry the same mutation.

GM Colony-Stimulating Factor Receptor Mutations and Autoantibody Development

- Results in immature alveolar macrophages, which are unable to catabolize and clear surfactant from the alveoli, causing pulmonary alveolar proteinosis (PAP)
- Eighty percent to 90% of all cases are autoimmune, and 5% are hereditary.
- Autoimmune and hereditary PAP are extremely rare in infants and children and are more typically seen in adults and some adolescents.
- The clinical course is variable; some patients present with respiratory failure as infants, while others have an indolent disease course that can persist and progress.

Diagnostic Considerations

- Figure 66-1 outlines a diagnostic approach to disorders of surfactant metabolism.
- Rule out more common causes of diffuse lung disease in children.
  - — Disorders of surfactant metabolism are rare, but one must have a high level of suspicion for the disease.
  - — If the child presents with severe respiratory failure at birth that resembles RDS, consider the presence of
    - Other causes of diffuse lung disease (see Chapter 85, Children's Diffuse and Interstitial Lung Disease)
    - Infection
    - Congenital heart disease
  - — For those with mild symptoms and/or a waxing and waning disease course, consider the presence of
    - Other causes of diffuse lung disease
    - Infection and/or immunodeficiency
    - Chronic aspiration
    - Cystic fibrosis and other more common lung diseases, such as RDS, infection, asthma, and chronic aspiration
- History
  - — Those presenting in childhood may have a history of neonatal respiratory distress.
  - — *(a)* A family history of death in the neonatal period or *(b)* childhood or adult interstitial lung disease should raise suspicion.
- Imaging
  - — Chest radiographs demonstrate diffuse alveolar and interstitial opacities.
  - — Thin-section chest computed tomography (CT) demonstrates diffuse ground-glass opacities with interlobular and intralobular septal thickening, which are suggestive of but not diagnostic for a surfactant metabolism defect.

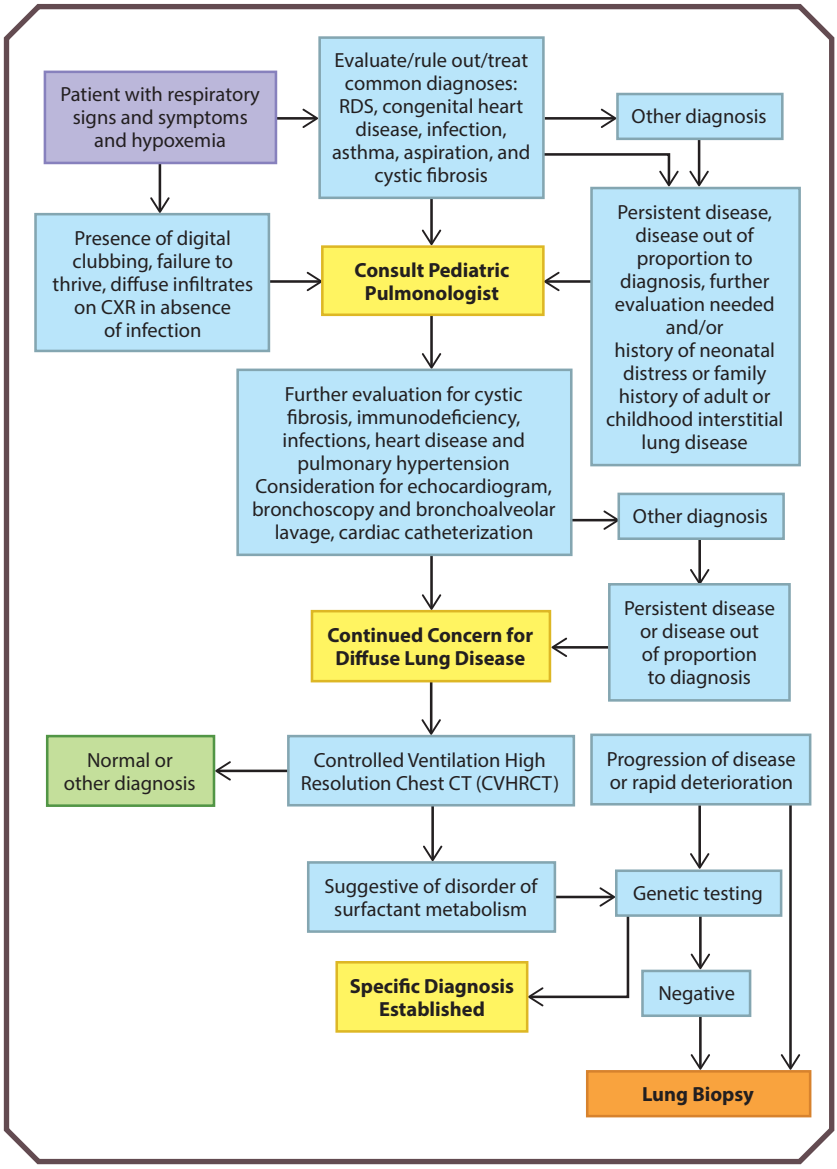

Figure 66-1. Proposed diagnostic approach for disorders of surfactant metabolism. CT = computed tomography, CXR = chest radiography, RDS = respiratory distress syndrome. Adapted from the diagnostic approach as published in Kurland G, Deterding RR, Hagood J, et al. An Official American Thoracic Society 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.

- Genetic testing
  - Depending on the stability of the patient, genetic testing is typically preferred prior to a more invasive evaluation, such as lung biopsy.
  - A list of available tests and laboratories that provide testing can be found at www.genetests.org.
  - The specificity and positive predictive value of genetic testing are good, but the sensitivity and negative predictive value are limited because all responsible gene mutations have not been discovered.
- Lung biopsy
  - Consider the need for lung biopsy when noninvasive testing fails to elucidate the disease.

Treatment

- Because of the rarity of these diseases and the lack of clinical trials, only anecdotal reports of treatment exist.
- Supportive therapy consists of supplemental oxygen for hypoxemia and work of breathing.
- Administer routine immunizations.
- Nutritional support is of utmost importance for growth in the setting of high caloric expenditure due to baseline increased work of breathing.
  - Nutritional supplementation
  - Gastrostomy tube
- Assess and treat other comorbidities, such as obstructive sleep apnea, gastroesophageal reflux, and secondary pulmonary hypertension, to protect the lung from further injury.

Medications

- Exogenous surfactant administration is not effective.
- Anti-inflammatory agents (hydroxychloroquine and azithromycin) may be helpful in some children with SP-C and ABCA3 defects.
- Corticosteroids
  - Intravenous and oral formulations are often used, although their overall effect is not clear.
  - There have been reports of varying effect in patients with *ABCA3* and *SFTPC* mutations, often in concert with hydroxychloroquine.
- Inhaled GM colony-stimulating factor for autoimmune PAP
  - Reports show it to be effective.
  - Studies are underway to determine dosing and long-term safety.

Whole-Lung Lavage for PAP

- Serial whole-lung lavage is standard therapy for hereditary and auto-immune PAP, with good effect.
- Frequency of lavage is determined individually on the basis of symptoms and severity of disease.

Lung Transplantation

- Lung transplantation may be performed for severe lung disease that is refractory to other therapies.
- Long-term outcomes are comparable to those of children undergoing lung transplantation for other indications.

Prognosis

SP-B Deficiency

- Except for some rare mutations, SP-B deficiency is fatal in the first days to months without lung transplantation.

ABCA3 Loss of Function or Reduced Function Defects

- For those who present in infancy and/or childhood, the prognosis is variable, with progressive respiratory failure and death, stable disease, or resolution of symptoms.

NKX2.1 Haploinsufficiency

- There is a paucity of information regarding prognosis, although case reports have demonstrated severe disease in infancy that progresses to death, as well as mild or no lung disease.

SP-C Dysfunction

- The disease course is highly variable and is not dependent on genotype.
- The disease severity spans *(a)* respiratory failure and death in the neonatal period to *(b)* developing disease late in life or not at all.

Autoimmune PAP and Hereditary PAP

- The disease course is variable, with some spontaneously resolving and others progressing to severe disease and death despite serial lung lavage.
- Disease recurrence has been reported after lung transplantation.

When to Refer

Having a low threshold for referral to a pediatric pulmonologist is advisable, especially in the setting of

- Persistent pulmonary findings not responsive to general therapies or worsening over time
- The presence of persistent hypoxemia or digital clubbing
- Before performing advanced imaging (chest CT), genetic testing, or lung biopsy
- Potential referral of the family for genetic counseling

Resources for Families

- Surfactant Deficiency (Children's Interstitial and Diffuse Lung Disease Foundation). www.child-foundation.com/what-is-child/types-of-child/surfactant-deficiency
- Genetics Home Reference: Surfactant Dysfunction (National Institutes of Health). ghr.nlm.nih.gov/condition/surfactant-dysfunction

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Chapter 67

Cystic Fibrosis

Jonathan Ma, MD, and Michael S. Schechter, MD, MPH

Introduction/Etiology/Epidemiology

- Cystic fibrosis (CF) is the most common life-shortening genetic disease in white people.
- It is an autosomal recessive disorder involving mutations in the gene that produces CF transmembrane conductance regulator (CFTR) protein.
- CFTR is a chloride channel that regulates the epithelial sodium channel.
- *CFTR* mutations result in abnormal ion and water transport across epithelial membranes, especially in the lungs, pancreas, intestines, biliary tract, sweat glands, and vas deferens.
- CF affects 30,000–40,000 people in the United States and 80,000–100,000 people worldwide.
- Incidence is approximately 1 in 3,000 white Americans, 1 in 4,000–10,000 Hispanic Americans, and 1 in 15,000–20,000 African Americans. It is rare in Asian Americans and Native Americans.

Pathophysiology

The pathogenesis of CF is depicted in Figure 67-1.

- More than 1,800 *CFTR* mutations have been identified.
  - The most common mutation is F508del (present in a homozygous or heterozygous form in 80% of people with CF).
  - *CFTR* mutations have been grouped into 6 classes on the basis of the functional abnormality. Class I–III mutations lead to virtually absent CFTR function; some residual CFTR function exists with the class IV–VI mutations, and these patients typically have pancreatic sufficiency.
    - Class I: No functional protein due to a premature stop codon in mRNA that leads to a truncated nonfunctioning protein
    - Class II: Unstable and/or misfolded protein that is improperly processed and degraded in proteasomes before reaching the cell membrane
    - Class III: Defective regulation of gating but properly positioned
    - Class IV: Reduced chloride conductance but properly positioned
    - Class V: Reduced synthesis of functional protein due to aberrant splicing
    - Class VI: Less stable functional protein with accelerated turnover

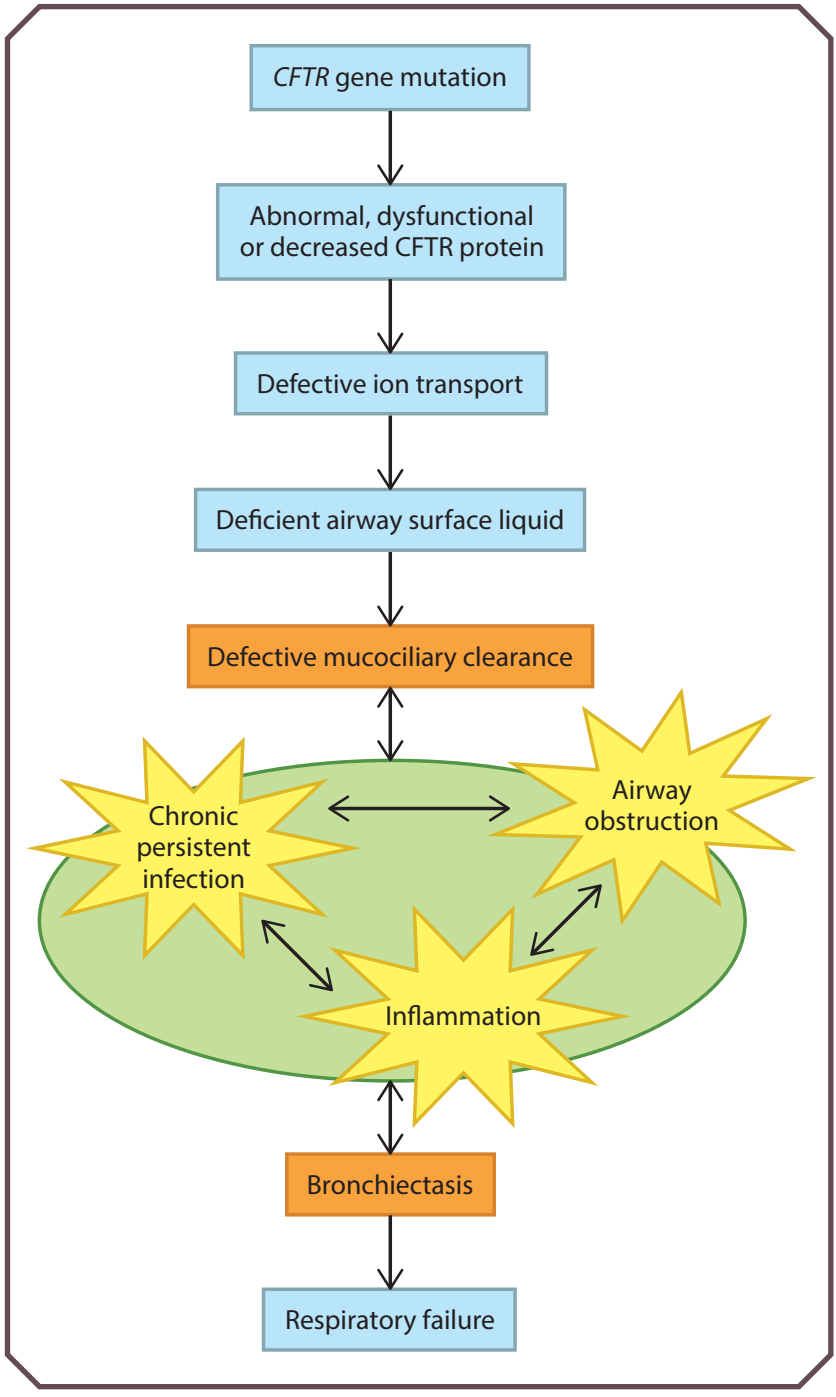

Figure 67-1. Cystic fibrosis pathogenesis. CFTR = CF transmembrane conductance regulator.

- CFTR dysfunction leads to excessive sodium absorption and deficient chloride secretion at the apical cell membrane, decreasing the osmotic driving force for water transport.
  - The resultant "low volume" of airway surface impairs mucociliary clearance of airway secretions.
  - The stasis of airway secretions inhibits the ability to clear inhaled bacteria, leading to an unrelenting airway infection that waxes and wanes in intensity but is never cleared.
- CFTR also causes an exaggerated inflammatory response to respiratory pathogens.
  - Persistent airway inflammation leads to bronchiectasis, declining lung function, and, ultimately, respiratory failure and death.
- In other organ systems, aberrant ion transport leads to ductal obstruction that results in pancreatic insufficiency and congenital absence of the vas deferens.

Clinical Features

Sweat Glands

- The hallmark of disease is high salt content in the sweat glands (sweat chloride >60 mEq/L [>60 mmol/L] in patients with CF vs <30 mEq/L [<30 mmol/L] in otherwise healthy patients).
- Hyponatremia is a risk in warm environments, particularly in infants.

Respiratory System

- Upper airway disease
  - Pansinusitis is universal, and nasal polyps are common.
  - Recurrence is common after surgery.
- Lower-airway disease
  - Chronic ineradicable airway infection begins in the first year after birth.
    - *Haemophilus influenzae* and *Staphylococcus aureus* are the most common infectious organisms early in life.
    - *Pseudomonas aeruginosa* becomes more common as children get older, and its acquisition is associated with an accelerated decline in lung function.
    - Other key pathogens include
      - ~ *Stenotrophomonas maltophilia*
      - ~ *Achromobacter xylosoxidans*
      - ~ *Burkholderia cepacia* complex
      - ~ Nontuberculous mycobacteria (*Mycobacterium abscessus*, *Mycobacterium avium* complex)
      - ~ *Aspergillus fumigatus* (primarily associated with allergic bronchopulmonary aspergillosis)

— Pulmonary function tests show obstructive disease, marked by decreased forced expiratory volume in 1 second (FEV_1) and increased residual volume.
— Pulmonary complications include atelectasis, pneumothorax, hemoptysis, and bronchiectasis (Figures 67-2 and 67-3).
— Respiratory failure is the most common cause of death.

Gastrointestinal Tract

- Small intestinal obstruction
- Meconium ileus
  — Inspissated material leads to obstruction in the distal ileum.
  — It is seen in 20% of patients with CF at birth.
  — It warrants prompt surgical consultation because of marked risk for perforation (Figure 67-4).

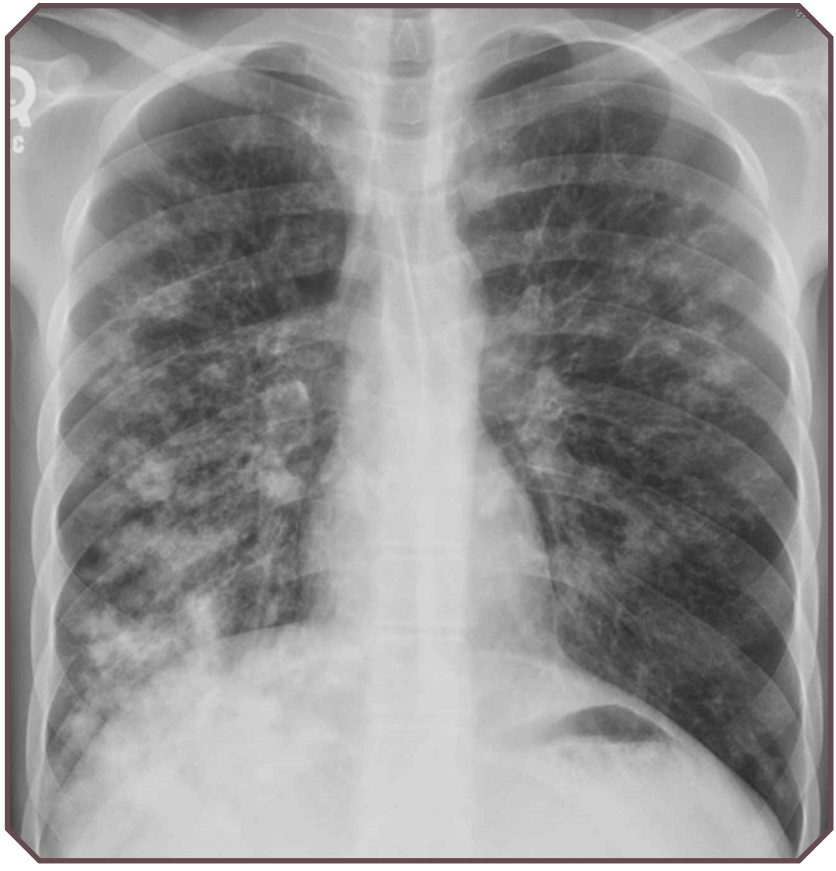

Figure 67-2. Cystic fibrosis in a 14-year-old girl. Frontal chest radiograph shows bilateral hyperinflation, extensive peribronchial thickening, scattered nodular foci consistent with mucous plugging, and scattered lucencies due to bronchiectasis.

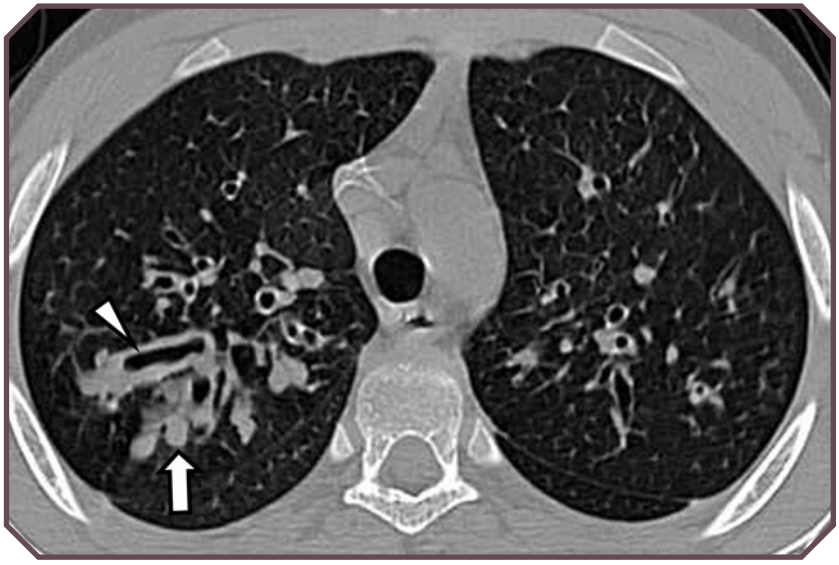

Figure 67-3. Cystic fibrosis (CF) in a 12-year-old girl. Axial unenhanced computed tomographic image demonstrates extensive peribronchial thickening, mucous plugging (arrow), and bronchiectasis (arrowhead), which are typical of CF.

- Distal intestinal obstruction syndrome
  - Accumulation of tenacious stool in the ileum and large bowel leads to acute or subacute obstruction.
  - In contrast to meconium ileus, this is usually medically treatable.
- Pancreatic insufficiency
  - Present in >90% of patients with CF
  - May evolve during the first 6–12 months after birth
- Results in malabsorption of fat and protein, leading to failure to thrive or gain weight, steatorrhea, and deficiency of fat-soluble vitamins (vitamins A, D, E, K)
- Hepatobiliary obstruction
  - Inspissated bile leads to obstruction of intrahepatic bile ducts.
  - It may result in progressive biliary cirrhosis.
  - Severe liver disease peaks in adolescence, and 5% of patients require transplantation.
- Cancer
  - Adults with CF have a relatively high incidence of gastrointestinal cancers.

Endocrine System

- CF-related diabetes
  - CF-related diabetes is a hybrid of type 1 and type 2 diabetes mellitus, with both decreased insulin production and decreased sensitivity.

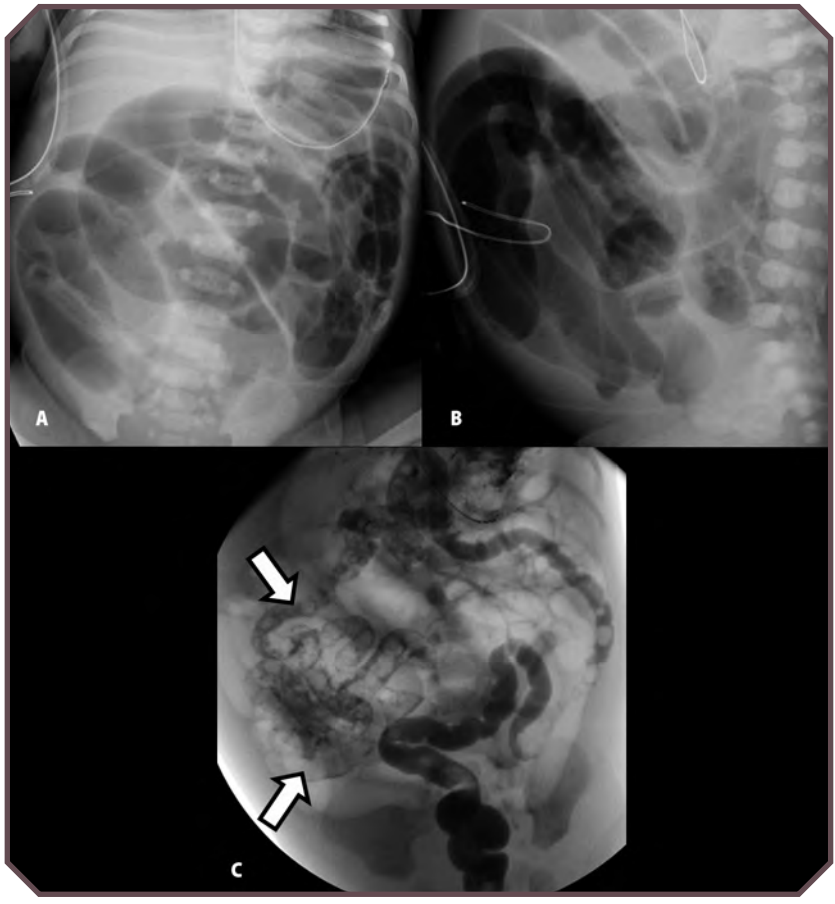

Figure 67-4. Meconium ileus in a 1.5-day-old male newborn who has not passed meconium. A. Frontal and B. lateral radiographs show multiple dilated bowel loops without rectal gas, indicating small-bowel obstruction. C. Frontal image obtained from a contrast-enhanced enema demonstrates a microcolon and multiple filling defects in the distal ileum (arrows).

  - It is rare in the first decade after birth but increasingly common in the second and third decades after birth.
  - The prevalence in adults with CF is 30%–50%.
- It is associated with poorer nutritional status and lung function.
- Osteoporosis can occur secondary to vitamin D deficiency, the chronic inflammatory state, and steroid use.

Reproductive Tract

- Male
  - Essentially all male patients with CF have infertility due to congenital bilateral absence of the vas deferens.
  - In vitro methods can be used to allow fertility.

- Female
  - — Female patients have cervical mucus abnormalities, but fertility is related to nutritional status, and pregnancies are increasingly common.
  - — Pregnancy in women with CF is associated with some short-term complications but no clinically significant long-term complications.

Diagnostic Considerations and Differential Diagnosis

- Prior to the adoption of newborn screening (NBS), half of all patients received a diagnosis of CF between 6 months of age and adulthood.
- Most patients now receive diagnoses because of the NBS (see Chapter 68, Cystic Fibrosis Newborn Screening, for a detailed discussion).
- There remain some patients without diagnoses who were born before the advent of the NBS, and the sensitivity of NBS protocols is high but is <100% (particularly for neonates born with meconium ileus).
- Features that should prompt evaluation and/or diagnosis include
  - — Recurrent or persistent respiratory symptoms (cough)
  - — Failure to thrive
  - — Steatorrhea
- The sweat test remains the standard of reference for the diagnosis of CF.
  - — It is performed by using pilocarpine iontophoresis and quantitative chloride concentration determination.
  - — The interpretation of results is as follows.
    - ▪ Sweat chloride level ≥60 mmol/L: CF
    - ▪ Sweat chloride level of 30–59 mmol/L: indeterminate
    - ▪ Sweat chloride level <30 mmol/L: normal
    - ▪ Patients with indeterminate values should be evaluated by a CF specialist.
    - ▪ Reliability can only be assumed when performed at an accredited CF Care Center.
- Genetic testing is a second-line test.
  - — Genetic testing is typically performed by using a screening panel of 20–40 of the most frequent *CFTR* gene mutations (depending on the laboratory).
    - ▪ This is also the approach typically used for NBS and prenatal screening.
    - ▪ Genetic testing with screening panels has a positive predictive value of nearly 100% but a lower negative predictive value (depending on the ethnicity of the patient). In other words, false-negative findings will occur.
  - — Gene sequencing is nearly 100% sensitive and specific but is much more expensive, and turnaround time can be prolonged. Its use should be left to the CF specialist.

Management

Nutritional Therapies

- Morbidity and mortality in CF are strongly tied to nutritional status.
- Goal body mass index (BMI) is the 50th percentile for age and sex.
- Pancreatic enzyme replacement is provided for patients with pancreatic insufficiency documented by low pancreatic fecal elastase-1 levels.
- Fat-soluble vitamin supplementation is provided for patients with pancreatic insufficiency.
- High-calorie diets are offered, beginning in infancy.
  - Enteral supplements are commonly given.
  - Appetite simulants, such as cyproheptadine, megestrol acetate, and oxandrolone, and antidepressants, such as mirtazapine, are given as needed.
  - Gastrostomy tubes may be inserted, especially during infancy and adolescence, when patients have the most difficulty meeting nutritional requirements.

Pulmonary Therapies

Airway Clearance Therapies

- Augment clearance of tenacious airway secretions
- Are performed daily for life, from the time of diagnosis
- Various modalities seem to be equivalent:
  - Manual percussive chest physiotherapy
  - High-frequency chest wall oscillation ("the vest")
  - Positive expiratory pressure devices, with or without oscillation
- Regular exercise is also important.

Bronchodilators

- Recommended by the Cystic Fibrosis Foundation (CFF) for those that benefit.
- Twenty-five percent of patients are consistently responsive to bronchodilators, and most are intermittently responsive.

Dornase Alfa

- Nebulized therapy administered once daily improves airway clearance by enzymatic breakdown of extracellular DNA that is present in secretions due to neutrophil necrosis.
- Dornase alfa is recommended by the CFF for patients >5 years of age and can be considered in those <5 years of age.

Hypertonic Saline

- Hypertonic saline serves as a hyperosmolar agent to draw water into the airways.
- Twice-daily therapy has been shown to benefit patients.

Infectious Disease

- Aerosolized antibiotics (tobramycin, aztreonam, others) are prescribed to those with chronic airway *P aeruginosa* infection.
- Systemic antibiotics are prescribed for the treatment of acute pulmonary exacerbations (see the Pulmonary Exacerbations and Their Management section in this chapter).

Anti-inflammatory Therapies

- Macrolide antibiotics (azithromycin) improve lung function and decrease the frequency of pulmonary exacerbations through what is thought to be an immunomodulatory mechanism.
- High-dose ibuprofen (20–30 mg/kg administered twice daily; maximum, 1,600 mg per dose) slows the decline in lung function but is not commonly used because of complexity of monitoring and potential side effects.
- Inhaled corticosteroids are prescribed to patients with asthma, but supporting evidence is unclear.
- Systemic corticosteroids are prescribed in selected situations but come with serious side effects.

CFTR Modulators

- This is a new class of drugs that recover CFTR function and hold the promise of substantial long-term benefit.
- Ivacaftor
  - A "corrector" that increases the gating function of CFTR molecules that have properly located to the apical cell membrane
  - Of substantial benefit for a limited number of patients with class III and class IV mutations
- Lumacaftor/ivacaftor
  - Lumacaftor is a "potentiator" that stabilizes misfolded F508del CFTR and allows it to locate to the apical cell surface, where ivacaftor corrects its function.
  - It is of mild benefit for the 50% of patients with CF who have F508del.
- A number of new CFTR modulators are in various states of development.

Pulmonary Exacerbations and Their Management

- Pulmonary exacerbations occur periodically and are associated with increased airway inflammation and obstruction.
- Signs and symptoms of a pulmonary exacerbation include
  - Increased cough
  - Shortness of breath
  - Hemoptysis
  - Increased sputum
  - Anorexia and/or weight loss
  - New wheeze or crackles

  - Decreased FEV_1 at pulmonary function testing
  - New chest radiographic findings
- Therapy
  - Increased airway clearance therapy
  - Systemic antibiotics
    - Typically start with oral antibiotics directed against organisms found at sputum culture.
    - If the patient has not recovered completely to baseline, treatment with intravenous antibiotics is indicated; in this situation, inpatient care has a higher success rate, but some patients may be effectively treated as outpatients.
- Incomplete recovery from these episodes is the primary driver of lung damage and decline in lung function.

Other Common Morbidities

- Allergic bronchopulmonary aspergillosis
- Anxiety and depression among patients with CF and caretakers
- CF-related diabetes (primarily after age 10)
- Osteoporosis (primarily in adults and those with severe disease)
- Hepatobiliary disease
- Distal ilial obstruction syndrome
- Gastrointestinal cancers (adults)

Expected Outcomes/Prognosis

- The median expected age at death is 40 years (as of 2016).
- More than 50% of patients are now >18 years of age.
- Mortality, morbidity, and quality of life continue to improve.

When to Refer

- Any child with abnormal or borderline sweat test findings should be referred to a CFF-accredited Care Center for further evaluation.
- All patients with CF should be treated by a clinical team at a CF Care Center in collaboration with their primary care physician.
- The CF Care Center should be contacted when
  - The patient has any increase in respiratory symptoms that lasts longer than a week.
  - There is any question regarding the choice of an appropriate antibiotic for a respiratory tract infection.
  - The patient is experiencing any abdominal pain.

When to Admit

- Admit the patient for signs and symptoms of a pulmonary exacerbation that are not reversed with oral antibiotics.
- Admit the patient for persistent abdominal pain.
- It is generally recommended that patients with CF be cared for by CF Care Center physicians when hospitalized.
- If hospitalization is considered by the general pediatrician, the CF Care Center should be contacted.

Resources for Families

- Cystic Fibrosis Foundation. www.cff.org
- CF Living. www.cfliving.com

Clinical Pearls

- The improving outlook for children with CF is due largely to proactive and expectant treatment of the disease.
- Owing to a clear association between anthropometric attainment and long-term lung function, the nutritional goal is for all children with CF is to attain the 50th percentile or greater for weight for length (<2 years) or BMI.
- Viral respiratory tract infections often lead to pulmonary exacerbations in children with CF; an increase in cough or other respiratory symptoms that persists for longer than a week is often grounds for prescribing an antibiotic.
- The respiratory flora in children with CF may include methicillin-resistant *S aureus* and gram-negative organisms. The CF Care Center routinely performs respiratory cultures and should be consulted before antibiotics are prescribed for a respiratory illness in children with CF.
- Given the high salt content of their sweat, children with CF are susceptible to developing hyponatremic dehydration in the summer. They should always be offered salt or a salty snack to go with oral fluids when they are thirsty in the hot weather.

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Chapter 68

Cystic Fibrosis Newborn Screening

Evans Machogu, MD, FAAP, and Clement L. Ren, MD, MS

Introduction

- The starting point for cystic fibrosis (CF) newborn screening (NBS) is currently the initial identification of a high level of immunoreactive trypsinogen (IRT) in the neonatal dried blood spot collected on a Guthrie card.
- Blockage of pancreatic ducts causes an increase of trypsinogen, a precursor for trypsin, in the blood of most newborns with CF.
- Because IRT levels can fluctuate throughout the year, the cutoff level is set by individual state NBS programs in which the newborn is tested as a percentile of that day's results (eg, the top 5% of specimens), although some states also set an absolute threshold for a very high IRT level.
- IRT levels may be increased for reasons unrelated to CF, such as neonatal asphyxia, chronic fetal distress, perinatal infection, or biological and genetic variability.
- On the other hand, false-negative NBS results may occur if the IRT level does not reach the set cutoff value, even in newborns who may actually have CF.
- CF NBS has been universally available in the United States since 2010.

Testing Algorithms for CF NBS

- IRT is a very sensitive test because levels are increased in almost all neonates with CF. However, it is not very specific, since many neonates without CF may also have a transiently increased IRT level. Therefore, a second stage of testing must be conducted.
- IRT level may be falsely decreased in neonates with CF who present with meconium ileus, but in this case, the diagnosis of CF should be already suspected on clinical grounds.
- Three strategies are currently used to improve the specificity of an increased IRT level in identifying newborns with CF. The specific choice of strategy varies by state.
  - IRT DNA strategy
    - This strategy is followed by most states.

- Blood immediately undergoes *CF transmembrane conductance regulator (CFTR)* gene mutation screening by using an initial panel of mutations.
- The specific choice of mutations in the panel varies by state.
  - ~ Because of its diverse population, the state of California chose to incorporate gene sequencing in its IRT DNA algorithm.
- Infants with 1 or 2 *CFTR* panel mutations are considered to have positive screening results and are referred for sweat testing.

— IRT-IRT strategy
- IRT level testing is repeated in a second sample obtained from the neonate at about 2 weeks of age.
- If the second IRT level is increased, a sweat test is performed.

— IRT–IRT DNA strategy
- The IRT-IRT strategy is followed.
- Newborns with an increased repeat IRT finding undergo *CFTR* mutation panel testing.
  - ~ Only infants with 1 or 2 *CFTR* mutations are then referred for sweat testing.
  - ~ This reduces the number of patients with false-positive results who are sent for sweat testing.

Reporting of CF NBS Results

Negative NBS results

- NBS results will be reported as "screen negative," and no further testing or follow-up is required when the initial IRT value does not meet the state-specific cutoff value.
- Likewise, a "screen-negative" result is reported in cases of an initial increased IRT level but negative *CFTR* DNA analysis findings. No further testing or follow-up is required.
- As previously noted, all newborns with meconium ileus should undergo a sweat chloride test, performed regardless of NBS results, because initial IRT values may be falsely low.
- A "screen-negative" result does not rule out CF, and diagnostic testing should be performed if the newborn or child develops clinical features that are concerning for CF.

Positive NBS results

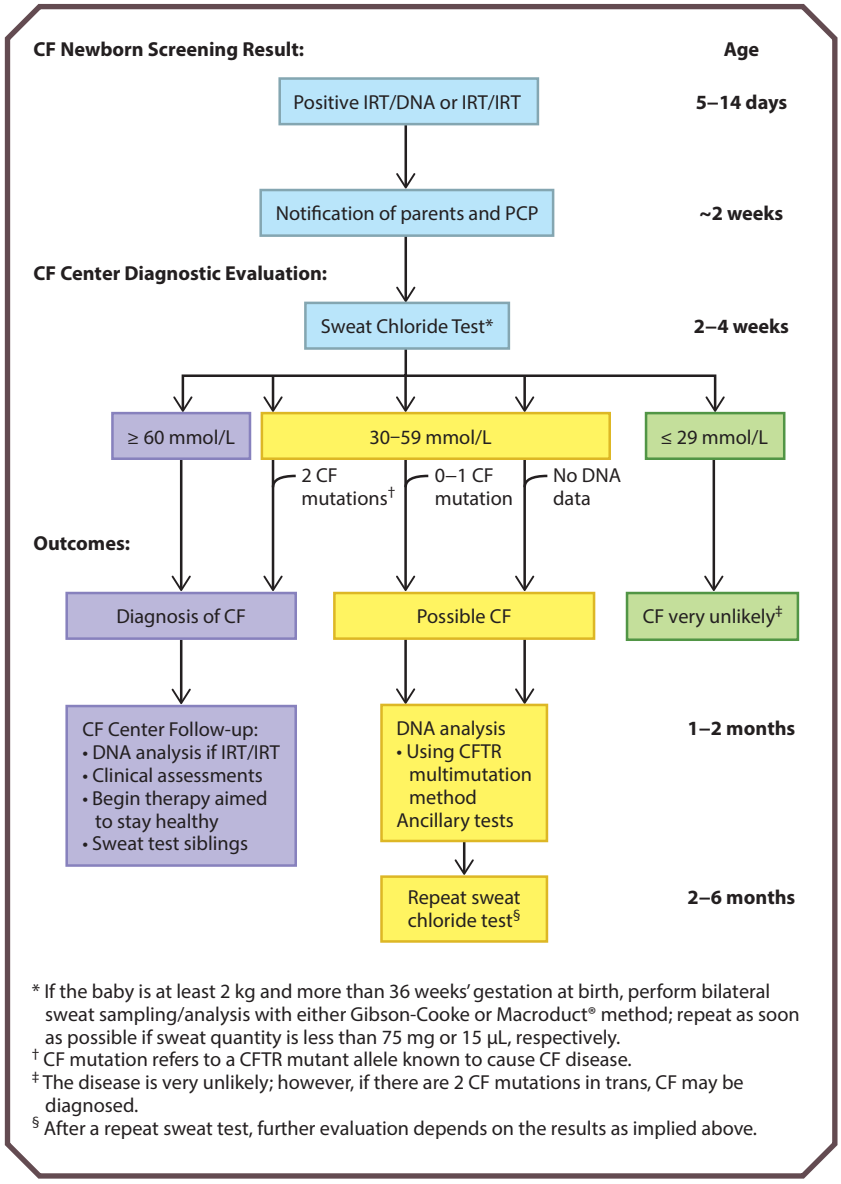
- Initial *CFTR* DNA testing may result in identification of 1 or more *CFTR* mutations within the state-specific mutation panel. This is reported as a positive CF NBS finding.
- If 2 or more mutations are detected in the initial *CFTR* DNA analysis, a presumptive diagnosis of CF can be established, but the diagnosis should be confirmed with sweat chloride testing.

- If 1 mutation is detected in the initial *CFTR* DNA analysis, the infant is a carrier, has *CFTR*-related metabolic syndrome (CRMS), or has CF with another rare, undetected mutation. A sweat test should be performed to determine if the infant has CF.
- Approximately 90% of infants with a positive NBS finding and 1 mutation are carriers.
- The primary pediatrician, as well as the newborn's parents, should be informed of a positive NBS result as soon as possible, and a referral to an accredited CF Care Center should be made for further evaluation and sweat chloride testing.
- The Cystic Fibrosis Foundation recommends that sweat chloride testing should be conducted by 2–4 weeks of age.

Potential Outcomes of Sweat Chloride Testing after Positive NBS Findings

The CF diagnostic process for screened newborns is depicted in Figure 68-1.

- Normal sweat chloride level (<30 mmol/L)
  - 1 mutation
    - This infant is a carrier, and no further testing is required.
    - Offer genetic counseling.
  - 2 mutations that have been classified as causing CF
    - This infant has presumptive CF.
    - Refer the patient to an accredited CF Care Center for evaluation, testing, and management.
  - 2 mutations with <2 mutations classified as causing CF
    - CRMS is likely.
    - See Chapter 69, *CFTR*-Related Metabolic Syndrome, for further guidance.
- Intermediate sweat chloride level (≥30–59 mmol/L)
  - 1 mutation
    - Repeat sweat testing is recommended by 2 months of age.
    - If the repeat sweat chloride concentration is still 30–59 mmol/L, the infant has CRMS.
  - 2 mutations that have been classified as causing CF
    - This infant has presumptive CF.
    - Refer the patient to an accredited CF Care Center.
  - 2 mutations with <2 mutations classified as causing CF
    - CRMS is likely.
    - See Chapter 69, *CFTR*-Related Metabolic Syndrome, for further guidance.
- Sweat chloride level ≥60 mmol/L and 1 or 2 panel mutations
  - This infant has CF.
  - Additional genetic analysis is recommended if only 1 mutation is identified in the screening panel.
  - Refer the patient to an accredited CF Care Center.



* If the baby is at least 2 kg and more than 36 weeks' gestation at birth, perform bilateral sweat sampling/analysis with either Gibson-Cooke or Macroduct® method; repeat as soon as possible if sweat quantity is less than 75 mg or 15 µL, respectively.
† CF mutation refers to a CFTR mutant allele known to cause CF disease.
‡ The disease is very unlikely; however, if there are 2 CF mutations in trans, CF may be diagnosed.
§ After a repeat sweat test, further evaluation depends on the results as implied above.

Figure 68-1. The CF diagnostic process for screened newborns. CF = cystic fibrosis, CFTR = transmembrane conductance regulator, IRT = immunoreactive trypsinogen, PCP = primary care provider. Adapted from Farrell PM, Rosenstein BJ, White TB, et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: cystic fibrosis foundation consensus report. *J Pediatr.* 2008;153(2):S4–S14. Copyright 2008, with permission from Elsevier.

- Some states also will refer neonates with very high IRT levels (eg, the top 0.1%) for sweat testing, even if no mutations are identified.
  - Neonates with a sweat chloride level <30 mmol/L do not have CF.
  - Neonates with a sweat chloride level ≥30–59 mmol/L may have CRMS.
  - Neonates with a sweat chloride level ≥60 mmol/L have CF and should undergo extended genetic analysis to potentially identify rare *CFTR* mutations.
- In states that use an IRT-IRT algorithm, no mutation data are available.
  - If the sweat chloride level is <30 mmol/L, then CF is very unlikely.
  - If the sweat chloride level is ≥30–59 mmol/L, then the neonate is likely to have CRMS.
  - If the sweat chloride level is ≥60 mmol/L, then the neonate has CF.

Genetic Counseling

Genetic counseling regarding implications for potential risk of CF in offspring of the child, other siblings, and extended family members should be offered to all parents whose infants have an abnormal NBS finding and have been determined to

- Be carriers of a CF gene mutation
- Have CRMS
- Have CF

Management of CF

- In 2009, the CF Foundation published guidelines for management of infants with CF.
- All infants who receive a diagnosis of CF should be seen at an accredited CF Care Center within 1–3 working days of the diagnosis, even in the absence of overt symptoms.
- All individuals with CF should be treated at an accredited CF Care Center.

Advantages of CF NBS

- Early diagnosis leads to better nutritional outcomes.
- Cognitive function may also be better.
- The effect on pulmonary outcomes has been more difficult to assess because of confounding factors.
  - Despite early diagnosis of CF via NBS, many infants still have abnormalities of lung function or structural lung damage.
  - Early detection may also result in less frequent hospitalizations through infection prevention and surveillance for any complications with early intervention.
  - There is a survival advantage in patients who receive a diagnosis via NBS.

Potential Disadvantages of CF NBS

- False-positive findings may result in unnecessary further testing and possibly unnecessary treatment.
- False-positive findings also cause undue parental anxiety.
- False-negative findings can potentially delay diagnosis for the child and provide false reassurance for parents.
- Carrier state reporting may provide unwanted information and lead to fear of future stigmatization by peers.
- Early detection and treatment could potentially lead to harm from side effects of therapies and early exposure to other individuals with CF.
- Indeterminate diagnostic testing may lead to diagnosis of CRMS and uncertain outcomes.

Resources for Families

- Newborn Screening for CF (Cystic Fibrosis Foundation). www.cff.org/What-is-CF/Testing/Newborn-Screening-for-CF
- An Introduction to Cystic Fibrosis for Patients and Their Families (Cystic Fibrosis Foundation). www.cff.org/PDF-Archive/An-Introduction-to-Cystic-Fibrosis-for-Patients-and-Their-Families
- Clinical and Functional Translation of CFTR (CFTR2). www.cftr2.org

Chapter 69

CFTR-Related Metabolic Syndrome

Evans Machogu, MD, FAAP, and Clement L. Ren, MD, MS

Introduction

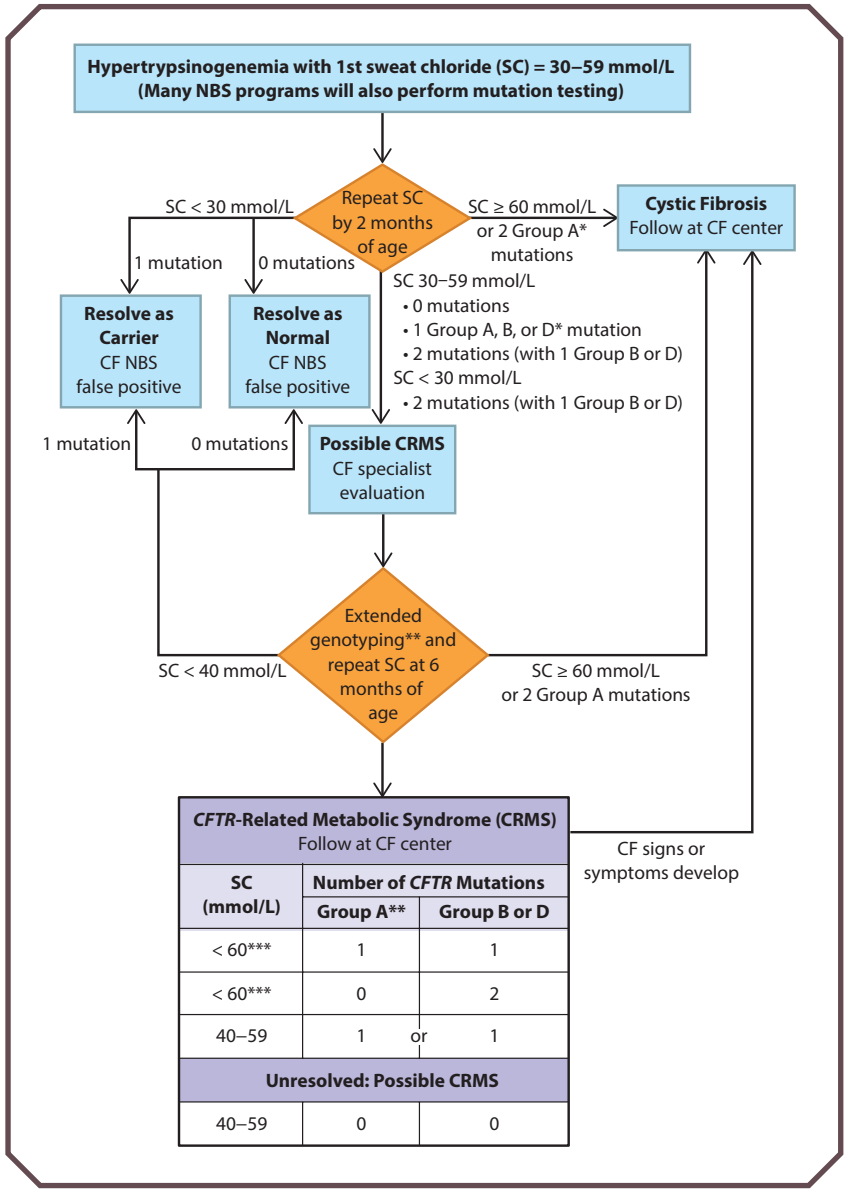
- *Cystic fibrosis (CF) transmembrane conductance regulator (CFTR)-related metabolic syndrome (CRMS)* is a term first proposed in 2009 to describe a group of infants found through newborn screening (NBS) to have increased immunoreactive trypsinogen (IRT) levels, in whom CF could be diagnosed or excluded on the basis of inconclusive sweat chloride concentration and/or extended DNA testing.
- Although CRMS is not a true metabolic disorder, the designation was proposed by a CF Foundation (CFF) guidelines committee to provide a name that could be associated with an *International Classification of Diseases, 10th Revision (ICD-10)*, code (E88.9; metabolic disorder, unspecified) to facilitate coding and billing of services for this group of individuals.
- In 2015, the European Cystic Fibrosis Society proposed use of the term *CF screen positive, inconclusive diagnosis (CFSPID)* to define the infant with a positive NBS finding and inconclusive second-tier testing results.
- The term *CRMS* will be used for the remainder of this chapter.

Diagnostic Considerations

- An infant is determined to have CRMS if he or she is asymptomatic, with a positive NBS test result and either of the following (Figure 69-1):
  - A sweat chloride level of 30–59 mmol/L on at least 2 occasions and fewer than 2 CF disease-causing mutations
  - A normal sweat chloride level (<30 mmol/L) and 2 *CFTR* mutations, of which no more than 1 is known to cause CF disease

Testing Algorithm Recommended by the CFF Diagnosis Consensus Conference

- The initial NBS sweat chloride level may be <30 mmol/L with 2 *CFTR* mutations detected (no more than 1 determined to cause CF disease) or 30–59 mmol/L with 0, 1, or more *CFTR* mutations (no more than 1 determined to cause CF disease).
- This results in an inconclusive diagnosis of CF, and a repeat sweat chloride test is recommended by 2 months of age.



CFTR-Related Metabolic Syndrome (CRMS) Follow at CF center		
SC (mmol/L)	Number of *CFTR* Mutations	
	Group A**	Group B or D
< 60***	1	1
< 60***	0	2
40–59	1 or	1
Unresolved: Possible CRMS		
40–59	0	0

Figure 69-1. Identification of infants with *CFTR*-related metabolic syndrome. * = Group A, cystic fibrosis (CF)-causing; Group B, *CFTR*-related disorder; Group D, unknown or uncertain clinical relevance. ** = Multimutation method, gene scanning or sequencing, duplication and deletion testing, and evaluation for IVS-8 TG repeats; consider family evaluation for phasing to confirm that mutations are *trans*. *** = A lower limit for sweat chloride level has not been defined. Adapted from Cystic Fibrosis Foundation, Borowitz D, Parad RB, et al. Cystic Fibrosis Foundation practice guidelines for the management of infants with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome during the first two years of life and beyond. *J Pediatr.* 2009;155(6 Suppl):S106–S16. Copyright 2009, with permission from Elsevier.

- Potential outcomes of repeat sweat chloride testing may include
  - Normal sweat chloride level (<30 mmol/L) and
    - 1 mutation
      - ~ The diagnosis is carrier status.
      - ~ No further evaluation or follow-up is required.
      - ~ Offer genetic counseling.
    - 2 or more mutations
      - ~ The diagnosis is CRMS.
      - ~ Repeat sweat testing at 6 months of age.
      - ~ Refer the patient to an accredited CF Care Center for further evaluation, testing, and management.
  - Intermediate sweat chloride level (30–59 mmol/L) and
    - 1 mutation
      - ~ The diagnosis is CRMS.
      - ~ Expanded *CFTR* DNA analysis is recommended.
      - ~ Repeat sweat testing is recommended at 6 months of age.
      - ~ Refer the patient to an accredited CF Care Center.
    - 2 or more mutations
      - ~ The diagnosis is CRMS.
      - ~ Repeat sweat testing is recommended at 6 months of age.
      - ~ Refer the patient to an accredited CF Care Center.
  - Repeat sweat chloride level ≥60 mmol/L
    - This infant has CF.
    - Further genetic testing is indicated to identify any additional *CFTR* mutations not included in the initial state panel (if only 1 mutation was identified).
    - Refer the patient to an accredited CF Care Center.

Prevalence

- Nationally, about 1 infant receives a diagnosis of CRMS for every 5–6 cases of CF.
- The prevalence may vary by state, depending on their NBS protocol, as well as IRT cutoff values.
  - States that use an IRT-IRT algorithm will not be able to identify infants with CRMS by using a sweat chloride level <30 mmol/L.
  - In California, the incorporation of *CFTR* gene sequencing is used to identify a large number of mutations with unknown or variable clinical consequences, which results in more CRMS cases than CF cases.

Outcomes

- Data on long-term outcomes of infants with CRMS are limited. However, most infants with CRMS will have minimal to no clinical consequences.

- A few patients may be reclassified as having CF on the basis of
  - Extended genetic analysis
  - Repeat sweat chloride testing level ≥60 mmol/L
  - Development of clinical features of CF, such as pancreatic insufficiency

Management

- Close monitoring of infants with CRMS is warranted because they may have an increased risk of developing CF-like symptoms or *CFTR*-related disorder. Patients with *CFTR*-related disorder do not meet the diagnostic criteria for CF, but they have clinical features of CF in a single organ system (eg, absence of the vas deferens or recurrent pancreatitis).
- Development of signs and symptoms associated with CF or a change in sweat chloride concentration may lead to reclassification and diagnosis of CF.
- Additionally, as further information regarding disease-causing *CFTR* mutations becomes available, subjects with CRMS may be reclassified if their mutations are determined to cause CF.
- Some individuals with CRMS have progressed to develop lung disease, yield a culture of *Pseudomonas aeruginosa* from their respiratory tract, or even develop pancreatic insufficiency, albeit to a lesser extent than subjects with CF.
- According to CFF guidelines for routine management, individuals with CRMS should be seen by a CF specialist at least twice during the first year after birth and annually thereafter.

Resources for Families

- Clinical and Functional Translation of CFTR (Cystic Fibrosis Foundation, Johns Hopkins University, and the Hospital for Sick Children). www.cftr2.org
- CFTR-Related Metabolic Syndrome (Cystic Fibrosis Foundation). www.cff.org/What-is-CF/Testing/CFTR-Related-Metabolic-Syndrome-(CRMS)
- My Baby Is a Carrier (Cystic Fibrosis Foundation). www.cff.org/PDF-Archive/My-Baby-is-a-CF-Carrier

Clinical Pearls

- CRMS occurs when an infant has an abnormal CF NBS finding but inconclusive diagnostic test results.
- A small proportion of CRMS can convert to CF, but most infants with CRMS do well.
- Recommended additional studies for CRMS include extended genetic analysis and serial repeat sweat testing.

Chapter 70

Primary Ciliary Dyskinesia

Bruce K. Rubin, MEngr, MD, MBA, FRCPC, FAAP

Introduction/Etiology/Epidemiology

- Primary ciliary dyskinesia (PCD) is a disorder that affects motile cilia in the airways, the female reproductive tract (fallopian tubes), the flagella of spermatozoa, and, in some patients, cilia in the ventricular aqueducts in the brain.
- PCD occurs in approximately 1 in 16,000 live births.
- PCD is usually inherited as an autosomal recessive disorder. As of this writing, 33 distinct genetic defects have been identified that lead to abnormal function of the ciliary axoneme. It is estimated that known genetic defects account for approximately two-thirds of reported cases of PCD.
- Motion of embryonic nodal cilia leads to normal visceral asymmetry, and absence of this normal motion results in a lack of definitive patterning, with just under half of patients having normal visceral placement (situs solitus).
- A similar proportion of patients have mirror image arrangement (situs inversus).
- Heterotaxy (situs ambiguus) occurs in approximately 12% of patients with PCD.
- Absence of ciliary beating leads to accumulation of infected secretions within the airway, eventually producing bronchiectasis but also leading to recurrent otitis media.
- Normal ciliary beating is thought to facilitate clearance of fluid from the lungs at birth, with most newborns who have PCD demonstrating respiratory distress.
- Normal flagellar beating is necessary for propelling the fertilized egg into the uterus and for normal spermatic motion.

History

- In 1904, the association between situs inversus and recurrent lung infections was described, and in 1936, Kartagener reported 4 patients with male infertility, situs inversus, and bronchiectasis.
- When abnormalities of ciliary axoneme structure were noted in 1976, the term *immotile cilia syndrome* was proposed for this disorder.

- In subsequent years, it was demonstrated that PCD occurs in patients with both normal and abnormal visceral situs and that airway cilia were not immotile but rather had ineffective dyskinetic beat patterns, leading to a change of nomenclature to *primary ciliary dyskinesia*.

Clinical Features

- Failure to clear airway secretions leads to recurrent otitis media, chronic cough, and recurrent pneumonia, eventually leading to bronchiectasis.
- Although cystic fibrosis (CF) and PCD both result in abnormal mucociliary clearance, PCD has unique clinical features that distinguish it from CF.
  - — Very few newborns with CF have respiratory distress, but approximately 80% of term neonates with PCD have tachypnea, transient hypoxemia, and respiratory distress in association with poor clearance of lung liquid.
  - — Also distinct from CF, children with PCD almost always have recurrent severe otitis media, often with purulent drainage from ruptured tympanic membranes.
- Similar to CF, patients with PCD have persistent sinusitis and chronic wet cough, and most eventually develop bronchiectasis.
  - — Pseudomonas lung infection is a late finding in patients with PCD, and it usually represents bronchiectatic changes.
- Because the structure of the spermatic flagella is similar to that of the ciliary axoneme, most men with PCD are infertile because of lack of spermatic motion. Women have decreased fertility and are at risk for tubal pregnancies because of poor transport of the fertilized egg down the fallopian tube and into the uterus.
- Gastroesophageal reflux disease (GERD) is common in patients with PCD and can be severe. GERD may result from persistent coughing and also from esophageal dysmotility. Severe GERD is more common in patients with heterotaxy (Figure 70-1).
- Patients with PCD are at increased risk for having cardiac abnormalities.
- The risk is highest among those with heterotaxy syndrome, with a prevalence approaching 20%.
- PCD is occasionally associated with hydrocephalus, presumably because of poor ciliary transport of cerebrospinal fluid.

Differential Diagnosis and Diagnostic Testing

A suggested diagnostic algorithm for PCD is shown in Figure 70-2.

- The differential diagnosis includes CF and other causes of bronchiectasis.
- Four criteria-defined clinical features in combination are highly effective in discriminating children and adolescents who are likely to have PCD, and the absence of these features should reduce the clinician's index of suspicion.

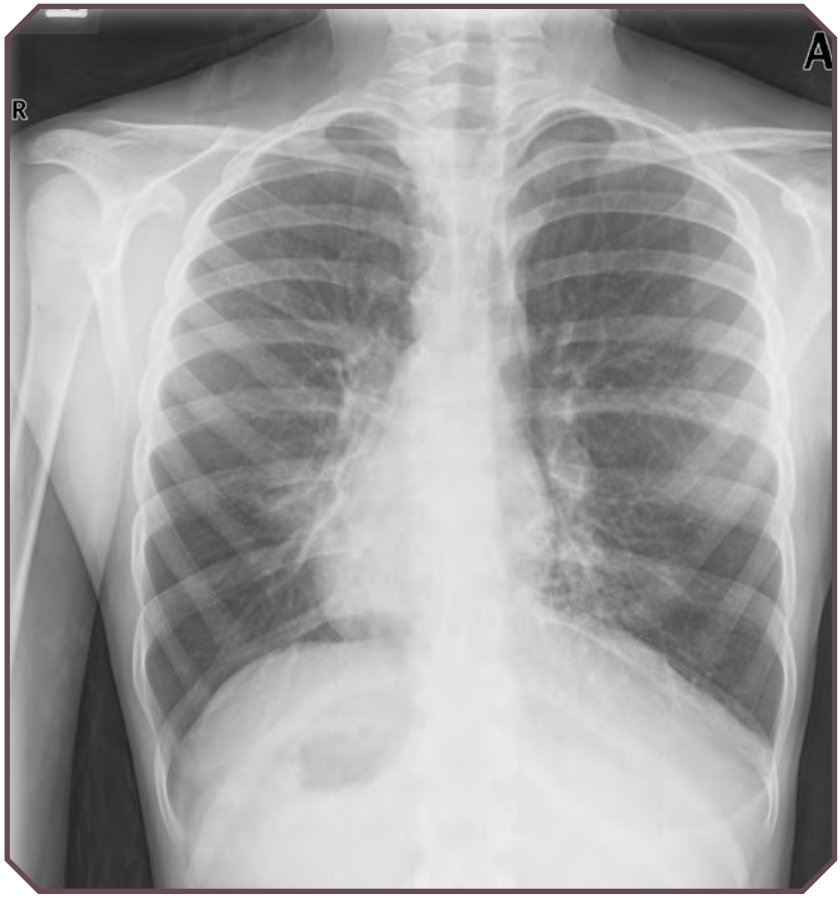


Figure 70-1. Ciliary dyskinesia syndrome. Frontal radiograph in a 16-year-old boy shows dextrocardia (heart apex on the right), which is typical of Kartagener syndrome.

  - Unexplained neonatal respiratory distress can persist for several days in term infants (although they commonly do not need supplemental oxygen).
  - The patient may have early-onset, year-round wet cough.
  - The patient may have early-onset, year-round nasal congestion.
  - The patient may have laterality defects.
- The sensitivity and specificity of these 4 criteria indicate that they can be used to identify at-risk children and direct decisions regarding further diagnostic testing.
- Further diagnostic testing includes
  - Nasal nitric oxide (NO) measurement
    - Because of defective NO synthase, NO production is profoundly decreased in the noses of patients with PCD, and its measurement is both sensitive and specific.

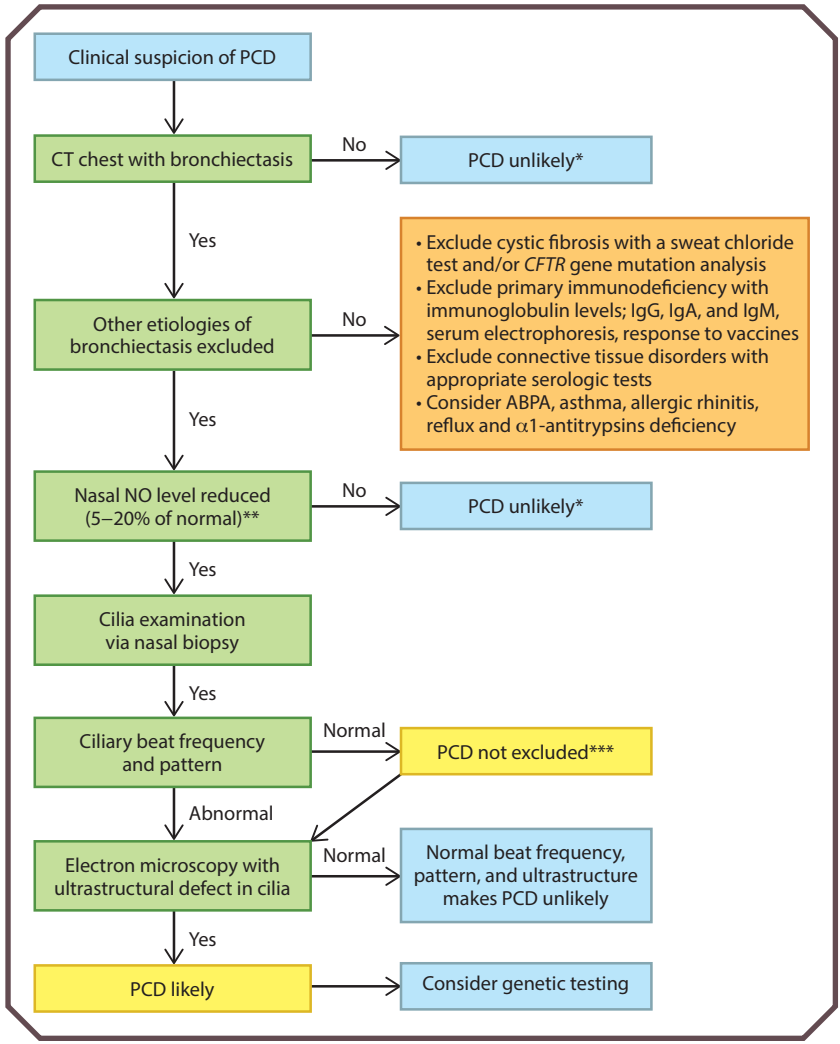


Figure 70-2. Suggested diagnostic algorithm. * = If clinical suspicion is still high for PCD, may go to other, more specific tests. ** = A nasal NO level less than 77 nL/min has a sensitivity and specificity of 0.98 and >0.99, respectively. *** = Normal ciliary beat frequency and pattern does not exclude PCD. ABPA = allergic bronchopulmonary aspergillosis, CT = computed tomography, Ig = immunoglobulin, Nml = normal, NO = nitric oxide, PCD = primary ciliary dyskinesia. From Lobo J, Zariwala MA, Noone PG. Primary ciliary dyskinesia. *Semin Respir Crit Care Med.* 2015;36(2):169–179.

- Testing is currently limited to cooperative children, typically 5 years of age and older, and can usually be performed only at PCD specialty centers. Nasal NO measurement requires special expertise and equipment that differ from those used for the more common measurement of exhaled NO performed for evaluation of lower-airway inflammation in asthma.

  - Ciliary biopsy
    - Many patients with PCD will have poor ciliary motility when fresh brushings of airway cells are examined under a phase-contrast microscope, and many will have characteristic abnormalities, particularly of the motility apparatus in the ciliary axoneme that consists of dynein arms and the 9 microtubule doublets.
    - However, obtaining biopsy specimens is uncomfortable for the patient and requires special expertise to harvest the epithelium from the nose or the airway and expertise in preparing these specimens for examination with transmission electron microscopy (TEM) or for phase-contrast microscopy evaluation. Furthermore, even in expert hands, the diagnostic reliability of the interpretation of these studies is variable.
- Several companies provide commercial genetic testing for a panel of abnormalities associated with PCD. As of this publication, approximately 65% of patients with PCD can be identified with genetic testing, including some with structurally normal cilia at TEM. Genetic testing for PCD has high positive predictive value but limited sensitivity (similar to that of microscopy). Most PCD centers now use nasal NO as the initial screen, followed by genetic testing as the initial evaluation.

Management

- When possible, patients should be comanaged by their primary care physician and a comprehensive PCD center capable of full diagnostic testing, close monitoring for complications, and access to clinical trials of new therapies. The development of registries in the United States, Europe, Japan, and Israel will facilitate the evaluation of proposed PCD therapies, as these may differ from CF therapy.
- The management of PCD includes avoiding airway irritants, such as tobacco smoke, and using antibiotics and airway clearance maneuvers to delay the development of bronchiectasis. This is similar to the use of antibiotics and airway clearance in patients with CF.
- Routine immunizations, including influenza and pneumococcal immunizations, may help prevent respiratory infections.
- Early and frequent use of antibiotics for ear infections allows most patients to avoid the insertion of tympanostomy tubes with subsequent hearing loss. However, some otolaryngologists recommend the early placement of tympanostomy tubes.
- Although often used, there is no clinical evidence regarding the use of hypertonic saline, dornase alfa, or N-acetylcysteine aerosol therapy. There is some evidence that the use of medications such as expectorants and cough suppressants may worsen disease.
- There is evidence that the chronic use of low-dose macrolide antibiotics (eg, azithromycin and clarithromycin) may ameliorate mucus hypersecretion and inflammation in patients with PCD, similar to CF and non-CF bronchiectasis therapy.

- Women should be counseled about the risk of tubal pregnancy and, should they desire to become pregnant, they will require careful monitoring by a maternal-fetal specialist familiar with PCD. Male infertility due to spermatic dyskinesia may be amenable to the use of advanced infertility techniques, such as intracytoplasmic spermatic injection.
- Surgical intervention may be needed for congenital heart disease and severe gastroesophageal reflux.

Expected Outcomes/Prognosis

- Conductive hearing loss due to persistent otitis media with effusion is common. Hearing abnormalities often improve in adolescence, but in some cases, they continue into adulthood.
- The rate of development of bronchiectasis is variable, but lung disease in childhood is typically not as severe as is seen in CF. Nonetheless, while management is directed against the prevention of bronchiectasis, it typically develops over time, and complications of suppurative lung disease, including respiratory failure, are seen as patients get older.

Resources for Families

- PCD Foundation. www.pcdfoundation.org
- PCD Foundation (Facebook login required). www.facebook.com/PCDFoundation
- PCD Family Support Group (United Kingdom). www.pcdsupport.org.uk

Clinical Pearls

- Unexplained transient respiratory distress in a full-term newborn may be the initial presenting sign of PCD.
- Chronic, perennial wet cough and nonallergic rhinitis beginning in infancy should prompt testing for PCD.
- A diagnosis of PCD should be considered in any child with situs inversus or other laterality defects.
- Half of all patients with PCD do not have situs inversus, and this can lead to delayed diagnosis.

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CHAPTER 68: CYSTIC FIBROSIS NEWBORN SCREENING

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Part VI. Miscellaneous Respiratory Diseases

Associate Editor: Lee J. Brooks, MD, FAAP

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Chapter 71

Bronchopulmonary Dysplasia

Molly K. Ball, MD, FAAP

Introduction/Etiology/Epidemiology

- Despite meaningful advances in fetal and neonatal care, bronchopulmonary dysplasia (BPD) continues to represent the major respiratory morbidity in preterm infants.
- With improved survival of increasingly preterm neonates, the pathophysiology, affected population, and definitions of BPD have evolved.
- BPD incidence remains stable, with diagnosis and severity inversely proportional to birth weight and gestational age.
- The high-risk population includes patients who weigh <1,200–1,500 g and/or are <30 weeks' gestational age at birth.
- Patients with BPD who are released from the neonatal intensive care unit (NICU) represent a high-risk population with multisystem complications and clinically significant post-NICU health care needs. For these children, primary care providers play a pivotal role.

Pathophysiology

- The immature lung is subjected to injurious environmental factors that result in the arrest of normal lung and pulmonary vascular development.
- Risk factors for development of BPD include
  - Antenatal infection
  - Increasing lung immaturity
  - Exposure to supplemental oxygen (oxidative stress injury)
  - Exposure to mechanical ventilation (ventilator-induced lung injury)
  - Postnatal infection
  - Immature inflammatory regulation
  - Genetic susceptibility

Clinical Features

- BPD constitutes a chronic lung disease of increasing prematurity, characterized by the following (Figure 71-1):
  - Fewer, larger, simplified alveoli
  - Decreased number of pulmonary blood vessels and capillary beds
  - Variable fibrosis and smooth-muscle overgrowth

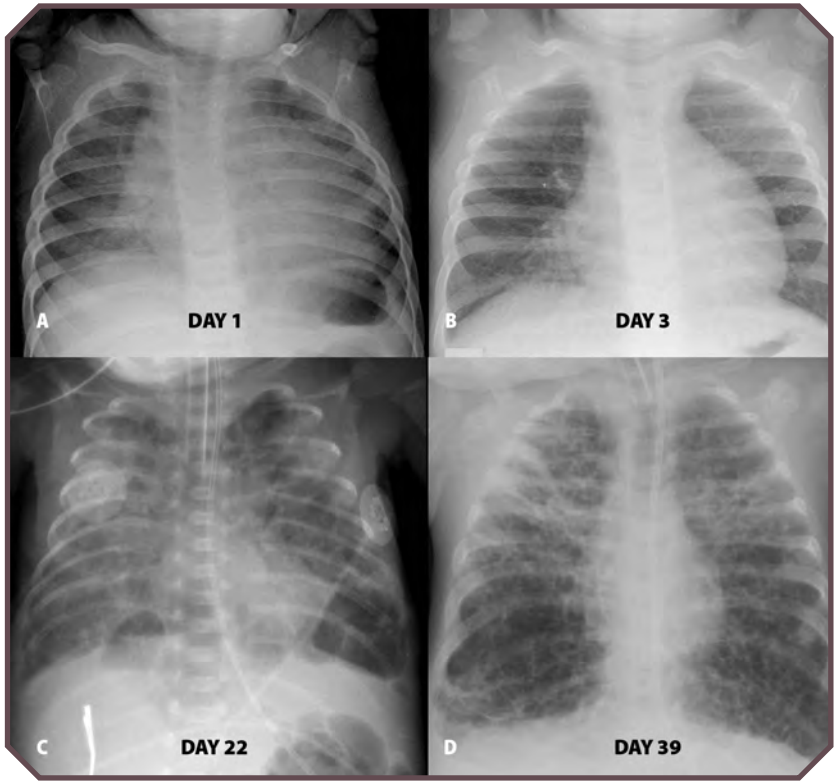

Figure 71-1. Progression of bronchhopulmonary dysplasia (BPD) radiographic findings (frontal views) in a premature neonate. A. Radiograph with normal findings was obtained on day 1, after birth. B. Respiratory distress syndrome is typified by diffuse, homogeneous, "ground-glass" opacities seen on day 3 after birth. C. Moderate BPD changes on day 22 after birth show hyperinflation with patchy atelectasis. D. Severe BPD changes on day 39 after birth are characterized by extensive, diffuse cystic areas and hyperinflation.

- Clinically, infants and children with BPD display respiratory symptoms that include tachypnea, retractions, increased work of breathing, and decreased oxygen saturation levels (hypoxemia).
- Functionally, lung volumes are reduced and develop bronchoreactivity, as well as airway obstruction with air trapping (hyperinflation).

Differential Diagnosis

- Recurrent pneumonia and/or pulmonary infection
- Chronic aspiration pneumonitis
- Airway malformations (including subglottic stenosis and tracheobronchomalacia)
- Alveolar capillary dysplasia
- Pulmonary interstitial lung disease

- Disorders of surfactant production and function (surfactant protein B, surfactant protein C, member A3 of the adenosine triphosphate–binding cassette family [ABCA3] diseases)
- Pulmonary hypoplasia
- Congenital lobar emphysema
- Wilson-Mikity syndrome (pulmonary dysmaturity syndrome)
- Congenital neuromuscular disorders

Diagnostic Considerations

- The diagnosis of BPD is established in the NICU, prior to discharging the patient to go home.
- BPD is a complex, heterogeneous, and multifactorial disease. Current definitions remain limited by poor prognostic ability for short- and long-term morbidities and outcomes.
- Current definitions of BPD are clinically derived and serve to stratify disease severity.
- The 2000 National Institutes of Health, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and the National Heart, Lung, and Blood Institute Workshop definition (Table 71-1) includes
  - — Dependence on supplemental oxygen for ≥28 days after birth
  - — Severity assessment based on oxygen and respiratory support needs around term-corrected gestation

Management

Prevention of BPD

- Disease prevention is focused on maternal and fetal factors.
  - — The mother and fetus should receive optimal prepregnancy and prenatal care, with management of maternal conditions, prevention of prematurity, and avoidance of infection.

Table 71-1. Diagnostic Criteria for BPD

Definition	Severity Classification	Gestational Age at Birth	
		<32 Weeks	≥32 Weeks
Treatment with supplemental oxygen for ≥28 d	Mild BPD	Breathing room air by 36 weeks' CGA	Breathing room air by 56 days after birth
	Moderate BPD	Need for <30% FIO_2 at 36 weeks' CGA	Need for <30% FIO_2 at 56 days after birth
	Severe BPD	Need for ≥30% FIO_2 or positive-pressure ventilation at 36 weeks' CGA	Need for ≥30% FIO_2 or positive-pressure ventilation at 56 days after birth

BPD, bronchopulmonary dysplasia; CGA, corrected gestational age; FIO_2, fraction of inspired oxygen. From Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *ARJCCM.* 2001;163(7):1723–1729.

  - Antenatal corticosteroids reduce mortality, induce lung maturation, and reduce BPD risk factors. However, data demonstrating the prevention of BPD are less clear.
- The early NICU approach to BPD prevention is as follows.
  - The goal is *(a)* to support respiratory insufficiency while avoiding ventilator- and oxygen-induced lung injury and *(b)* early extubation.
  - Surfactant therapy has revolutionized neonatal lung disease through improved pulmonary mechanics and early survival. However, as with antenatal corticosteroids, a direct effect on BPD prevention has been difficult to establish.
  - Data support the avoidance of fluid overload, while the role of the ductus arteriosus remains controversial.

Evolving BPD

- NICU management of BPD is aimed at minimizing ongoing lung injury (oxygen and ventilator induced), avoiding infection, and optimizing nutrition and growth.
- The routine use of systemic steroids has been limited by adverse neurodevelopmental outcomes.

Established BPD

- Long-term management of BPD and its comorbidities remains challenging but is optimized by a longitudinal multidisciplinary care team.
- Oxygen and ventilation
  - Home oxygen therapy may be necessary to support tissue oxygen delivery during waking hours, feeding, and sleeping. These infants may require a home pulse oximeter monitor.
  - For severe BPD, chronic ventilation via tracheostomy tube may be required to support respiratory needs.
  - Chronic hypoxia is associated with pulmonary hypertension and poorer growth and neurodevelopment. However, optimal oxygen saturations and weaning parameters remain areas of research.
- Pulmonary medication
  - Mainstays of symptomatic treatment include bronchodilators, inhaled corticosteroids, and diuretics.
  - The chronic use of these medications should be approached with caution and in conjunction with a BPD or pulmonary team, because data supporting the effectiveness of widespread use are lacking.
- Routine prophylaxis should be used against respiratory infections (see the Prevention of Respiratory Morbidities section in this chapter).
- Nutrition continues to play a key role in the growth and maturation of the lungs and brain. Growth should be assessed monthly, with increased frequency if concerns arise.
- The treatment of associated conditions should occur with a focus on neurodevelopmental optimization (see the next section).

Treating Associated Conditions

- BPD affects many organ systems, which results in systemic complications. While the incidence of medical comorbidities is greatest in the first years after birth, long-term complications may persist (Box 71-1).

Box 71-1. BPD-Associated Comorbidities

Cardiovascular

- Pulmonary hypertension
- Cor pulmonale
- Pulmonary vein stenosis (acquired)
- Systemic hypertension

Respiratory and airway

- Airway malacia
- Airway stenosis
- Glottic and/or subglottic damage or stenosis
- Aspiration
- Susceptibility to bacterial and/or viral infections
- Airway reactivity and/or wheezing

Gastrointestinal

- Gastroesophageal reflux
- Feeding intolerance
- Oral aversion
- Constipation

Metabolic

- Failure to thrive or poor growth
- Osteopenia
- Iron deficiency

Brain and neurodevelopmental

- Developmental delays, including motor, cognitive, speech, and language deficits
- Strabismus
- Retinopathy of prematurity
- Hearing loss

Adapted from Groothuis JR, Makari D. Definition and outpatient management of the very low-birth-weight infant with bronchopulmonary dysplasia. *Adv Ther.* 2012;29(4):297–311.

- Pulmonary hypertension may result from disruption of pulmonary vascular growth, chronic hypoxemia, altered vasoreactivity, and other factors.
  - Increased pulmonary artery pressure causes right-sided heart strain and ultimate potential for cor pulmonale and is associated with high mortality.
  - While cardiac catheterization remains the standard of reference for diagnosis, echocardiography is increasingly used to follow pulmonary pressures and right-sided heart function.
  - Oxygen and/or pulmonary vasodilator medications (most commonly sildenafil) may be used to control pulmonary hypertension.
- Increased metabolic demands translate into high risk for growth failure and greater caloric requirements to achieve adequate growth.
  - Plot the patient's weight, length, and head circumference monthly to trend growth (by using a preterm corrected growth chart, such as the Fenton preterm growth chart).
  - Formula or expressed breast milk can be fortified to 24, 27, or 30 kcal/oz to achieve sufficient calories for growth.
  - Gavage feedings or gastrostomy tube placement may be indicated for respiratory, gastrointestinal, neurological, or other concerns.
- Neurodevelopmental delay may occur, due to the increased risk for global impairment and long-term cognitive deficits.
  - Delay is believed to be multifactorial, including recurrent hypoxia, impaired nutritional status, prolonged hospitalization, and postnatal steroid administration.
  - Severe BPD nearly doubles the risk for cerebral palsy, neurodevelopmental impairment, and lower IQ scores.
  - Infants should undergo regular neurodevelopmental screening and testing and be evaluated in early intervention programs, with therapies initiated as appropriate.
  - School-aged children should undergo annual educational and behavioral testing to identify emerging concerns and deficits.
- Households with medically complex children remain at high risk for stress, anxiety, and depression. Assess parent-child interactions and provide psychosocial support and referrals.
- Routine well-child care, preventive guidance, and administration of standard childhood vaccines by chronological age should be continued.

Expected Outcomes/Prognosis

- Infants with BPD have an approximately 2 times higher hospital readmission rate over the first 2 years than that of preterm populations without BPD.
- Lung function, pulmonary compliance, fluid sensitivity, and airway reactivity typically improve over the first years after birth.
- However, respiratory symptoms that include coughing and wheezing, as well as decreased pulmonary function testing results, persist in school-aged children with BPD when compared to their peers.

- Long-term pulmonary function data remain limited; however, data suggest there are long-term airflow abnormalities with both airway hyperreactivity (asthma-like symptoms) and obstruction (chronic obstructive pulmonary disease [COPD]) in adulthood.

When to Refer

- Research supports improved outcomes for all patients with BPD when enrolled in longitudinal multidisciplinary follow-up programs. However, the pediatrician is often the primary family contact and plays a critical role in evaluation and triage.
- Concern for acute change in respiratory status or decreased oxygen saturation should prompt urgent evaluation and consideration of inpatient monitoring (see the next section).
- Concern for poor growth or neurodevelopment warrants referral to an appropriate subspecialist for complete evaluation.

When to Admit

- Because infants and children with BPD have underlying large- and small-airway disease with decreased pulmonary reserve, routine respiratory viruses and illnesses may be life-threatening in this population.
- Any decline in respiratory or clinical status should prompt a full physical examination, including assessment of heart rate, respiratory rate, oxygen saturation level, work of breathing, and aeration. Blood gas analysis and chest radiography may also be helpful.
- Points to remember for stabilization of patients with acute BPD include the following.
  - — Bronchodilator therapy may be beneficial for acute airway obstruction; however, many patients will fail to respond and will demonstrate no improvement in airflow.
  - — Patients with BPD are often uniquely fluid sensitive; fluid resuscitation should be approached cautiously.
  - — Lungs with BPD require prolonged inhalation and exhalation times because of increased airway resistance; use a ventilatory strategy with a low rate (and therefore a higher tidal volume to achieve minute ventilation) to match this pathophysiology.

Prevention of Respiratory Morbidities

- Infants with BPD are highly susceptible to respiratory infections: respiratory syncytial virus (RSV), influenza, pertussis, and other routine viruses can result in substantial morbidity and mortality.
- RSV prophylaxis decreases respiratory morbidity and hospital readmission.
  - — Palivizumab (human monoclonal antibodies) is administered monthly during RSV season to provide passive immunity (refer to published American Academy of Pediatrics prophylaxis guidelines).

- Pertussis vaccination should be administered to all family members and care providers.
- Influenza vaccination should be administered annually to all family members >6 months of age (and to infants once they are 6 months of age).
- Ongoing family education on the dangers of secondhand smoke on lungs with BPD (and the risks of primary smoking as the patient enters school age) is vital.

Resources for Families

- What Is Bronchopulmonary Dysplasia? (National Heart, Lung, and Blood Institute). www.nhlbi.nih.gov/health/health-topics/topics/bpd
- RSV: When It's More Than Just a Cold (American Academy of Pediatrics). www.healthychildren.org/English/health-issues/conditions/chest-lungs/Pages/RSV-When-Its-More-Than-Just-a-Cold.aspx

Clinical Pearls

- Lungs with BPD are characterized by large- and small-airway disease, with decreased pulmonary reserve; hyperreactivity (asthma-like symptoms) and obstruction (COPD) may persist beyond childhood.
- Routine respiratory infections may be life-threatening in this population. Acute changes in respiratory status or oxygenation should prompt urgent evaluation and careful consideration of inpatient monitoring.
- Mainstays of treatment for symptoms include bronchodilators, inhaled corticosteroids, and diuretics. However, data do not support their routine use as chronic therapies.
- BPD is associated with pulmonary hypertension, growth failure, and developmental delay. Addressing each of these comorbidities is critical for the patient's overall health.

Chapter 72

Pneumothorax

Georgia Koltsida, MD, Casandra Arevalo-Marcano, MD, and Lee J. Brooks, MD, FAAP

Definition

- *Pneumothorax,* an unusual but life-threatening condition in children, is defined as the accumulation of air in the pleural space that can enter via disruption of any surface of the pleura.
- Pneumothorax can be classified as spontaneous or traumatic.
- Spontaneous pneumothorax usually occurs without a clear precipitating factor, such as iatrogenic or traumatic causes. It can be further categorized as primary (idiopathic) pneumothorax or secondary pneumothorax, based on the etiologic origin.

Etiology

- The overall incidence is 5 to 10 per 100,000 children <18 years of age.
- Pneumothorax is most common in newborns and teenaged boys. Spontaneous pneumothorax has a strong male predominance (it is 6 times more prevalent in boys than in girls).
- It can present in reproductive-age girls as catamenial pneumothorax.

Risk Factors and Presentation

- The most common risk factors are smoking (creating a six- to ninefold increase in incidence), male sex, family history of spontaneous pneumothorax, tall stature, premature delivery, and asthma. However, any disease that promotes air leakage will increase the risk.
- Pneumothorax can be associated with a Valsalva maneuver but usually occurs in a resting individual.
- Symptomatology will depend on the amount of air leakage.
- The most common symptoms are acute chest pain (stabbing pain that radiates to the ipsilateral shoulder) and dyspnea. Sometimes a popping sensation is reported by patients.
- In small pneumothorax, the resolution of pain is observed in 24 hours.
- Spontaneous pneumothorax can be an incidental finding noted as part of routine chest radiography.

Clinical Features and Key Points in the History

- Causes of secondary pneumothorax should be investigated. Special attention should be given to a history of smoking or the use of inhaled drugs, as well as a history of asthma.
- Body habitus should be noted, since pneumothorax occurs more frequently in tall boys.
- Note a history of Valsalva maneuver surrounding the event.
- Physical examination findings will be more pronounced with a larger pneumothorax. Findings can range from a mild decrease in aeration to complete absence of breath sounds in the affected lung.
- Subcutaneous emphysema is a common finding. Although it may be alarming for the patient and family, it does not create an increased risk of local infections, and management is focused on symptoms.
- Tension pneumothorax manifests with alarming signs and symptoms. There is a complete absence of breath sounds, with deviation of the trachea on chest radiographs to the contralateral hemithorax. Cardiac tamponade may result in vascular instability. Tension pneumothorax is an emergency and should be treated with prompt decompression (Figure 72-1).

Secondary Pneumothorax

- Secondary pneumothorax occurs as a complication of chronic or acute lung disease. It is a potentially life-threatening event because patients already have decreased cardiopulmonary reserve in the setting of their underlying disease. It also has a greater risk of recurrence.
- Secondary pneumothorax could occur because of
  - Airway abnormalities: asthma, cystic fibrosis
  - Parenchymal diseases: interstitial lung disease, emphysema

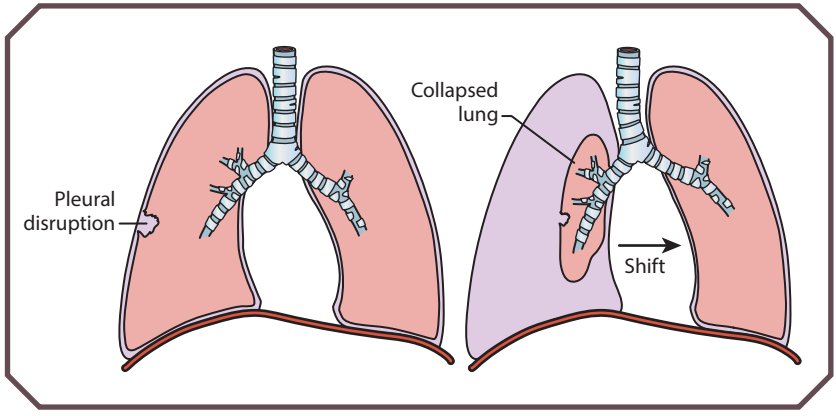

Figure 72-1. Tension pneumothorax. Pleural disruption causes the entry of air into the pleural space during inspiration, resulting in air accumulation within the pleural space. Intrapleural pressure rises and causes lung collapse and mediastinal shift away from the affected side.

  - Infections: necrotizing pneumonia from anaerobic bacteria, *Pneumocystis jirovecii* pneumonia in immunocompromised hosts, *Staphylococcus aureus* pneumonia, tuberculosis
  - Malignancy: lymphoma, metastasis
  - Connective tissue disorders: Marfan syndrome, Ehlers-Danlos syndrome, juvenile idiopathic arthritis, systemic lupus erythematosus, polymyositis, dermatomyositis, sarcoidosis, Langerhans cell histiocytosis, α_1-antitrypsin deficiency, Birt-Hogg-Dubé syndrome
- Nonspontaneous pneumothorax
  - Iatrogenic causes include thoracentesis, central venous cannulation, cardiothoracic surgery, transbronchial and transthoracic biopsy, mechanical ventilation, and cardiopulmonary resuscitation.
  - Traumatic causes include thoracic trauma and blunt and penetrating injuries to the chest.

Tension Pneumothorax

- Tension pneumothorax occurs when intrapleural air accumulates progressively in such a way as to exert positive pressure on mediastinal and intrathoracic structures. It is a life-threatening occurrence that could lead to cardiorespiratory arrest without rapid recognition and treatment (Figure 72-1).

Diagnostic Considerations

- A thorough history and physical examination findings usually lead to the diagnosis. Chest radiography is the standard of reference for diagnosis and usually shows a "pleural line" of air in the pleural space.
- An upright radiograph is more useful in older, cooperative children. Decubitus radiographs may also be used, especially in infants (Figure 72-2).
- The role of computed tomography (CT) is to search for the cause of pneumothorax when it is unclear. For example, CT is helpful in the evaluation of small blebs that are difficult to discern on chest radiographs.
- Transillumination of the thorax may be helpful in guiding the diagnosis in very young infants and newborns.

Management

- The therapeutic approach to pneumothorax depends on the size, symptomatology, etiologic origins, and intercurrence.
- Although there is no clear consensus in the evaluation of the size of a pneumothorax in pediatric patients, the distance between the lung apex and the ipsilateral dome of the thoracic cavity, as seen on an upright chest radiograph, is often used. When this distance is <3 cm, pneumothorax is considered small, and when it is >3 cm, it is considered large.

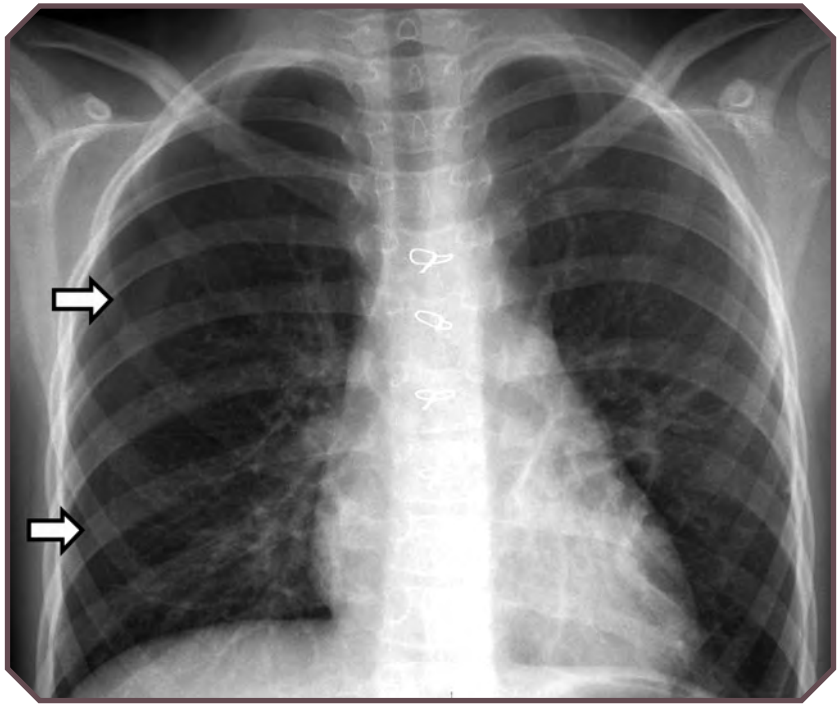

Figure 72-2. Pneumothorax in a 7-year-old girl with chest pain and shortness of breath. Frontal chest radiograph shows a right pleural line (arrows) that indicates a pneumothorax. Due to recurrence, surgery was performed and demonstrated that the pneumothorax was caused by an apical bleb.

Conservative Management

- Most cases of spontaneous pneumothorax resolve with conservative treatment.
- A small pneumothorax generally requires only observation.
- A high concentration of supplemental oxygen generates a partial pressure gradient between the pleural cavity and end-capillary blood by decreasing the partial pressure contribution of nitrogen, which theoretically increases the reabsorption of gas from the pleural cavity.
- For secondary spontaneous pneumothorax, treat the underlying disease.

Chest Tube Placement

- Large pneumothorax requires hospitalization and insertion of an intercostal chest catheter (chest tube).
- Small "pigtail" intrapleural catheters are generally preferred over larger chest tubes for patient comfort when there is only air accumulation. These can be placed by a pulmonologist or an interventional radiologist.
- The chest tube is placed in the midaxillary line, at the fourth to fifth intercostal space, over the lower rib to avoid injury of major blood vessels or nerves.

- After insertion, the chest tube is connected to a Heimlich valve or an underwater seal device.
  - The Heimlich valve allows air and fluid to pass through in 1 direction only and is connected to a bag.
  - In the underwater seal device, the chest tube is connected to a tube submerged 2 cm below the water level in a capped, covered bottle. Most often, a 3-bottle system is used that includes a suction bottle and a drainage bottle.

Surgical Treatment

- Indications for surgical management include second ipsilateral pneumothorax, bilateral pneumothorax, first contralateral pneumothorax, and persistent air leakage. Secondary spontaneous pneumothorax has a higher recurrence rate; therefore, a lower threshold for surgical intervention should be considered.
- Persistent air leakage could indicate the presence of bronchopulmonary fistula, which is a communication between the bronchial tree and the pleural space. Bronchopulmonary fistulae can occur as a complication of large pneumothorax, especially in patients receiving positive invasive mechanical ventilation. Treatment includes surgical approaches as discussed herein, as well as new interventional bronchoscopy techniques, by using an endobronchial one-way valve or endobronchial expandable stents.
- Prevention of the recurrence of pneumothorax can be accomplished with pleurodesis and pleurectomy.
  - Pleurodesis is the insertion of an agent, such as talc or bleomycin, into the pleural space, which creates an inflammatory response and results in adherence between the visceral and parietal pleura.
  - Pleurectomy involves resection of the parietal pleural membrane, which results in adherence between the pleurae.
- If pleural blebs or pleural bullae are the cause of pneumothorax, then surgical intervention is aimed at their resection (blebectomy or bullectomy) or apical resection.
- The surgical approach could be either limited axillary thoracotomy surgery or video-assisted thoracoscopic surgery (VATS). VATS is associated with lower rates of recurrence and morbidity.
- Complications of chemical pleurodesis include clinically significant pain, acute lung injury, widespread dissemination, and hypercalcemia.
- In certain cases, acceptable patient outcomes can be achieved with a combination approach that includes blebectomy plus either chemical or mechanical pleurodesis.

Resources for Families

- Spontaneous Pneumothorax (Children's Hospital of Philadelphia). www.chop.edu/conditions-diseases/spontaneous-pneumothorax
- Pneumothorax (Collapsed Lung) (Vanderbilt Children's Hospital). healthlibrary.vanderbilthealth.com/Library/Wellness/AtWork/3,85307

Clinical Pearls

- Pneumothorax should always be included in the clinician's differential diagnosis of dyspnea and chest pain. When encountered, pneumothorax often requires hospitalization.
- Watchful waiting and clinical monitoring are adequate strategies for stable, small idiopathic pneumothorax.
- The prognosis is often favorable. It varies, depending on baseline disease and on the patient's baseline pulmonary reserve.
- If the patient has recurrent pneumothorax, surgical options can be considered.
- Tension pneumothorax is a medical emergency.

Chapter 73

Pulmonary Aspiration: Foreign Bodies and Massive Aspiration

John L. Colombo, MD, FAAP, and Paul H. Sammut, MB, BCh, FAAP, FCCP

Introduction

- Aspiration of materials that are foreign to the lower respiratory tract is a relatively common event seen in the typical pediatric practice, in terms of both prevalence and severity of illness.
- Aspiration may occur in healthy children and adults and may be clinically undetectable, but it may also be a normal event, occurring particularly during sleep.
- Acute aspiration may be life-threatening, particularly when it involves massive aspiration of gastric contents, hydrocarbons, or foreign bodies.
- Dysphagia with aspiration is reportedly the most common cause of recurrent pneumonia that results in hospitalization.
- The 3 major types of aspiration lung disease are *(1)* airway foreign body, *(2)* massive aspiration, and *(3)* recurrent small-volume aspiration (discussed in Chapter 74, Gastroesophageal Reflux and Recurrent Small-Volume Aspiration).
- While infectious consequences may develop secondary to any of these events, infectious pneumonia is discussed in Part IV, Section 2 of this book: Parenchymal Infections.

Airway Foreign Body: Mechanical Obstruction

- Aspiration of foreign bodies is most common at 1–3 years of age, but it occurs in all age groups. The incidence is up to twofold higher in boys.
- Food is the most commonly aspirated material in toddlers, whereas small, nonedible objects are more commonly aspirated in older children (see Box 73-1).
- Most children have a sudden onset of symptoms. However, in ≥25% of cases, the parents are not aware of any aspiration or choking event.
- There is often an asymptomatic period after the choking spell, once the foreign body becomes lodged in the lower tracheobronchial tree.

Box 73-1. Foreign Bodies Commonly Aspirated by Children

Food	Nonorganic
Peanuts	Toy parts
Popcorn	Pen pieces
Seeds	Pins
Hot dogs	Crayons
Vegetables	Tacks
Grapes	Nails
	Screws

Clinical Features

- The most common presentation is a history that includes a choking event, followed by acute cough, but parents will often not associate an acute short coughing event with a foreign body.
- A careful history should be obtained to elicit the details surrounding the beginning of a cough. Transient or persistent cough is the primary symptom in approximately 75% of children with foreign bodies in the airway (Box 73-2).
- Physical findings may demonstrate asymmetrical chest expansion, decreased breath sounds over the affected lung, and/or localized wheezing, or findings may be normal. However, a tracheal foreign body is more likely associated with bilateral wheezing, which is usually monophonic in nature.

Box 73-2. When to Suspect Foreign-Body Aspiration[a]

- **Sudden onset of respiratory symptoms (stridor, wheeze, cough)**
- **Patient is in the highest-risk age group of 1–3 years**
- **Patient has a history of choking events**
- **Radiographic findings include air trapping and/or atelectasis, especially on decubitus or inspiratory-expiratory views**

[a] Refer the patient if there is a high or low level of suspicion for foreign-body aspiration in the presence of persistent symptoms or findings.

Diagnostic Considerations

- Chest radiographic findings, carefully reviewed, are often highly suggestive of either radiopaque or radiolucent opaque foreign bodies (see Figure 73-1).
- Most foreign bodies are radiolucent; thus, indirect evidence is usually needed for a diagnosis. Bilateral decubitus radiographs are most useful in children because they require no patient cooperation (Figure 73-2). Inspiratory-expiratory radiographs can yield a diagnosis in older, cooperative children (Figure 73-3). Foreign bodies cause air trapping on the affected side from a ball-valve effect. Regardless of whether decubitus or inspiratory-expiratory radiographs are obtained, the abnormal lung is identified by the fact that it does not deflate and remains unchanged on all images. Tracheal or bilateral foreign bodies, which are fortunately rare, may not cause asymmetrical findings.
- A chest radiograph with normal findings does not exclude a foreign body in the airway. Fluoroscopy, preferably pulsed low-dose fluoroscopy, is an option for quickly and inexpensively further evaluating children with unclear radiographic findings and uncooperative children.
- Atelectasis may be a later finding and may occur with complete airway obstruction.
- Low-dose multidectector computed tomography and virtual bronchoscopy are most useful for detecting residual foreign bodies after bronchoscopies if the patient remains symptomatic or has continued abnormalities on plain radiographs (Figure 73-4).

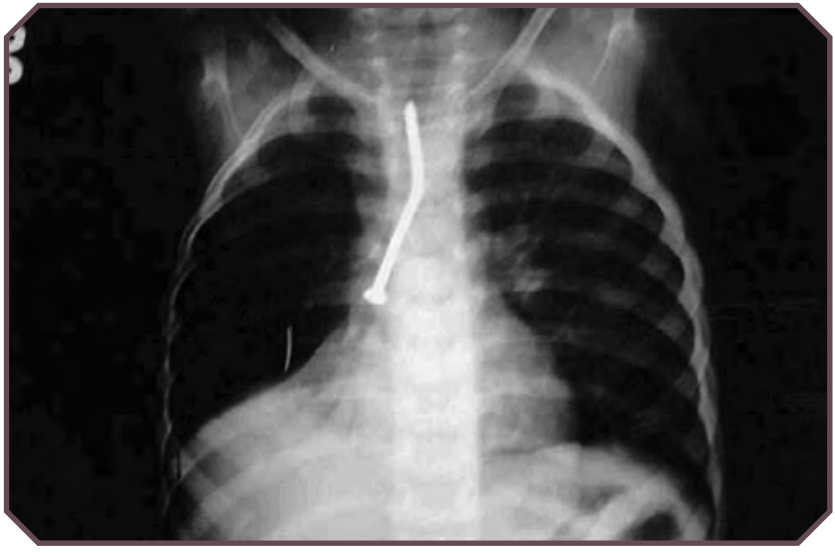

Figure 73-1. Foreign body in a young child. Frontal chest radiograph in a 9-year-old boy shows a large nail lodged in the trachea and the right mainstem bronchus, which is causing right middle lobe atelectasis and obscuring the right-sided heart margin and right hemidiaphragm. Air bronchograms are also noted.

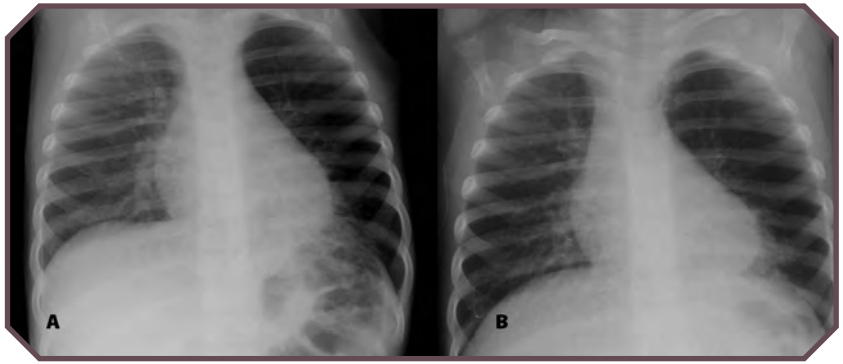

Figure 73-2. Foreign body (peanut) in the right mainstem bronchus. A. Right and B. left lateral decubitus radiographs show no change in the volume of the right lung with a change in patient position, which indicates air trapping. Conversely, the left lung changes in volume with the change in patient position, which is a normal finding that indicates no air trapping. The peanut was removed via a bronchoscope.

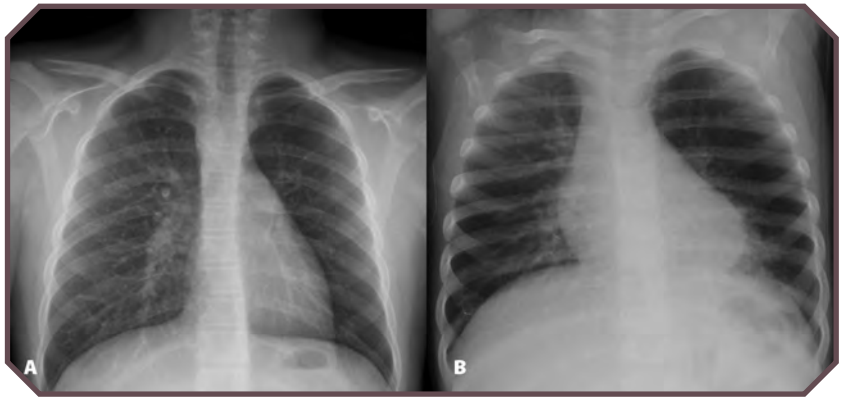

Figure 73-3. Chest radiographs of an 11-year-old boy with a left mainstem foreign body (a tire chip). Frontal A. inspiratory and B. expiratory images are shown. The normal right lung deflates during expiration, whereas the abnormal left lung remains unchanged in volume. The incidental finding of right aortic arch is noted. From Colombo J, Sammut PH. Aspiration (foreign body, food, chemical). In: Light MJ, Blaisdell CJ, Homnick DN, Schechter MS, Weinberger MM, eds. *Pediatric Pulmonology.* Elk Grove Village, IL: American Academy of Pediatrics; 2011:619–636.

Management

- If complete airway obstruction occurs with a witnessed choking event, abdominal thrusts (Heimlich maneuver) are indicated for children >1 year of age. For infants <1 year of age, place the infant in the head-down position and perform chest thrusts and back blows.
- If a foreign body is likely, on the basis of the history, physical examination findings, or radiographic findings, referral for bronchoscopy should be made as soon as possible. Rigid bronchoscopy should be performed as

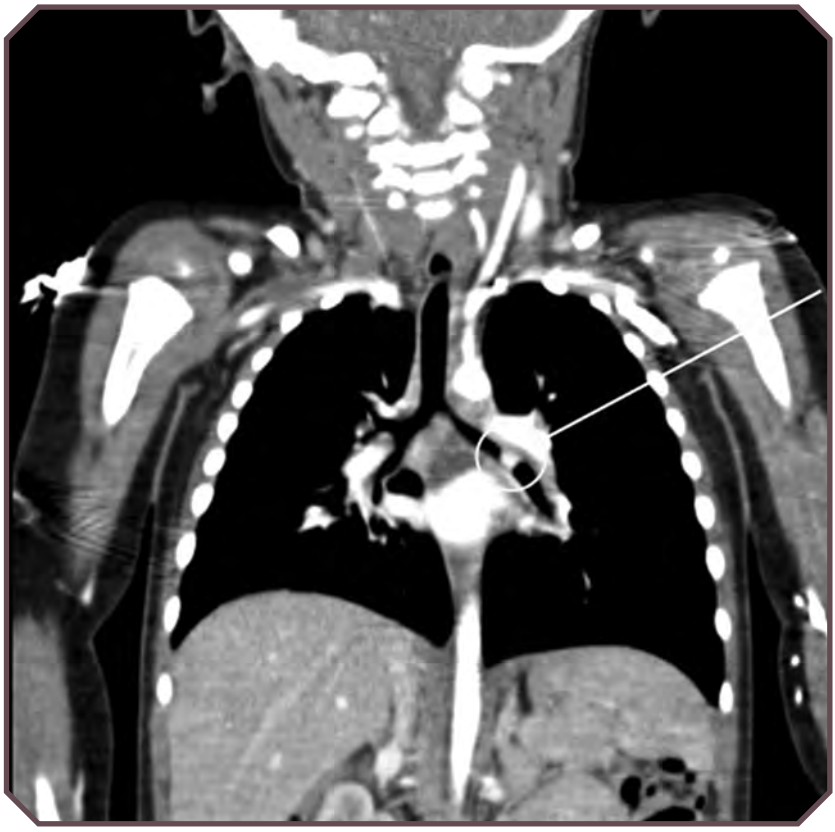

Figure 73-4. Foreign body in a 3-year-old boy. Coronal computed tomographic image shows the foreign body (circled) at the takeoff of the left upper lobe bronchus.

soon as safely possible *(a)* to prevent possible dislodgement of the foreign body into a more central and potentially life-threatening position in the airway, *(b)* to reduce local inflammation, which might make the foreign body more difficult to remove, and *(c)* to reduce parenchymal lung complications, including pneumothorax, atelectasis, and bronchiectasis.

- Small distal foreign bodies may require special instrumentation and, sometimes, fiber-optic bronchoscopy. If the diagnosis of foreign body is less certain, flexible bronchoscopy can be used to confirm this diagnosis, provide another diagnosis, and, sometimes, prevent the need for more invasive, rigid bronchoscopy.
- Rarely, a thoracotomy with bronchotomy may be necessary to remove a deeply embedded foreign body.
- Providing preemptive education to parents of infants and toddlers should be standard in pediatric practice. This includes advising parents that commonly aspirated foods, such as peanuts or similarly sized foods and other objects, should be kept out of reach, that food should be cut into small pieces, and that latex balloons should not be allowed in the home.

When to Refer

- A history of acute choking should never be ignored.
- Any child with a sudden onset of choking, followed by coughing or wheezing, should be referred for evaluation via rigid bronchoscopy.
- Refer the patient if the diagnosis is in question.
- A child with a choking event but no further symptoms, such as cough, dyspnea, fever, and normal physical examination and chest radiographic findings, may not require bronchoscopy. However, if the choking event is followed by any of these findings, referral should be immediate.
- Refer any child for flexible bronchoscopy in the presence of *(a)* chronic problems, such as persistent chest radiographic abnormalities, wheezing, or cough that is unresponsive to asthma therapy, or *(b)* recurrent pneumonias in the same location, even if there is no history for choking. Although flexible bronchoscopy is generally not used for removal of a foreign body, it has advantages for the initial procedure in that infected secretions are easier to culture (common in retained foreign bodies), and it can be used to help plan the best strategy for subsequent removal with a pediatric surgeon and/or otolaryngologist.
- Follow-up is important to monitor the patient for late-onset signs or symptoms and to obtain repeat radiographs if these symptoms develop.

When to Admit

- Admit any child that has *(a)* chronic problems, such as persistent chest radiographic abnormalities, wheezing, or cough that is unresponsive to asthma therapy, or *(b)* recurrent pneumonia, if bronchoscopy cannot be performed promptly. The child should be hospitalized for close observation with nil per os (nothing by mouth) status until bronchoscopy can be performed.
- Extracorporeal membrane oxygenation has been lifesaving in unusually complicated cases when a tracheal foreign body could not be removed without the potential loss of airway support.

Massive Aspiration

- Large-volume aspiration is typically associated with vomiting, particularly with an altered level of consciousness, during which upper-airway protective reflexes are diminished.
- This may occur in children with trauma, seizures, or clinically significant underlying neuromotor disorders, as well as during general anesthesia.
- Animal studies have shown that volumes >1 mL/kg or pH levels <2.5 are associated with the most severe outcomes, although aspiration of particulate material also contributes to clinically significant lung injury.
- When acute massive aspiration is suspected, immediate management is paramount.

Clinical Features

- There is no difficulty in establishing the diagnosis of acute aspiration when the patient is observed to vomit and choke immediately afterward. Whether witnessed or not, the patient typically presents with dyspnea and, possibly, cyanosis.
- Evidence of vomitus may still be present in the oropharynx. If the child has a tracheostomy tube, suctioning of the tube should be performed and may return some formula or stomach contents.
- Clinical observation frequently reveals accessory muscle use and retractions. Coarse inspiratory crackles may be auscultated throughout the chest. Wheezes of varying pitch may also be found. In severe cases, the patient may have lost consciousness or experienced respiratory arrest. Generalized seizures may occur secondary to associated hypoxic encephalopathy.

Diagnostic Considerations

- If it is suspected that inhaled substances had large particulate matter, bronchoscopy may be warranted once a secure or safe airway is established.
  - Identification and removal of large airway particles are of diagnostic value, as well as potential therapeutic value.
  - If no large particles are seen in the airways, bronchoalveolar lavage may still demonstrate 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.
- The classic findings are "asthma-like," as described by Mendelson, whose original description was of complications of aspiration during obstetric anesthesia.
  - These findings may include coughing, wheezing, tachypnea, and possibly cyanosis.
  - After a latent period of 1–3 hours, fever and crackles may develop.
  - Initial radiographic findings typically show bilateral multilobar infiltrates, which then worsen over the next 24–36 hours secondary to the inflammatory response (Figure 73-5).
  - Perioperative aspiration is uncommon with anesthesia today.

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.
- Corticosteroids have not been shown to be beneficial. However, if administered immediately—essentially simultaneously with an aspiration event—there may be some benefit.

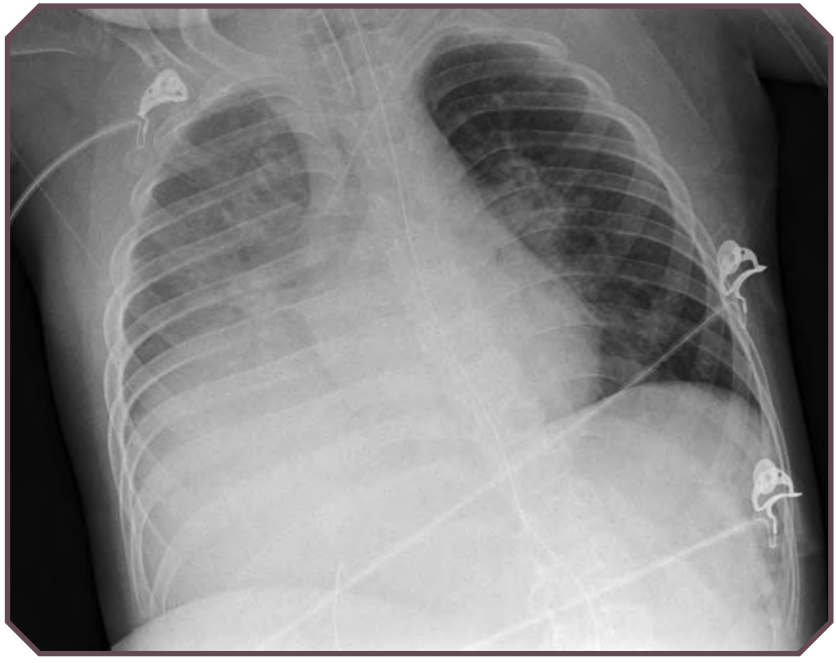

Figure 73-5. Aspiration due to foreign body in a 3-year-old girl who vomited and aspirated a large volume of gastric material. Frontal chest radiograph shows right lower lobe focal opacity. An endotracheal tube, nasogastric tube, and central line overlie the midtrachea, stomach, and superior vena cava, respectively.

- Antibiotics are not indicated in the immediate treatment of most cases of large-volume aspiration.
- General supportive measures, including supplemental oxygen, bronchodilators, and mechanical ventilation, are the mainstays of acute treatment.
- Antibiotics are generally reserved for suspected infectious complications of a chemical pneumonitis. If antibiotics are deemed necessary for a severely compromised patient or for other reasons, they should be individualized, depending on the clinical situation.
  - For example, if the patient has been institutionalized, more broad-spectrum antibiotics would be warranted, including coverage for gram-negative bacteria, as well as methicillin-resistant *Staphylococcus aureus* and anaerobes.
- For patients at risk for vomiting and aspiration:
  - Gastric volume should be minimized.
  - Gastric acid suppression should be considered.
  - Elevating the head of the bed to 30–45 degrees, avoiding excess sedation (if possible), and monitoring gastric residual volumes during enteral feedings may all be helpful preventive measures.
  - If vomiting is witnessed in a patient with a poorly protected airway or an artificial airway, immediate suctioning of the airway is critical.

When to Refer

- A child with recurrent pneumonia or persistent chest radiographic abnormality, dysphagia, coughing or choking with feedings, or recurrent wheezing that is not responsive to routine asthma therapy should be referred for further evaluation.
- Refer the patient if aspiration is suspected in the presence of severe underlying disease, such as congenital heart disease or pulmonary hypertension.

When to Admit

- All patients who become rapidly dyspneic from large-volume aspiration should be admitted.
- Unless the physical examination findings, oxygen saturation level, and chest radiographic findings are normal, all patients suspected to have large-volume aspiration should 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 [F_{IO_2}] <0.6), is only mildly or moderately dyspneic, is not in an altered neurological state, and can be monitored by experienced staff, it is reasonable that he or she 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, 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 likely that, in these situations, the patient will require prolonged and intensive treatment and will require extended follow-up in specialty clinics.

Resources for Families

- Choking Prevention (American Academy of Pediatrics). www.healthychildren.org/English/health-issues/injuries-emergencies/Pages/Choking-Prevention.aspx
- Responding to a Choking Emergency (American Academy of Pediatrics). www.healthychildren.org/English/health-issues/injuries-emergencies/Pages/Responding-to-a-Choking-Emergency.aspx

Clinical Pearl

- A high index of suspicion is necessary for airway foreign body because the history, physical examination findings, and radiographic findings may be normal. The ultimate diagnosis can often only be established by means of bronchoscopy. Choking episodes should never be ignored.

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Chapter 74

Gastroesophageal Reflux and Recurrent Small-Volume Aspiration

Paul H. Sammut, MB, BCh, FAAP, FCCP, and John L. Colombo, MD, FAAP

Introduction

- Recurrent aspiration of small volumes of food or gastric, oral, or nasal contents leads to acute and chronic respiratory problems.
- Risk factors include
  - Neurological impairment
  - Congenital anomalies of the airways (such as laryngeal cleft, vascular ring, and tracheoesophageal fistula)
  - Craniofacial anomalies
  - Muscular diseases
  - Dysautonomia
  - Poor oral hygiene, poor feeding techniques
  - Gastroesophageal reflux (GER)
  - Swallowing immaturity
- Other causes:
  - Aspiration of feedings has been reported with respiratory syncytial virus bronchiolitis.
  - Chronic aspiration with isolated swallowing dysfunction may occur in otherwise healthy young children.
  - The most common reason for hospitalization is oropharyngeal incoordination.
  - In patients with multisystem disease, factors such as Down syndrome, asthma, tube feeding, oral care, and GER disease appear to be more important than swallowing dyscoordination.
  - GER may be associated with respiratory symptoms, such as hypersecretion and wheezing, without causing aspiration. This likely occurs through vagally mediated reflexes (Box 74-1).

Clinical Features

- Clinical respiratory findings include tachypnea, chronic cough, recurrent wheeze, stridor, rattly breathing, and apnea.
- GER may appear as recurrent bronchitis or bronchiolitis, recurrent pneumonia, and atelectasis at presentation.

Box 74-1. Disorders Associated With Gastroesophageal Reflux

- Asthma
- Chronic cough
- Pneumonia, bronchitis
- Atelectasis
- Bronchiectasis
- Pulmonary abscess
- Bronchiolitis obliterans
- Pulmonary fibrosis
- Laryngitis, hoarseness
- Stridor
- Apnea, bradycardia
- Acute, life-threatening events
- Failure to thrive

- "Silent" aspiration (ie, without choking or coughing) occurs especially in neurologically impaired patients.
- GER may be a coincident finding in patients with other chronic conditions, such as cystic fibrosis, primary ciliary dyskinesia, and asthma.

Diagnostic Considerations

- Considerable clinical judgment is required to diagnose microaspiration (frequent aspiration of small volumes).
- A careful history should include the timing of symptoms and the relationship to feedings, positional changes, spitting, vomiting, or arching of the back. In older children, gastric discomfort or increased nocturnal symptoms of coughing or wheezing may be reported.
- The value of observing a feeding cannot be overemphasized.
  - A child who presents with repeated gagging, coughing, wheezing, or crackles after feeding or after visible regurgitation may need very little further evaluation.
  - Other findings may include difficulty with sucking, nasopharyngeal reflux, decreased or markedly increased gag reflex, drooling, or pooling of oral secretions.
  - Postprandial crackles or wheezes may be heard.

Laboratory Studies

- The initial imaging study for a child suspected of having recurrent aspiration is plain chest radiography. However, there are no findings specific to aspiration, and the results may range from normal to classically described consolidations in dependent lobes or segments, similar to pneumonia.
- Computed tomography (CT) is usually not necessary, but CT may show infiltrates with decreased attenuation, which are suggestive of lipoid pneumonia, particularly in dependent areas.

- A barium esophagram is useful for evaluating the presence of anatomic abnormalities, such as hiatal hernia, tracheoesophageal fistula, and vascular rings. This brief examination is typically completed in <120 seconds. Thus, it will only demonstrate aspiration or GER that is nearly constant or occurs during the short imaging time. A negative barium esophagraphic finding does not rule out GER.
- The video swallow study (VSS) (Figure 74-1), generally considered the standard of reference for GER, should be performed with the assistance of a pediatric feeding specialist 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 situated in a normal eating position by using various consistencies of barium or food soaked in barium.
- While very sensitive for oropharyngeal aspiration, VSS cannot be used to evaluate lower esophageal motility or GER.
  - False-positive results may occur because at times, aspiration (particularly with thin barium) is seen and does not correlate with the respiratory status of the patient.
  - VSS has also been shown to have a considerable false-negative rate in the prediction of whether oropharyngeal aspiration will progress to produce pneumonia.
- Gastroesophageal scintigraphy (milk scanning) is insensitive for the detection of aspiration.

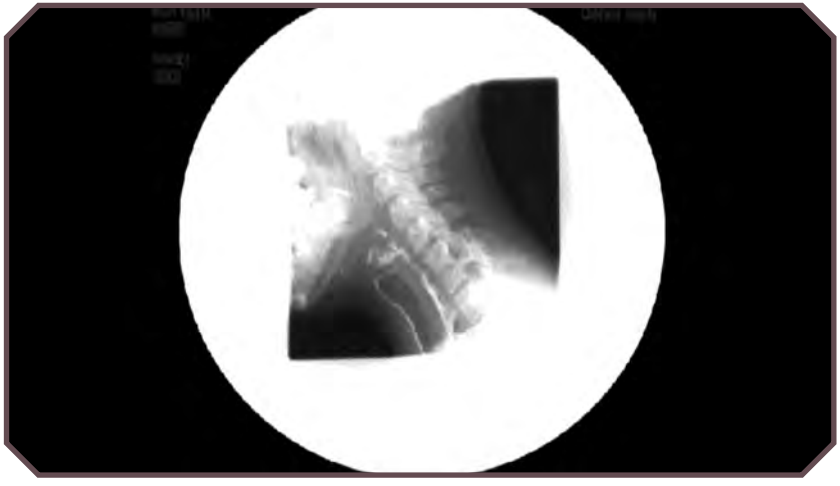

Figure 74-1. Image from a video swallow study shows tracheal aspiration of a large volume of thin barium.

- The salivagram has been used to assess the aspiration of oropharyngeal contents.
  - A small amount (approximately 0.1 mL) of radionuclide is given orally, and scanning is performed to look for tracheal or pulmonary aspiration.
  - This test is probably more sensitive than a gastroesophageal scintiscan and has approximately the same sensitivity as VSS, but it has far less radiation exposure than VSS.
  - When used in conjunction with plain chest radiographs, it can help to determine, with a substantial degree of accuracy, which children are at risk for lung disease due to the aspiration of saliva.
- Fiber-optic endoscopic evaluation of swallowing (FEES) is shown to be of similar sensitivity to VSS, without the radiation.
  - FEES and VSS can be used to assess only 1 brief period of time, which can lead to both false-positive and false-negative results.
  - An advantage to both VSS and FEES is that they can be used to assist with providing treatment recommendations, such as thickening of feedings or special positioning.
- In patients with a tracheostomy or endotracheal tube, a small amount of dye or food coloring can be placed on the tongue or mixed into food, followed by suctioning to look for stained tracheal secretions. Reports of sensitivity and specificity are varied. Using large volumes of dye is not advised, since this technique is highly insensitive for detecting aspiration and also has the potential for causing severe toxicity and even death.

Diagnosing GER

- GER may produce respiratory symptoms, with or without aspiration.
- Numerous disorders have been associated with GER (see Box 74-1). Mechanisms include aspiration, reflex irritation of the airways, and vagal reflex without aspiration.
- Less commonly, GER can be a cause of respiratory disease due to diaphragm flattening and changes in the abdominal-pleural pressure gradient.
- The standard of reference for diagnosing acid reflux from the stomach has been 24-hour esophageal pH level monitoring.
- Esophageal impedance monitoring allows detection of nonacid GER; its use doubles the likelihood of determining that symptoms are caused by reflux.
- A cause-effect relationship between GER and respiratory symptoms is difficult to prove. Even if the results of studies for GER are "normal," if episodes of GER result in aspiration or respiratory symptoms, the "normal" GER test results are pathologic in nature. It is for primarily this reason that an empirical trial of conservative and medical treatment for GER is often the best and most cost-effective diagnostic test.

- Examination of tracheobronchial aspirates obtained at bronchoscopy or deep samples from artificial airways that can yield valuable information regarding aspiration include analysis for the following:
  - Glucose
  - Vegetable or meat fibers
  - Lipid-laden macrophages
  - Pepsin analysis can only be used to detect aspiration that occurs from GER, not from dysphagia, although detection of pepsin in bronchoalveolar lavage fluid may aid in the decision whether or not to recommend an antireflux surgical procedure.
  - The finding of lipid-laden macrophages is nonspecific to aspiration, but when these cells are semiquantitated, this has been shown to have a high correlation with other test results for aspiration. By using proper histologic technique, the absence of lipid-laden macrophages highly suggests that lipid aspiration is not occurring.
  - Other limited studies have been used to look at various substances added to foods, such as carbon or polystyrene microspheres.
- 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 study findings that indicate aspiration, thus markedly delaying diagnosis of their primary problem.

Management

- Treatment should be directed at the underlying condition that contributes to aspiration, if known.
- Other treatment will depend on the severity of respiratory problems and whether the aspiration is caused by a swallowing dysfunction or GER.
- Conservative measures to improve aspiration during swallowing include thickening of food, pacing feedings, performing swallow stimulation, and changing the feeding position.
- Thickening food, eating in the upright position, avoiding bottle propping and smoke exposure, and losing weight (if the child is obese) can all be helpful in reducing GER.
- Medical treatment with histamine-2 blockers or proton pump inhibitors can reduce acid reflux but has not been shown to reduce nonacid reflux.
- Prokinetic agents available in the United States include metoclopramide and erythromycin. The effectiveness of either drug is not well substantiated, and side effects are common with metoclopramide.
- A trial of nasogastric feedings can be used while waiting for temporary swallowing dysfunction to improve.
- With significant GER, postpyloric feedings may be considered.

- Surgical treatment is reserved for patients with more severe problems, such as recurrent hospitalization for pneumonia or evidence of progressive lung injury. It should also be considered early in children who have pulmonary hypertension or who have undergone lung transplantation and have evidence of renewed lung abnormalities.
- Fundoplication is usually successful in eliminating GER and should be performed in conjunction with gastrostomy tube placement in children with clinically significant GER. Judgment must be used to decide if this should be performed at the time of gastrostomy in children without clinically significant GER, since many patients develop GER after gastrostomy tube placement.
- Recurrent pneumonia may continue even after both fundoplication and gastrostomy, owing to the continued aspiration of oral secretions, especially in neurologically impaired children.
  - Anticholinergic agents, such as glycopyrrolate and scopolamine, may reduce excess salivation, but tolerance can develop, and adverse side effects may occur, such as blurred vision, behavioral change, and difficulty urinating.
  - These agents also affect airway mucus hydration, and thickened mucus may be problematic, particularly in children with a tracheostomy.
- Salivary gland injection of botulinum toxin has been shown to reduce salivation, but the effects are usually short term.
- Surgical intervention with salivary gland removal, ductal ligation, or laryngotracheal separation may be considered in children who are not responsive to more conservative therapy.
- Tracheotomy, although often associated with an increase in aspiration, can be considered in a patient with chronic aspiration and poor ability to clear the airway as a means to improve pulmonary hygiene and to provide ventilatory assistance and oxygen delivery.
- The care of children with chronic aspiration is difficult. There are many variables with diagnosis and treatment that are best individualized for the patient by means of close collaboration between the primary physician, pulmonologist, family, and, surgical subspecialists.

When to Refer

- Refer a child who has recurrent pneumonia or persistent chest radiographic abnormality, dysphagia, coughing or choking with feedings, or recurrent wheezing that is not responsive to routine asthma therapy.
- Refer a child when aspiration is suspected in the presence of severe underlying disease, such as congenital heart disease or pulmonary hypertension.

When to Admit

- Admit a child for clinically significant dyspnea, hypoxemia, progressive pulmonary signs or symptoms, equivocal history, and acute life-threatening events. Any of these may indicate acute or cumulative effects of chronic aspiration.

Resource for Families

- Gastroesophageal Reflux & Gastroesophageal Reflux Disease (American Academy of Pediatrics). www.healthychildren.org/English/health-issues/conditions/abdominal/Pages/GERD-Reflux.aspx

Clinical Pearls

- Oropharyngeal aspiration from swallowing dysfunction is reportedly the most common cause of recurrent pneumonia in children.
- There is no test for aspiration that is both highly sensitive and specific. Clinical judgment is always necessary to determine if aspiration is a likely cause of existing respiratory disease.
- Esophageal monitoring of pH level cannot be used to detect nonacid reflux (for example, postprandial reflux), which may be the major culprit in chronic pulmonary aspiration.
- Although esophageal impedance monitoring can be used to detect nonacid reflux, it does not indicate if reflux, even a normal amount, leads to pulmonary aspiration.
- Oropharyngeal aspiration is more likely to be associated with recurrent pneumonia. GER disease is more likely to be associated with respiratory symptoms, such as wheezing and cough.
- Acid suppression therapy cannot be expected to markedly improve recurrent aspiration if aspiration is related to nonacid GER or swallowing dysfunction.

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Chapter 75

Hypersensitivity Pneumonitis

Katharine Kevill, MD, MHCDS, FAAP

Introduction/Etiology/Epidemiology

- Hypersensitivity pneumonitis (HP), also called *extrinsic allergic alveolitis,* has no consensus definition. Most definitions include several common features.
  - It is a pulmonary disease with or without systemic manifestations (such as fever and weight loss).
  - It is caused by the inhalation of an antigen to which the subject is sensitized and hyperresponsive.
  - Sensitization and exposure alone in the absence of symptoms do not define the disease.
- HP was first reported in children in 1967 as *pigeon breeder's lung,* with clinical features that included
  - Severe interstitial pneumonitis and prolonged exposure to pigeons.
  - Chronic cough, progressive dyspnea, weight loss, and acute symptoms of fever and chest pain.
- Before this, HP was thought to be a disease in adults that results from occupational exposure to environments such as moldy hay (farmer's lung) and sugar cane residue (bagassosis).
- Epidemiologically, HP is rare, but probably underreported.
  - Between 1960 and 2005, 95 cases of HP in children were reported in the literature. Inciting antigens included various birds and molds.
  - The incidence of HP is unknown.
  - Twenty-three cases over 3 years in all of Germany were identified by the German Surveillance Unit for Rare Pediatric Disorders.

Pathophysiology

- HP is one of many heterogeneous disorders found in the broader category of diffuse and interstitial lung disease.
- It is not mediated by immunoglobulin E (IgE).
- Features of both immune complex–mediated (type III) and T cell–mediated (type IV) reactions have been described.

- The patient with HP develops immunoglobulin G (IgG) antibodies to the inciting environmental agent. However, the presence of serum IgG antibodies released in response to the antigen also occurs in individuals who have been exposed but have no symptoms.
- Murine model studies indicate that toll-like receptors linked to the MYD88 intracellular pathway play a role in the response to the inciting antigens.

Clinical Features

- Clinical features are variable and depend on the severity of the disease at presentation.

Symptoms

- Usually include cough, dyspnea, and fatigue
- Sometimes include fever and weight loss

Signs

- Usually include crackles and hypoxemia
- Often include tachypnea and clubbing
- Occasionally include wheezing

Radiographic Findings

- Plain chest radiographs usually show a reticulonodular pattern of interstitial markings.
- Thin-section chest computed tomography usually demonstrates nodules in a centrilobular distribution; it sometimes shows ground-glass opacities; in late stages, it shows lobar volume loss and honeycombing.

Pulmonary Function Test Findings

- Usually include a restrictive pattern (decreased lung volumes)
- Usually include decreased diffusing capacity for carbon monoxide (DLCO)
- Can include an obstructive pattern or mixed restrictive and obstructive disease

Findings at Bronchosopy

- Usually lymphocytosis

Findings at Lung Biopsy

See Figure 75-1 for lung biopsy findings of HP.

- Bronchiolocentric, chronic inflammation is always found.
- Alveoli are often filled with lymphocytes—usually T cells.
- Often, noncaseating histiocytic granulomas with multinucleated giant cells are found.

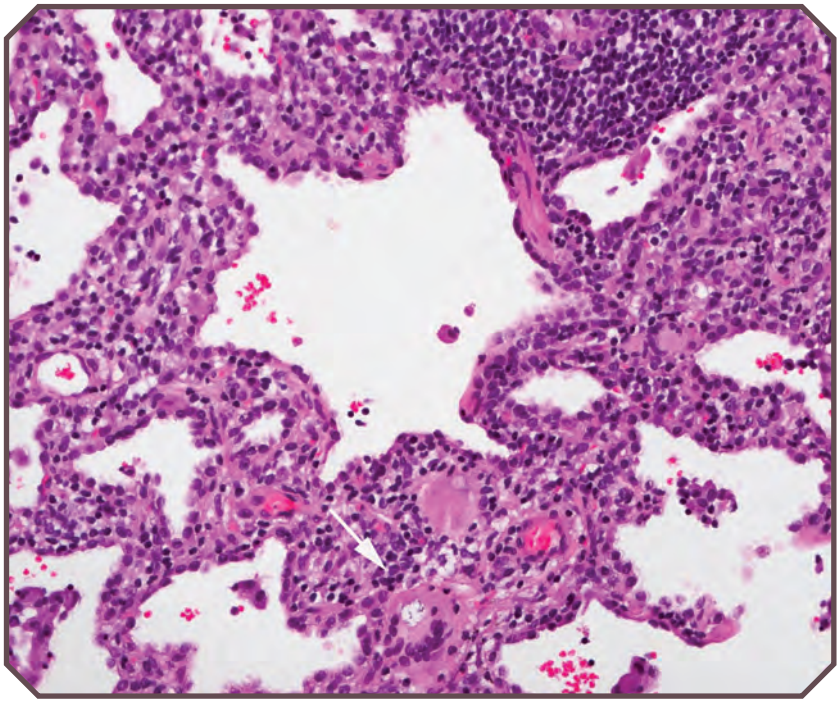

Figure 75-1. Photomicrograph (hematoxylin-eosin stain; original magnification, ×20) of a lung biopsy sample from an 8-year-old boy with a recent history of cough, shortness of breath, and fever shows a cellular interstitial lymphocytic infiltrate admixed with multinucleated giant cells (arrow). Courtesy of Gail H. Deutsch, MD, Seattle, WA.

Differential Diagnosis

- The signs and symptoms of HP overlap with a range of infectious, respiratory, and systemic diseases. See Box 75-1.
- Consider HP in the differential for
  - Any child in whom diffuse and interstitial lung disease is suspected
  - Restrictive respiratory disease without a clear cause
  - Fulminant respiratory symptoms that resolve in the hospital and then recur
  - Any child with persistent respiratory symptoms of unclear etiologic origin

Diagnostic Considerations

- There is no definitive test for HP.
- Start with a detailed history and physical examination. Include environmental history–ask specifically about exposures to birds and mold.
- If HP is included in the differential, order DLCO and lung volume studies, in addition to spirometry.

Box 75-1. Differential Diagnosis of Hypersensitivity Pneumonitis in Children

Infectious

- Bacterial pneumonia
- *Mycoplasma* infection
- Histoplasmosis
- Coccidioidomycosis
- Blastomycosis
- Brucellosis
- Psittacosis
- *Legionella* infection
- Tuberculosis
- HIV infection, particularly with lymphocytic interstitial pneumonia

Respiratory

- Asthma
- Cystic fibrosis
- Allergic bronchopulmonary aspergillosis
- Bronchiolitis obliterans, organizing pneumonia
- Recurrent pneumonia
- Interstitial and diffuse lung disease of childhood of unknown etiologic origin

Other

- Systemic lupus erythematosus
- Sarcoidosis
- Malignancy
- Immune deficiency

Adapted from Kevill K. Hypersensitivity pneumonitis. In: Light MJ, Blaisdell CJ, Homnick DN, Schechter MS, Weinberger MM, eds. *Pediatric Pulmonology*. Elk Grove Village, IL: American Academy of Pediatrics; 2011:209–220.

- IgE levels will neither rule in nor rule out HP, but they may aid in the evaluation for other diseases in the differential (such as allergic bronchopulmonary aspergillosis).
- Positive precipitating antibodies specific to the suspected agent confirm adequate exposure to the agent to generate a humoral immune response. A positive IgG finding is supportive of a diagnosis but can also occur in individuals exposed to the antigen who have not developed the disease.
- Commercial tests are of limited use because of potential false-negative findings.

- Consider challenging the individual to the suspected antigen. Formal studies are limited to experienced investigators in research centers with the appropriate equipment, expertise, and staff to respond to an allergic reaction.

Management

- The first key to management is removal of the patient from the identified source of exposure.
- Although there are no limited data in children, systemic and inhaled corticosteroids are used and may hasten the initial recovery, but they do not alter the long-term course of the disease.
- In pediatric populations, high-dose pulse intravenous methylprednisolone has been used and may prevent some of the side effects of daily oral steroid therapy.
- Immunosuppressive drugs such as hydroxychloroquine, azathioprine, and cyclosporine have been used.

Treating Associated Conditions

- Consider using echocardiography to screen the patient for signs of pulmonary hypertension.
- Provide nutritional support for patients who have experienced weight loss.

Expected Outcomes/Prognosis

- The prognosis varies, from complete resolution to death.
- The prognosis in adults is generally good and is influenced by the stage at which HP is diagnosed. Prompt diagnoses with immediate removal from the antigen can result in complete cure. If the disease has progressed to a point of clinically significant permanent lung damage, such as fibrosis or emphysema, the disease may continue to progress, even after cessation of exposure to the antigen.
- In a pediatric center in Copenhagen, researchers retrospectively studied the records of 19 biopsy-confirmed cases between 1998 and 2009 and reported the following:
  - All children were treated with high-dose monthly pulse methylprednisolone.
  - Six months after diagnosis, spirometry and DLCO levels improved markedly but did not completely normalize.
  - At the end of 6 months, 69% of patients were regarded as healthy and completed their treatment.
- At the same pediatric center in Copenhagen, investigators performed a cross-sectional study on 25 patients who received a diagnosis of HP between 2001 and 2014.
  - The lung clearance index (LCI) was abnormal in 47% of patients. LCI is a measure of peripheral airway involvement obtained from using the multiple-breath washout technique.

— Forced expiratory volume in 1 second was abnormal in only 9% of patients.

When to Refer

- Refer any child in whom diffuse and interstitial lung disease is suspected.
- Refer any child with a presumed diagnosis of asthma or infection who doesn't improve as expected.

When to Admit

- Admit patients with worsening clinical status who are in need of inpatient support and monitoring.
- Admit patients for diagnostic studies, such as bronchoscopy and/or lung biopsy.
- Admit patients to test whether there is improvement with removal from the antigen (it may be difficult to get insurance approval).

Prevention

- There is no known way to prevent HP, other than avoiding exposures.
- Many people are exposed to the potential HP that causes antigens (such as hay), but relatively few develop HP. It is not known why some people are more susceptible, but it is suspected that environmental or genetic cofactors are necessary to trigger the disease.

Resources for Families

- Children's Interstitial and Diffuse Lung Disease Foundation. www.child-foundation.com
- Hypersensitivity Pneumonitis (National Heart, Lung, and Blood Institute). www.nhlbi.nih.gov/health/health-topics/topics/hp

Chapter 76

Pulmonary Hemorrhage

Karen Z. Voter, MD, FAAP, and Clement L. Ren, MD, MS

Introduction/Etiology/Epidemiology

- Hemoptysis in children is uncommon and is frequently related to a known underlying condition.
- Reports of "coughing up blood" can be related to bleeding from the nasopharynx, esophagus, lower airways, or lung parenchyma.
- Underlying conditions associated with pulmonary bleeding include
  - Tracheostomy
  - Cystic fibrosis (CF)
  - Pulmonary hypertension, usually associated with congenital heart disease
  - Autoimmune diseases, including granulomatosis with polyangiitis (formerly known as *Wegener granulomatosis*), systemic lupus erythematosus, microscopic polyangiitis, and Goodpasture syndrome
  - Infection, usually tuberculous or fungal, though it can be bacterial
  - Endobronchial mass
  - Foreign body

Pathophysiology

- Mucosal irritation from dry secretions or trauma
- Mucosal trauma, especially with a tracheostomy or foreign body
- Pulmonary hypertension from congenital heart disease or arteriovenous malformation
- Pulmonary embolism
- Autoimmune vasculitis
- Erosion through pulmonary tissue into bronchial vessels
  - Can be massive if a bronchial artery is eroded
  - Occurs in CF
- Idiopathic pulmonary hemosiderosis (IPH)
  - Thought to be immune mediated, but without detectable autoantibodies
  - Heiner syndrome is a subform of IPH associated with allergy to milk protein

Clinical Features

- Coughing or suctioning up blood is the most common presentation.
- Anemia (iron deficiency) may be present.
- There may be opacities on chest radiographs that are typically more transient than those of pneumonia.
- The patient may have multiple episodes of bleeding.
- Especially with massive bleeding, patients can often localize the site.
- Signs of infection include fever and leukocytosis.
- Signs of pulmonary embolism may be present.
  - Risk factors include therapy with oral contraceptives.
- The presence of renal disease or rash suggests an autoimmune disorder.

Differential Diagnosis

- Nonpulmonary source of bleeding
  - Nose
  - Upper airway
  - Gastrointestinal
- Pneumonia
- Complication of an underlying diagnosis
- Congenital heart disease
- IPH
- Autoimmune disease
- "Coughing up blood"
  - Consider Munchausen syndrome by proxy *(a)* when the workup results are entirely negative, *(b)* when coughing up blood is only observed by a parent or other caregiver, or *(c)* when respiratory distress is absent.

Diagnostic Considerations

- Chest radiographs may demonstrate nonspecific transient opacities.
- Blood tests
  - Complete blood cell count to follow the hemoglobin and hematocrit levels and evaluate the patient for ongoing bleeding
  - White blood cell count to evaluate the patient for infection
  - Blood typing if there is suspicion that the blood may not be from the patient
- Sputum for culture, including mycobacteria and fungi
- Bronchoscopy and bronchoalveolar lavage may be useful to
  - Establish that the source of bleeding is the lung
  - Identify a source of bleeding (if there is active bleeding at the time of the procedure)
  - Identify a foreign body or mass
  - Detect hemosiderin-laden macrophages
- Nasal endoscopy to evaluate the patient for the presence of nasal bleeding or upper-airway foreign body

- Esophagogastroduodenal endoscopy to evaluate the patient for GI bleeding
- Clotting studies to evaluate the patient for the risk of ongoing bleeding
- Cardiac evaluation, including echocardiography and/or catheterization to detect pulmonary hypertension and congenital heart disease
- Lung biopsy
  - Rarely needed
  - Can be used to detect autoantibodies or demonstrate vasculitis present in IPH

Management

- Resuscitation may be required, including intubation and positive pressure ventilation if needed.
- Identify the location of the bleeding site with bronchoscopy, if there is active bleeding.
- Treat any infection, if required.
- Address issues related to an underlying process.
  - Humidification of tracheostomy
  - Treatment of CF pulmonary exacerbation
  - Treatment of underlying autoimmune process with immune-modulating therapy
- Treat any coagulopathy.
- Limit ongoing trauma to the airway by decreasing the frequency and vigor of the airway clearance.
- Consider conducting a cardiac evaluation.
- Severe bleeding may require bronchial artery embolization by an interventional radiologist.
- Massive life-threatening pulmonary hemorrhage may require emergent lobectomy.
- Immunosuppressive therapy for IPH may include
  - Glucocorticoids
  - Hydroxychloroquine
  - Azathioprine
  - Cyclophosphamide

Treating Associated Conditions

- Tracheostomy-associated bleeding usually requires increased humidification and/or antibiotics. Re-evaluation of suctioning technique can be helpful to make sure that suctioning is not occurring past the tracheostomy tube tip.
- CF-related bleeding requires antibiotics and temporary restraint in airway clearance. Patients are at risk for vitamin K deficiency. Massive or recurrent bleeding may require bronchial artery embolization by an interventional radiologist.

- Congenital heart disease requires evaluation by a cardiologist and may require specific treatment of a cardiac defect, pulmonary hypertension, or arteriovenous malformation.
- Autoimmune diseases with pulmonary hemorrhage are usually seen at times of disease exacerbation and suggest a need for increased treatment of the underlying disorder.
- Pulmonary emboli therapy may require stopping medications that place the patient at risk and continuing ongoing anticoagulation therapy.

Expected Outcomes/Prognosis

- Most patients with small amounts of pulmonary hemorrhage do well, especially with successful treatment of the underlying condition.
- Massive bleeding (>400 mL/d) can be life-threatening and may require therapies such as intubation, resuscitation, and embolization.
- Recurrent episodes of alveolar bleeding can be life-threatening and require vigilance to identify subsequent bleeding episodes.

When to Refer

- Massive hemoptysis requires emergent evaluation and therapy, which will usually require the resources of a tertiary care center for bronchoscopy, interventional radiology, and/or cardiology.
- Recurrent episodes of pulmonary bleeding are likely to necessitate diagnostic studies at a tertiary care center.
- Localization of bleeding to optimize therapy may require diagnostic testing, including bronchoscopy, chest computed tomography, magnetic resonance arteriography, echocardiography, or even lung biopsy.

When to Admit

- Massive hemoptysis
- Sustained hemoptysis
- Hemodynamic instability
- Localization of the site of bleeding, if undetermined

Prevention

- Awareness of the risk factors for pulmonary bleeding in patients with tracheostomy tubes allows for improving humidification and decreasing trauma to the airway.
- Treat and control underlying conditions associated with pulmonary hemorrhage (eg, CF, granulomatosis with polyangiitis, Goodpasture syndrome).

Resource for Families

- Coughing Up Blood (Hemoptysis) (WebMD). www.webmd.com/lung/coughing-up-blood#1

Clinical Pearls

- It is important to establish the site of bleeding, which can be from the nasopharynx, esophagus, lower airway, or lung parenchyma. In rare cases (eg, Munchausen by proxy syndrome), the blood may even be from a different person.
- Underlying conditions are frequently causes of airway bleeding and are best addressed by treating the specific condition. These include infection, dry secretions (particularly if a tracheostomy is in place), foreign-body aspiration, pulmonary hypertension, vascular abnormalities (including clots), and autoimmune disorders.
- Radiographic changes can be transient.
- Severe bleeding may require bronchial artery embolization.

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Chapter 77

Pulmonary Hypertension

Nicholas L. Friedman, DO, FAAP, and Samuel B. Goldfarb, MD

Introduction

- Pulmonary hypertension is an increase in the pulmonary arterial pressure that results from a decrease in functional pulmonary vasculature.
- Pulmonary arterial pressure = left atrial pressure + (pulmonary flow × pulmonary vascular resistance).
- Any single factor that increases left atrial pressure, pulmonary flow, or pulmonary vascular resistance can cause pulmonary hypertension.
- Pulmonary hypertension is defined via cardiac catheterization by a resting mean pulmonary arterial pressure of ≥25 mm Hg at sea level beyond 3 months of life.

Etiology

Five Major Categories of Pulmonary Hypertension

The World Health Organization classification of pulmonary hypertension per the Fifth World Symposium (in 2011 in Nice, France) is as follows:

1. Pulmonary arterial hypertension
    a. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
    b. Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension secondary to left-sided heart disease
3. Pulmonary hypertension due to lung diseases or hypoxia
4. Chronic thromboembolic disease
5. Pulmonary hypertension with unclear or multifactorial mechanisms

Categories of Pediatric Pulmonary Hypertension

The 2013 Panama Pulmonary Hypertension Classification is as follows:

1. Prenatal or developmental pulmonary hypertensive vascular disease
2. Perinatal pulmonary vasculature maladaptation
3. Pediatric cardiovascular disease
4. Bronchopulmonary dysplasia
5. Isolated pediatric pulmonary hypertensive vascular disease (isolated pediatric pulmonary artery hypertension [PAH])
6. Multifactorial pulmonary hypertensive vascular disease in congenital malformation syndromes
7. Pediatric lung disease

8. Pediatric thromboembolic disease
9. Pediatric hypobaric hypoxic disease
10. Pediatric pulmonary vascular disease associated with other system disorders

Epidemiology

- According to the United Kingdom Service for Pulmonary Hypertension, the incidence of childhood idiopathic PAH is about 0.5 per 1 million children per year, with a prevalence of about 2 children per 1 million.
- The Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension, or TOPP, registry is the largest international pediatric pulmonary hypertension database, with records for >350 children.
  - In this database, there is an overall female-to-male predominance of 1.4 to 1. Eighty-eight percent of children in the database have PAH; of those, 36% have pulmonary hypertension associated with congenital heart disease (CHD). Twelve percent of children have pulmonary hypertension with a respiratory etiologic origin.
- Trisomy 21 is the most common associated chromosomal abnormality (Box 77-1).
- *BMPR2* gene mutation has been found to cause 75% of hereditary PAH cases.
  - May be inherited in an autosomal dominant fashion or occur de novo.
  - Only 6% of patients with pulmonary hypertension reported a family history of the condition in the prospective National Institutes of Health registry.
- Pulmonary hypertension may also be associated with hereditary hemorrhagic telangiectasia and mutations in the genes that cause hereditary hemorrhagic telangiectasia (*ALK1* and *ENG*).

Box 77-1. Associated Conditions

- Trisomy 21
- Congenital diaphragmatic hernia
- Pulmonary hypoplasia
- Chronic lung disease and/or bronchopulmonary dysplasia
- Severe interstitial lung disease
- Severe cystic fibrosis
- Severe obstructive sleep apnea
- Congenital heart disease
- Sickle cell disease
- Thromboembolism
- Pulmonary vasculitis
- Hereditary hemorrhagic telangiectasia

Pathophysiology

- The exact pathophysiology is dependent on the etiologic mechanism.
- There are 3 primary mechanisms for pediatric pulmonary hypertension development, which may occur singularly or in combination.
  - Developmental arrest of the growth of the pulmonary vasculature
  - Lung destruction from pulmonary inflammation
  - Imbalance of vasodilators and vasoconstrictors

Clinical Features

History

- Exertional dyspnea and fatigue are the earliest and most common complaints. They are not relieved with rest or other initial measures (ie, bronchodilators).
- Syncope, presyncope, or chest pain may also occur on exertion. These may also occur frequently or be unrelieved with other therapies.
- Tiring with feeding and failure to thrive may manifest in infancy.
- Patients with underlying pulmonary disease may also have frequent episodes of cough or wheezing.
- Hemoptysis (associated with pulmonary infarction secondary to thrombosis) may be a late, and possibly fatal, finding.

Physical Examination

- The physical examination findings in pulmonary hypertension can range from normal to fulminant right-sided heart failure.
- Cyanosis and cool extremities may be present.
- Digital clubbing may be present, with persistent hypoxemia.
- Hyperdynamic right ventricular impulse in the subxiphoid region (subxiphoid impulse)
- Single second heart sound
- Holosystolic tricuspid regurgitation murmur at the left lower sternal border
- Hepatomegaly
- Peripheral edema
- Jugular venous distention

Differential Diagnosis

- Asthma
- Lower respiratory tract infection
- Pulmonary arteriovenous malformations
- Congestive heart failure
- Noncardiogenic pulmonary edema
- Arrhythmias
- CHD

Diagnosis and Evaluation

The following evaluations should be performed when the history or physical examination findings are concerning for pulmonary hypertension.

Electrocardiography

- Findings may be normal or have evidence of cor pulmonale with right-axis deviation with right ventricular hypertrophy.

Radiography

- Chest radiographs may demonstrate an enlarged cardiac silhouette, engorged central pulmonary arteries, and reduced peripheral pulmonary vascularity (see Figure 77-1).

Echocardiography

- Should be performed 2-dimensionally, with Doppler imaging and M-mode
- Echocardiography may demonstrate
  - — Right ventricular hypertrophy
  - — Right atrial hypertrophy
  - — Small or normal left ventricular dimensions

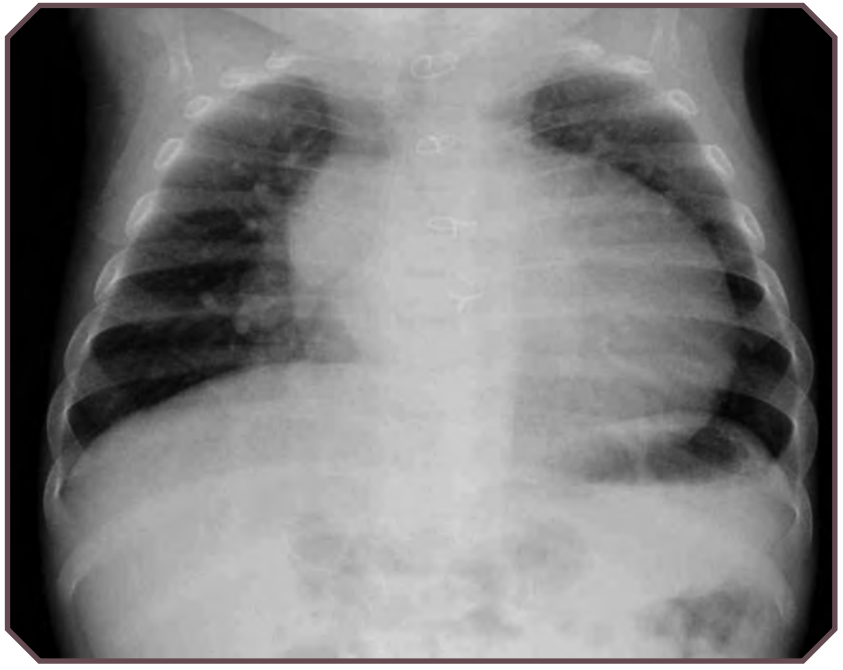

Figure 77-1. Cardiomegaly caused by pulmonary hypertension in 3-year-old girl. The frontal chest radiograph also shows prominent bilateral perihilar pulmonary vascularity. Sternotomy wires are in place because of a previous surgery for congenital heart disease.

- — Abnormal interventricular septal motion and thickened interventricular septum
- — Tricuspid regurgitation
- — Pulmonary regurgitation
- — If there is an intracardiac shunt present, right-to-left flow through the lesion may be seen

Cardiac Catheterization

- Necessary to confirm the presence and severity of pulmonary hypertension
- Can perform pre- and postvasodilator administration to determine if the patient's pulmonary hypertension is caused by active vasoconstriction ("vasodilator responders") or permanent changes in the pulmonary arterioles ("vasodilator nonresponders")

Other Studies

- Complete blood cell count
- Comprehensive metabolic panel, magnesium level assessment, phosphorous level assessment (to evaluate hepatic and renal function)
- Urinalysis (to evaluate renal function)
- Brain natriuretic peptide (normal <100 pg/mL [<100 ng/L] in adults, no normative values in children)
- Arterial blood gas
- Inflammatory markers, such as erythrocyte sedimentation rate and C-reactive protein

Management

- Oxygen may act as a pulmonary vasodilator. Attempt to maintain as normal an oxyhemoglobin saturation as possible. One must be cautious, because supplemental oxygen can decrease the respiratory drive in patients with hypercapnic lung disease.
- Inhaled nitric oxide (NO) acutely vasodilates pulmonary vasculature by increasing cyclic guanosine monophosphate (cGMP) to cause smooth-muscle relaxation. NO is cleared by the phosphodiesterase type 5 (PDE-5) enzyme activity. Inhaled NO is used in the acute inpatient management of pulmonary hypertension.
- PDE-5 inhibitors (sildenafil and tadalafil) prevent the breakdown of cGMP and subsequently cause vasodilation. They may be used either as a chronic therapy or emergently in conjunction with inhaled NO.
- Prostanoids (treprostinil, epoprostenol, iloprost) are powerful vasodilatory agents that stimulate cyclic adenosine monophosphate, or cyclic AMP, and result in vasodilation, inhibition of platelet aggregation, and anti-inflammatory effects. They may be administered intravenously, subcutaneously, or orally, or they may be inhaled. They can be used in the management of acute exacerbations or for chronic outpatient management.

- Endothelin-1 receptor antagonists (bosentan, macitentan) block the receptor for endothelin-1 (a potent vasoconstrictor) and lower pulmonary vascular resistance. They are administered orally in the chronic management of pulmonary hypertension.
- Calcium channel blockers (nifedipine, diltiazem, amlodipine) inhibit calcium influx in vascular smooth muscle. They are not for use in children <1 year of age. They are not effective for long-term management of pulmonary hypertension.
- Surgical management may be necessary in severe cases that are refractory to medical therapies.
  - — Atrial septostomy may be performed to create a right-to-left atrial shunt to maintain cardiac output in the presence of increased hypoxemia.
  - — A Potts shunt may be created from the descending aorta to the left pulmonary artery.
- Ultimately, lung or heart-lung transplantation may be necessary.

Treating Associated Conditions

- Manage underlying etiologic conditions to prevent pulmonary hypertension from developing.
- Correct congenital cardiac defects in a timely manner, before obstructive changes can occur in the pulmonary vasculature.
- Perform tonsillectomy and adenoidectomy or administer nasal positive airway pressure when severe upper airway obstruction is the cause of the pulmonary hypertension.
- Administer anticoagulation therapy when pulmonary hypertension occurs secondary to blood flow obstruction by a thrombus.

Expected Outcomes/Prognosis

- Prognosis is ultimately dependent on the underlying etiologic origin and associated comorbidities.
- With the development of targeted pulmonary vasodilators, the survival rate of children with pulmonary hypertension has been increasing.
- Despite recent advancements in the diagnosis and management of pediatric pulmonary hypertension, the 5-year mortality rate remains at 20%–25%.

When to Refer

- All children with suspected pulmonary hypertension or clinically significant risk factors for it (ie, severe prematurity, pulmonary hypoplasia, interstitial lung disease with hypoxemia, end-stage cystic fibrosis, or trisomy 21) should be referred to a pediatric cardiologist, particularly one who specializes in pulmonary hypertension, for evaluation.
- Children should also be referred to a pediatric pulmonologist for management of their lung disease.

- Children with suspected obstructive sleep apnea should be referred for a polysomnogram to evaluate their obstructive sleep apnea, which should then be managed by a pediatric sleep medicine specialist.

When to Admit

- Any child with signs or symptoms of an acute pulmonary hypertension exacerbation or right-sided heart failure should be admitted to a center with special expertise in pediatric pulmonary hypertension.

Prevention

- Management of the underlying etiologic origins can best prevent worsening of pulmonary hypertension and the likelihood of acute exacerbations.

Resources for Families

- Parents of Children With PH (Pulmonary Hypertension Association). www.phassociation.org/Parents
- Pulmonary Hypertension (Children's Hospital of Philadelphia). www.chop.edu/conditions-diseases/pulmonary-hypertension/about#.Vqeh5E8UXcs

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Chapter 78

Vocal Cord Dysfunction

Paula Barson, MA-CCC, SLP, and Joseph Piccione, DO, MS

Introduction/Etiology/Epidemiology

- Vocal cord dysfunction (VCD) can be described as inappropriate adduction or closure of the true vocal folds during inspiration and/or expiration and may result in upper-airway obstruction, stridor, or wheezing.
- VCD has been previously called
  - Fictitious asthma
  - Mimicking asthma
  - Irritable larynx
  - Laryngeal dysfunction
- Epidemiology
  - Increasing prevalence in children and adolescents
  - Can occur in children as young as 6 years of age
  - Female-to-male ratio of approximately 3:1
  - Often affects "high achievers" in academics and/or athletics
  - Possible comorbid psychiatric conditions include
    - Anxiety
    - Depression
    - Obsessive compulsive disorder
    - Borderline personality disorder

Pathophysiology

- The vocal cords adduct, leaving only a small posterior glottic opening.
- Adduction occurs during inhalation and/or exhalation.
- The exact etiologic origin is unknown.
- The laryngeal reflexes are mediated by the vagus nerve.
  - A change in laryngeal tone can lower the sensory threshold and induce laryngospastic reflexes.
- Triggers include
  - Exercise (especially competitive events) associated with increased body tension of the chest, shoulders, and neck
  - Strong smells (eg, perfumes, chlorine, certain foods)
  - Respiratory tract irritants
  - Allergens
  - Singing
  - Laughing
  - Hot and/or cold air

  - Reflux (gastroesophageal and/or laryngopharyngeal)
  - Postnasal drip
  - Upper respiratory infections
  - Psychological factors, including anxiety and stress

Clinical Features

- Sudden, episodic shortness of breath (resting or exertional)
- Intermittent hoarseness
- Most commonly associated with inspiratory stridor
- May have coexisting monophonic expiratory wheeze
- Chronic cough and/or frequent throat clearing
- Chest and/or throat tightness
- Difficulty with inhalation and/or exhalation
- Patient may describe "just having trouble getting air in"
- Patient may describe feeling like "breathing through a straw"
- No response to bronchodilators and/or corticosteroids
- May occur primarily indoors or outdoors for some individuals
- Commonly manifests during exercise
  - Lack of response to treatment of exercise-induced bronchoconstriction with albuterol
  - Description of "difficulty in getting air in" (with no cough, wheeze, etc)
  - In elite athletes, a minor degree of narrowing produces more limitation than might be expected
  - Many teenagers with VCD fit the psychological profile, as well

Differential Diagnosis

- Asthma (Box 78-1)
  - Patients often have asthma, but their symptoms are exaggerated by VCD.
- Panic attack
- Heart disease
- Physical deconditioning
- Croup
- Other fixed laryngeal obstruction

Diagnostic Considerations

- Obtain a detailed clinical history, with improvement or resolution of symptoms after treatment.
- Auscultation will demonstrate the origin of the respiratory noises in the neck, rather than the chest.
- A panting maneuver will open the glottis and result in improvement and/or resolution of the respiratory noises.

Box 78-1. Differentiating Vocal Cord Dysfunction from Asthma

Vocal Cord Dysfunction	Asthma
Chest tightness	Chest tightness
Throat tightness	No throat tightness
Stridor with inhalation	No stridor with inhalation
No true wheezing with expiration	Wheezing with expiration
Multiple triggers	Multiple triggers
Onset occurs <5 min after beginning exercise	Onset occurs >5–10 min after beginning exercise
Recovery period of 5–10 min	Recovery period of 15 min to several hours
No response to bronchodilators	Good response to bronchodilators
Patient rarely awakens at night	Patient almost always awakens at night with symptoms

- Laryngoscopy
  - — Considered the standard of reference; however, dysfunction is often not visualized at laryngoscopy
  - — Most commonly, the vocal cords appear healthy, and the voice quality is good
  - — Important for ruling out other laryngeal pathologic conditions
- Spirometry can show flattening on inspiratory limbs of the flow-volume curve.

Management

- Speech therapy consultation for breathing exercises
  - — Increases awareness of breathing patterns
  - — Clavicular versus diaphragmatic focus on inspiratory muscles
  - — Promotes relaxation of laryngeal mechanism
  - — Uses subglottic pressure
  - — Promotes the abducted position of the vocal folds
  - — Other therapeutic interventions
    - ▪ Progressive relaxation
    - ▪ Tensing and/or relaxing
    - ▪ Increasing awareness of body posture
    - ▪ Long-hard swallowing
    - ▪ Coughing
    - ▪ Throat clearing

  - Maximize vocal hygiene
  - Practice each exercise to maintain adequate technique skills
    - Slow, calm breathing to avoid hyperventilation
  - Hypnosis

Treating Associated Conditions

- Administer medical therapies for any comorbid gastroesophageal reflux disease and asthma.
- Consider referral to a mental health expert for evaluation and management of anxiety and stress.

Expected Outcomes/Prognosis

- Prognosis is excellent, with symptoms adequately treated or resolved in most patients within weeks to months.

When to Refer

- Evaluation should include laryngoscopy and speech therapy consultation, ideally by a team familiar with treating patients with VCD.

When to Admit

- VCD rarely requires hospital admission because the condition is self-limited.
- Admission may be required when VCD is associated with severe asthma exacerbation.

Prevention

- The patient's own awareness of the underlying mechanism for their respiratory distress may help prevent escalation of symptoms, from mild and brief to severe and prolonged.

Clinical Pearls

- VCD is a common cause of exertional dyspnea in adolescents and should be considered when symptoms do not improve with a trial of inhaled bronchodilators.
- Patients and families should be reassured that VCD is a self-limited problem that responds well to breathing exercises in most cases.

Chapter 79

Tic Cough (Habit Cough)

Casandra Arevalo, MD, and Lee J. Brooks, MD, FAAP

Introduction/Epidemiology/Etiology

Introduction

- Tic cough, also called *somatic cough syndrome,* is a dry cough without an organic cause. It may be subacute or chronic. It may also be known as *honking cough*, *barking cough*, and *nervous cough.*
- Tic cough is often mistaken for asthma, postnasal drip syndrome, or gastroesophageal reflux disease (GERD).
- It can manifest as a chronic cough that disturbs parents, teachers, or any other caretakers.
- It may lead to social disruption (school absence) and becomes more frequent in the presence of teachers and/or parents. It might decrease in intensity with an enjoyable activity (parties, sports, etc).
- It can manifest subsequent to an organic disease, such as a viral illness. In other patients, it can primarily be associated with a psychological disorder, such as anxiety or depression.
- Tic cough might coexist with other cough causing diseases (asthma, GERD, allergies, sinusitis).
- Cough tics can be viewed as a form of a vocal tic and may not be the sole tic in children with tic disorders. A careful history reveals that many children with cough tics have had other tics previously. For some children with cough tics, this is the first of many tics they will develop through childhood.

Epidemiology

- Onset occurs as early as 2 years of age.
- There is no sex predilection in children.
- More than 90% of cases of habit cough have been reported in patients <18 years of age.

Etiology

- One hypothesis is that an initial illness creates a learned subconscious model for the cough (a habit).
- It can be associated with psychogenic stress or with an initial viral respiratory tract infection illness, with subsequent coughing.
- An initial irritant sets up a pattern of coughing.
- There may be secondary gain, such as absence from school.

Clinical Features

- Characteristic features of tic cough include
  - Harsh, loud, honking or barking cough
  - Disruption of normal activities
  - Frequent presence of a secondary gain
- Timing
  - Intermittently throughout the day, usually disrupting activities
  - May worsen when parents, teachers, or doctors are present
  - May improve if the child is focused on other activities
  - Disappears during sleep
- May be associated with
  - Absence of wheezing, shortness of breath, and nighttime cough
  - Psychiatric disorders, such as conversion disorder or mixed anxiety and depressive disorder
  - Somatic manifestation of psychosocial problems, including school phobia, family problem, attention seeking, bullying
- Even though the cough sounds annoying, the child is usually unperturbed ("La belle indifference")
- May be accompanied by chin-on-chest posture, with the hand against the throat (as if to support the larynx)
- Can be very disturbing to parents, teachers, and other caregivers, often leading to school and social disruption
- Organic causes can be associated with habit cough

Diagnostic Considerations

- Habit cough is a diagnosis of exclusion.
- Careful history includes
  - Onset of cough
  - Factors that exacerbate or relieve the cough
  - Improvement of the cough at night or lack of improvement
  - Lack of response to therapy (antibiotics, inhaled or systemic steroids)
  - Symptoms and family history of asthma, GERD, cystic fibrosis, or other pulmonary disorders
  - Consider neurological tic disorders
- Evaluation of chronic cough may include
  - Physical examination
  - Chest radiography
  - Pulmonary function testing (pre- and postbronchodilator)
  - Methacholine challenge
  - Sputum cultures
  - Exhaled nitric oxide measurements
  - Evaluation for GERD
- Clinical findings, laboratory results, and imaging findings are usually negative.
- Cough generally does not wake the patient during sleep, although a child who wakes up at night for some other reason may then start coughing.

- Patients typically don't respond to medications such as antibiotics, inhaled steroids, antihistamines, decongestants, and cough suppressants.
- Diagnosis of tic cough should be established when the patient's cough manifests clinical features of tics, such as suppressibility, distractibility, suggestibility, variability, and presence of premonitory sensation.
- It is very important to obtain a careful history of other tics, such as sniffing, throat clearing, and blinking; such a history suggests that the patient has a multiple-tic disorder and may benefit from a neurological or psychiatric evaluation. If evidence for other tics is found, additional laboratory tests may be ordered, as appropriate.

Treatment

- Most cases of tic cough are managed conservatively.
- Psychological counseling and psychiatric intervention should be encouraged.
- Therapy is oriented to breaking the cough cycle, such as making suggestions that the cough can be stopped.
- Behavioral modification therapy, relaxation and guided imagery techniques, biofeedback, and suggestion therapy are usually curative.
- Nebulized lidocaine, benzocaine lozenges, and sips of water can break the cough cycle.
- A variety of pharmacological therapies prescribed by neurologists for tic disorders can be used successfully for cough tics. Many of these medications have clinically significant potential adverse effects and are therefore usually reserved for cough tics that don't resolve spontaneously, don't respond to behavioral approaches, and have a marked effect on the child's lifestyle, such as resulting in missing a lot of school.

Prognosis

- Many tic coughs resolve in weeks or months and never or rarely recur. If chronic, a tic cough can be a debilitating disorder that can affect patient and family quality of life.
- Tic cough is associated with rib fractures, vomiting, incontinence, syncope, bradycardia, laryngitis, and rupture of the subconjunctival veins and anal vasculature.

Clinical Pearls

- Tic cough should be considered in the differential diagnosis, with chronic cough in patients who do not show improvement with conventional therapies.
- Consider the diagnosis on the basis of the character of the cough, its absence during sleep, its improvement with distractions, and its intensification during stressful situations.
- Providing reassurance to both patients and their parents is the most important first step.

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Chapter 80

Smoke Inhalation

Juan C. Martinez, MD, FAAP

Introduction/Etiology/Epidemiology

- Smoke inhalation affects a small population of pediatric patients admitted for burns. In a retrospective review of 5,959 pediatric patients admitted to Parkland Burn Center over 35 years, inhalation injury was identified in 3.1% of burned individuals.
- Smoke inhalation injury can involve the upper airway (supraglottic), lower airway (infraglottic), or lung parenchyma. The degree of airway injury depends on the duration of smoke exposure and the composition of the smoke. Toxic combustion products are simple asphyxiants, irritant toxins, and chemical asphyxiants.
- Flame and inhalation injuries are more common in older children, according to some large series.
- Inhalation injury with burns significantly increases the odds of mortality to 14:1.
- Toxic by-products of smoke—carbon monoxide and cyanide—are primarily responsible for mortality. Other potential smoke compounds that may contribute to pathologic findings include acrolein/propanol, aldehydes, ammonia, hydrogen chloride, hydrogen sulfide, phosgene, and sulfur dioxide.

Pathophysiology

- Mouth breathing promotes laryngeal and large-airway damage.
- Injury can be classified as upper-airway thermal injury, chemical irritation of the respiratory tract, or systemic toxic gas toxicity.
- The main pathologic features are bronchospasm, pulmonary edema, bronchopneumonia, and ventilation-perfusion mismatch.
- Systemic inflammatory response syndrome is promoted by excess formation of reactive oxygen species.
- Carbon monoxide is likely the primary cause of death in most cases.
- Carbon monoxide and cyanide gas exposure, derived from sources such as nylon, silks, and plastics, contribute to death.
- Airway necrosis contributes to poor mucociliary clearance and infection.
- Small-airway obstruction predominates, with mucus plugging and bacterial infection common manifestations.

Clinical Features

- Important historical factors include location and duration of exposure, enclosed area, and loss of consciousness.
- Altered consciousness is seen in severely affected victims. This could be due to hypoxia from pulmonary injury or the toxic effects of increased carbon monoxide and/or cyanide levels in the body.
- Facial and upper-airway burns may be present.
- Soot may be present in the airway secretions.
- Lack or absence of symptoms does not exclude clinically significant pulmonary pathologic findings.
- Stridor, wheezes, rales, cough, or diminished breath sounds may be present.
- Cyanosis may be present.
- Hypoxemia from ventilation-perfusion mismatch is usually reflective of lower-airway involvement.

Diagnostic Considerations

- Clinical history and physical examination findings may include the presence of superficial burns, especially facial and upper-airway involvement.
- Direct evidence of superficial lower-airway burns may be found via bronchoscopy.
- Chest radiographs may demonstrate patchy atelectasis, pulmonary edema, bronchopneumonia, and hyperinflation if bronchospasm is present.
- Arterial blood gas and co-oximtery: Although carboxyhemoglobin levels should be obtained, the level of carboxyhemoglobin is a poor predictor of the severity of smoke inhalation. Metabolic acidosis with an increased lactate level >10 mmol/L in the setting of smoke inhalation suggests cyanide poisoning and supports empirical antidotal treatment of severely affected victims.

Management

- Administer 100% oxygen (fraction of inspired oxygen [F_{IO_2}] of 1.00) immediately (preferably at the scene) to reduce carboxyhemoglobin levels.
- Perform fluid resuscitation, with care not to promote worsening pulmonary edema.
- Perform close serial monitoring of arterial blood gas and carboxyhemoglobin levels.
- Intubation is generally indicated in the case of extensive face and neck burns and evidence of inhalation injury. Early intubation should be considered because of edema of the supraglottic larynx, which develops within minutes to hours. A major pitfall is the failure to appreciate the possibility of rapid deterioration.
- Wean the F_{IO_2} to below 0.4 as rapidly as tolerated to limit oxygen toxicity.
- Minimize ventilator-induced lung injury with low tidal volume and permissive hypercapnia strategy.

- Consider inhaled nitric oxide as short-term rescue therapy if needed for acute pulmonary hypertension and/or hypoxemia.
- Chest radiographic abnormalities can occur within the first 24–48 hours, so consider repeating radiography at that time if clinically indicated.
- Monitor the patient for lower-airway infection with sputum culture and gram stain.
- Bronchoscopy has a limited role, primarily to clear debris and enable diagnosis of infection. It may become more useful as the grading criteria improve and become standardized.

Treating Associated Conditions

- Administer appropriate antibacterial agents, guided by culture findings.
- β-agonists may optimize oxygenation and improve ventilation-perfusion ratio mismatch.
- Hydroxocobalamin is the cyanide antidote of choice and should be administered promptly if cyanide poisoning is suspected.
- Pulmonary hygiene can improve mucociliary clearance.

Expected Outcomes/Prognosis

- Mortality has improved overall (Figure 80-1) but remains most affected by inhalation injury and, to a lesser extent, total body surface area burn.

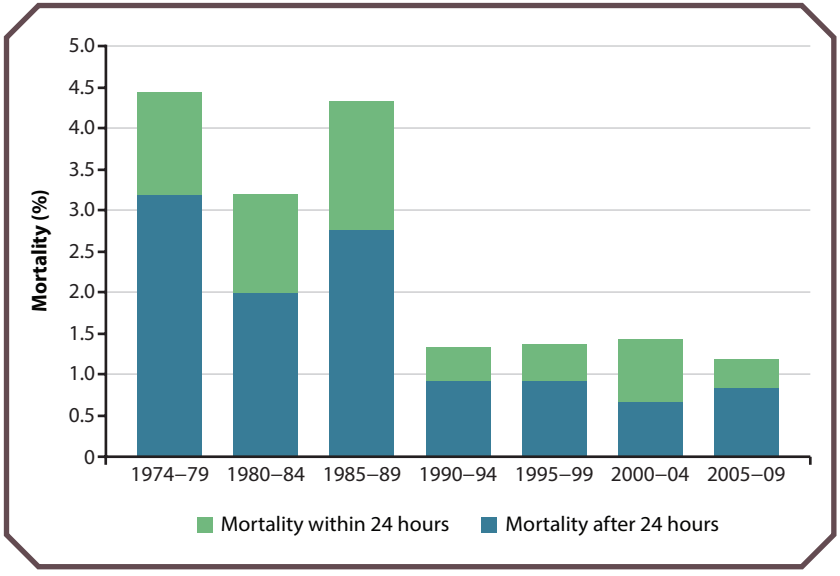

Figure 80-1. Changes in mortality due to burn injury over the past 40 years. From Saemon M. Epidemiology and outcomes of pediatric burns over 35 years at Parkland Hospital. *Burns*. 2016;202–208. Copyright 2016, with permission from Elsevier.

Resource for Families

- Home Fire Safety (American Red Cross). www.redcross.org/get-help/prepare-for-emergencies/types-of-emergencies/fire

Chapter 81

Hydrocarbon Aspiration

Juan C. Martinez, MD, FAAP

Introduction/Etiology/Epidemiology

- The main pediatric exposures to hydrocarbons include accidental ingestion and intentional inhalational abuse by adolescents.
- Most accidental ingestions occur in children <5 years of age. The highest-risk exposures occur in boys 1–2 years of age.

Pathophysiology

- Toxicity is related to the amount of hydrocarbons ingested, as well as volatility, surface tension, viscosity, and lipid solubility. Vomiting increases the risk of pulmonary involvement.
- Rapid and severe pulmonary edema is likely related to loss of surfactant and direct tissue destruction.
- Hydrocarbons with low viscosity and surface tension and high volatility (eg, gasoline, kerosene, lighter fluid) are associated with increased respiratory symptoms and greater risk of aspiration (Figure 81-1).
- Hydrocarbons disrupt surfactant and dampen pulmonary compliance.
- They can cause direct pulmonary injury, with direct inflammatory response and pulmonary edema, necrosis, and chemical pneumonitis.
- Bronchospasm, edema, and ventilation perfusion mismatch may all contribute to hypoxemia.
- Inhaled hydrocarbons are absorbed through the lungs and act as central nervous system (CNS) depressants. Inhibition of N-methyl-D-aspartate receptors with acute exposure is believed to contribute to CNS depression.
- Pneumatoceles can occur and usually resolve over weeks to months.

Clinical Features

- Respiratory symptoms usually develop quickly after the aspiration event, but there may be a delay in presentation (Table 81-1). Forty-six percent to 65% of patients are asymptomatic at presentation.
- The most common signs and symptoms include fever, vomiting, cough, and tachypnea.
- Symptoms typically worsen during the initial 24–48 hours and resolve over 10–14 days.
- Fever, tachypnea, and tachycardia suggest pneumonia.

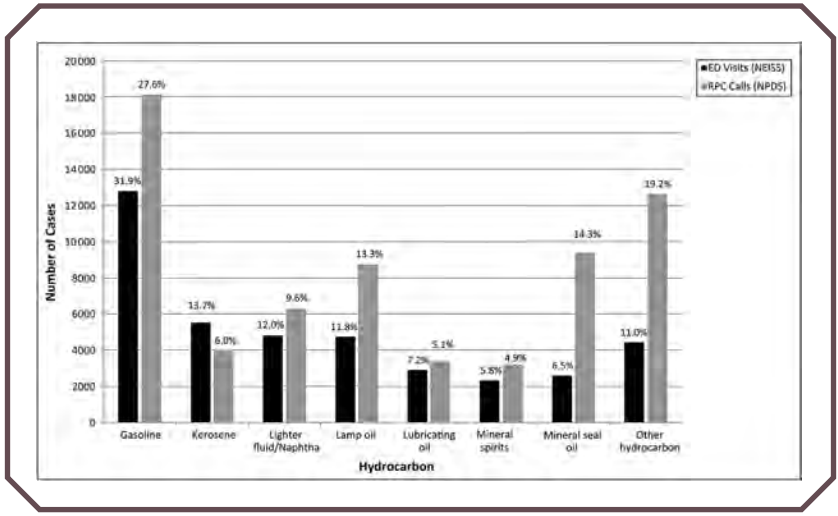

Figure 81-1. National Electronic Injury Surveillance System (NEISS) and National Poison Database System (NPDS) hydrocarbon products involved in exposure. All NEISS data represent national estimates of patients with hydrocarbon-related exposures treated in U.S. emergency departments (ED), and all NPDS data represent the actual number of hydrocarbon-related human exposure calls placed to regional poison centers (RPC). From Jolliff HA, Fletcher E, Roberts KJ, Baker SD, McKenzie LB. Pediatric hydrocarbon-related injuries in the United States: 2000–2009. *Pediatrics.* 2013;131:1139–1147.

- Adventitious breath sounds are often absent early in presentation. When present, wheezing and rales are often localized to the lower lobes.
- One-third of patients develop CNS symptoms, such as CNS depression, agitation, and restlessness. CNS symptoms correlate with pneumonia.
- Leukocytosis is a marker of lower-airway involvement and severity.
- Severe respiratory complications include respiratory failure that necessitates mechanical ventilation, development of acute respiratory distress syndrome, air leak syndrome, and multiple organ failure.

Diagnostic Considerations

- The typical history of hydrocarbon ingestion and/or aspiration may or may not include respiratory manifestations. Initial coughing, choking, or vomiting may suggest aspiration, but symptoms may not progress.
- Initial radiographic findings are often normal. However, caution must be exercised because pulmonary opacities may develop up to several hours after hydrocarbon ingestion. Radiographic findings may include increased bronchovascular markings, coalescing areas of atelectasis, and localized air trapping in the lower lobes (see Figure 81-2). Pleural effusion, pneumatocele, pneumomediastinum, and pneumothorax are less common.

Table 81-1. Progression of Respiratory Manifestations and Chest Radiographic Abnormalities after Hydrocarbon Aspiration				
Time Since Ingestion and Potential Outcomes	**Respiratory Symptoms**	**Signs from the Respiratory System**	**Chest Radiographic Findings**	**Other Findings and Comments**
Phase I: 0–1 h				
Ingestion without or with aspiration	Asymptomatic (45%–65% of ingestions) or Gasping, choking, and cough	Absent or Tachypnea, grunting, retractions (if rapidly progressive pneumonitis)	Absent	Vomiting, gagging, prolonged cough, and gasping (suggest aspiration)
Phase II: >1–8 h				
No lung involvement (approximately 85% of all ingestions) Pneumonitis (15% of all ingestions) Rapidly progressive pneumonitis (5% of pneumonitis cases)	Asymptomatic or Cough (if pneumonitis)	Usually absent (20%–40%) of pneumonitis cases) Tachypnea, wheezing, or crackles (if pneumonitis) Grunting, intercostal retractions (if rapidly progressive pneumonitis)	Unilateral or bilateral linear perihilar densities or alveolar infiltrates involving middle and lower lung fields (70% of patients presenting to the emergency department)	Fever (30%–65% of pneumonitis cases) Lethargy, tachycardia, hypoxemia, and hypocapnia (if rapid progression)
Phase III: 9–48 h				
Zenith of pneumonitis symptoms ARDS and cardiorespiratory failure (if rapidly progressive pneumonitis—5% of pneumonitis cases)	Cough and dyspnea Hemoptysis, pink and frothy sputum (signs of pulmonary edema in severe cases)	Tachypnea Cyanosis, grunting, increased work of breathing (in severe cases) Dullness on percussion Crackles, wheezing, decreased breath sounds or bronchial sound	Progression of radiographic abnormalities Alveolar infiltrates coalesce to form consolidation Pneumatoceles and air leak syndrome may develop	Fever, tachycardia, restlessness, agitation, hypoxemia Stupor and seizures (in severe cases) Deaths might occur within the first 24 h (if ARDS)

Table 81-1. Progression of Respiratory Manifestations and Chest Radiographic Abnormalities after Hydrocarbon Aspiration, *continued*

Time Since Ingestion and Potential Outcomes	Respiratory Symptoms	Signs from the Respiratory System	Chest Radiographic Findings	Other Findings and Comments
Phase IV: 3–10 d				
Pneumonitis improves (90% of cases) Air leak syndrome (especially in severe cases)	Amelioration of cough and dyspnea Intense symptoms if severe lung involvement or air leak syndrome	Tachypnea, decreased breath sounds or Absence of abnormal findings Variable findings if rapidly progressive pneumonitis and respiratory failure in previous stages	Alveolar infiltrates coalesce until the fourth day Pleural effusion, atelectasis Pneumatoceles and air leak syndrome—that is, subcutaneous emphysema, pneumomediastinum, pneumothorax (especially if on mechanical ventilation)	If fever persists or recurs: potential bacterial superinfection
Phase V: 11 d to weeks or months				
Pneumatoceles Gradual resolution of clinical and radiographic abnormalities Persistent lung disease in cases of severe pneumonitis	Usually asymptomatic	Usually unremarkable or Tachypnea and decreased breath sounds may persist (in severe cases)	Pneumatoceles become apparent as infiltrates resolve Late air leak syndrome	Mechanically ventilated children may stay in the intensive care unit for several weeks

ARDS, acute respiratory distress syndrome. From Makrygianni EA, Palamidou F, Kaditis AG. Respiratory complications following hydrocarbon aspiration in children. *Pediatr Pulmonol.* 2016;51:560–569.

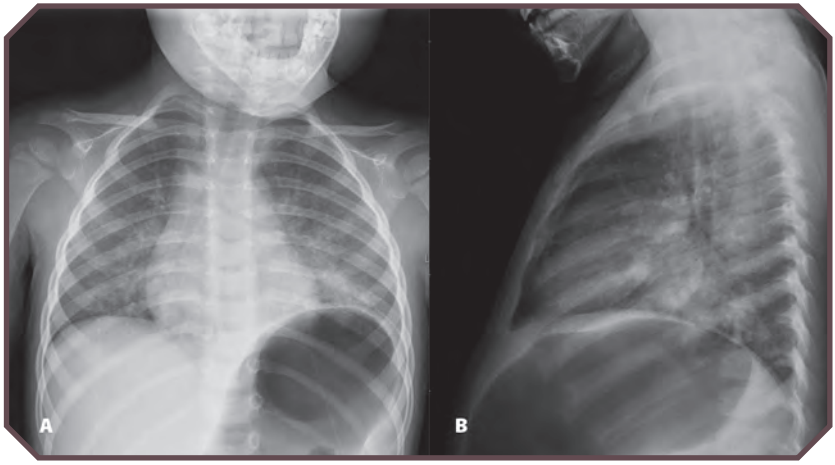

Figure 81-2. Hydrocarbon ingestion in a 2-year-old boy who drank furniture polish. A. Frontal and B. Lateral chest radiographs obtained 5 hours after presentation demonstrate left basilar and perihilar patchy opacities. (Not shown: The initial chest radiographic findings obtained 1 hour after ingestion were normal.)

Management

- Avoid gastric lavage or emetic therapy (Figure 81-3).
- Symptomatic therapy should be guided by a reasonable observation time of 6–8 hours.
- Asymptomatic children with normal chest radiographic findings do not typically require hospitalization. Asymptomatic children with abnormal chest radiographic findings may not require admission if they do not develop symptoms over 6 hours of observation. Children who are symptomatic with abnormal chest radiographic findings usually require hospital admission.
- Hospitalization is indicated if respiratory symptoms such as tachypnea or mental status changes manifest within the first 2 hours.
- Provide supportive care with bronchodilators if bronchospasm is present.
- Empirical antibiotic therapy is controversial but may have a role if there is a high suspicion of pneumonia.
- Surfactant may improve gas exchange abnormalities in ventilated patients.

Expected Outcomes/Prognosis

- Most children experience complete clinical recovery.
- Pulmonary function recovery can be complete, but flow deficits with residual small-airway obstruction can persist. Most radiographic abnormalities resolve completely.

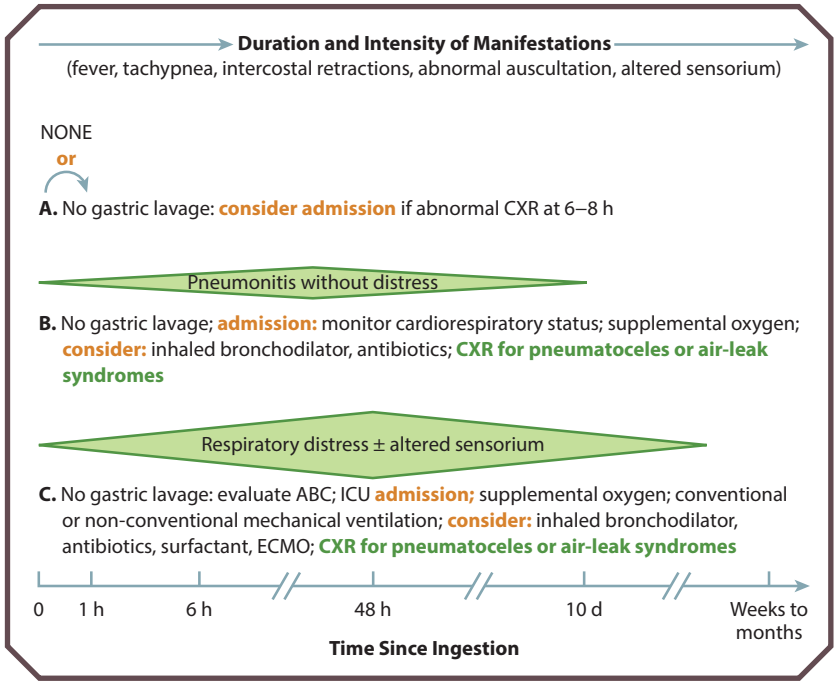

Figure 81-3. Three potential clinical scenarios are shown after ingestion of petroleum distillates and the proposed management plan for each of them. A. The child has no or minimal symptoms briefly after ingestion; admission may be considered in the presence of abnormal findings on a chest radiograph (CXR). B. Initial symptoms deteriorate over the first 6–8 hours and reach maximum intensity at 48 hours, followed by progressive improvement. Admission for monitoring of cardiorespiratory status is indicated. C. Rapid progression of aspiration pneumonitis leads to acute respiratory failure. Evaluation of airway, breathing, and circulation (ABC) is required, and admission to an intensive care unit (ICU) is recommended. Extracorporeal membrane oxygenation (ECMO) may be necessary. From Makrygianni EA, Palamidou F, Kaditis AG. Respiratory complications following hydrocarbon aspiration in children. *Pediatr Pulmonol*. 2016;51:560–569. © 2016 Wiley Periodicals, Inc.

Prevention

- Child-resistant packaging of low-viscosity products has been mandatory since the 2001 U.S. Consumer Product Safety Commission Report.
- Improperly labeled, unsecured, and improperly stored products remain a risk.
- Parental education about proper storage of chemicals and dangerous household products is essential. Direct supervision and identification of high-risk areas of the home are important. Store dangerous products in elevated locations, and use safety locks.

Resources for Families

- Poison Proofing Your Home (eMedicine). www.emedicinehealth.com/poison_proofing_your_home/article_em.htm
- National Poison Control Center. 800/222-1222

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Chapter 82

Drowning

Christopher M. Cielo, DO, FAAP

Introduction/Epidemiology

- Drowning is the process of experiencing respiratory impairment from submersion or immersion in liquid.
- Drowning outcomes can be classified as "death," "no morbidity," or "morbidity" (further categorized as "moderately disabled" or "severely disabled"). According to the World Health Organization, there were 360,000 drowning deaths worldwide in 2015. It is the leading cause of death for boys 5–14 years of age worldwide.
- Drowning is second only to motor vehicle injury as the leading cause of death from unintentional injury in the United States.
- Most drowning deaths in children <1 year old occur in the bathtub.
- The highest rate of drowning occurs in 1- to 4-year-olds left unattended at residential pools. Flooding and irrigation ditches are other sources of drowning.
- Older children are more likely to drown in open water. Risk factors include male sex, black race, and alcohol use.
- Medical conditions, including epilepsy and prolonged QT syndrome, increase the risk for drowning.

Pathophysiology

- Drowning may occur from the airway going below the surface of the water (submersion) or liquid being splashed over the face (immersion).
- Young children may struggle for 10–20 seconds, and adolescents may struggle for 30–60 seconds before submersion.
- Initially, water entering the mouth is spat out or swallowed and/or the victim holds his or her breath.
- When the inspiratory drive becomes too high to resist, water is aspirated into the airways.

Pulmonary

- Aspiration of water may lead to laryngospasm.
- Additional aspiration continues, and hypoxemia quickly leads to loss of consciousness.
- Water in the alveoli causes washout of surfactant and disrupts the osmotic gradient. This disrupts the integrity of the membrane, increasing permeability and causing electrolyte shifts.
- The end result is pulmonary edema, atelectasis, and bronchospasm.

Cardiovascular

- Initial tachycardia leads to bradycardia, then pulseless electrical activity and ultimately asystole.
- A progressive decrease in cardiac output contributes to hypoxia. By 3–4 minutes, myocardial hypoxia leads to circulatory failure.
- There is a progressive decrease in arterial blood oxygen saturation, and the victim loses consciousness from hypoxia.

Neurological

- Profound hypoxia and medullary depression eventually lead to death.
- Hypothermia can reduce the consumption of oxygen in the brain, delaying cellular anoxia and adenosine triphosphate depletion.

First Response

Rescue

- In areas where lifeguards are present, fewer than 0.5% of rescues require cardiopulmonary resuscitation (CPR), but almost 30% of rescues by bystanders require CPR.
- If possible, assist the victim from outside the water by using a pole or buoy.
- Emergency medical services should be notified as soon as safely possible.

Initial Resuscitation

- In-water resuscitation may increase the likelihood of a good outcome if performed by a trained rescuer.
- If only in respiratory arrest, the victim will usually respond to rescue breaths alone.
- If there is no response to rescue breaths, the victim should be removed from the water as quickly as possible. Immediate CPR efforts are critical.
- Five rescue breaths should be given because water in the airways makes ventilation more difficult.
- Because drowning causes a primary respiratory failure, CPR with chest compressions alone is not recommended.
- Vomiting is common in drowning resuscitation. Abdominal thrusts should not be used to remove fluid because they may cause aspiration.

Initial Management

- The goal is to reverse anoxia from submersion as quickly as possible and limit secondary hypoxic injury.
- When available, bag-mask ventilation with 100% oxygen should be used to correct hypoxia.
- The cervical spine should be protected if there is potential for traumatic neck injury.
- Wet clothing should be removed to prevent ongoing heat loss.

Hospital-Based Care

- Patents with increased work of breathing or hypercapnia should be treated with mechanical ventilation.
- In unconscious patients, after securing the airway and restoring circulation, serial blood gases should be monitored for resolution of respiratory or metabolic acidosis. Respiratory acidosis is caused by hypoventilation, and metabolic acidosis is caused by lactic acidosis induced by tissue hypoxia.
- Patients should be rewarmed if hypothermic during resuscitation.
- Management in the intensive care unit (ICU) is similar to treatment of acute respiratory distress syndrome.
- Because ongoing pulmonary edema may occur, ventilator settings should not be weaned in the first 24 hours.
- In some patients, pulmonary collapse will require extracorporeal membrane oxygenation.
- Most victims should be observed for at least 6–8 hours, with serial vital sign checks and examination for signs of respiratory distress or pulmonary edema, even if asymptomatic at arrival to the emergency department.

Treating Associated Conditions

- Pulmonary: Pneumonia is uncommon in the initial presentation but may occur from polluted water, aspiration, or nosocomial pathogens. If pneumonia is suspected, antibiotic coverage should include waterborne pathogens, such as *Pseudomonas* and *Proteus*.
- Cardiovascular: Management of shock with intravenous fluid resuscitation and inotropic agents may be necessary.
- Neurological: Because of the risk for irreversible central nervous system injury due to hypoxia, restoring oxygenation is critical. Seizures may be difficult to treat. If the patient has good oxygenation but is unresponsive, consider performing head computed tomography and a toxicology screen. Therapeutic hypothermia after initial resuscitation may reduce neurological damage. Consider measures to reduce increased intracranial pressure (elevating the head of the bed in the absence of cervical spine injuries).

Expected Outcomes/Prognosis

- Bimodal outcomes: Most victims have either very good outcome or severe neurological sequelae or death.
- Cardiopulmonary arrest usually leads to multiorgan failure and frequent poor neurological outcome when compared to those with just respiratory arrest.
- Outcome is dependent on the duration of submersion and the time until initiation of treatment. There is no clear difference in survival between cold-water and warm-water drowning.
- The need for >30 minutes of CPR after submersion can be used to predict poor outcomes.

- Initially comatose children may recover but usually do so in the first 1–3 days after drowning.
- Almost one-half of deeply comatose drowning victims admitted to the pediatric ICU die of hypoxic brain injury or have severe neurological damage.
- Intracranial hypertension is a predictor of poor outcome.

Prevention

- Anticipatory guidance provided by the pediatrician can be effective in reducing the incidence of drowning.
- Prevention strategies include appropriate supervision, swimming lessons, use of lifeguards, barriers to pools, and the use of personal flotation devices (PFDs) (Table 82-1).
- A family-centered approach can help identify risks specific to each child.
- For children who cannot swim, the caregiver should be a responsible adult who stays within an arm's reach of the child whenever he or she is in or near water.
- Appropriate PFDs should be worn in the pool at all times.
- No one should swim alone. Lifeguards rescue >100,000 Americans each year from drowning.

Table 82-1. Drowning Prevention Strategies

	In and Around the Home	Recreational
Sources of drowning	Buckets, bathtubs, pools, ponds, irrigation ditches	Swimming (lake, pool, ocean, water park), boating
Risks for drowning	Inadequate supervision, unanticipated access to water	Change in water conditions, reliance on inappropriate flotation devices, risky behavior
Strategies for prevention	Constant adult supervision around water, 4-sided fences for pools, teaching water safety to children and adults	Swimming in lifeguarded areas, wearing appropriate personal flotation devices, teaching water safety, avoiding alcohol and drugs

Adapted from Caglar D, Quan L. Drowning and submersion injury. In: Kliegman R, ed. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia, PA: Elsevier; 2015:561–568. Copyright 2015, with permission from Elsevier.

Resources for Families

- Sun and Water Safety Tips (American Academy of Pediatrics). www.aap.org/en-us/about-the-aap/aap-press-room/news-features-and-safety-tips/pages/sun-and-water-safety-tips.aspx
- Life Jacket Wear/Wearing Your Life Jacket (U.S. Coast Guard). uscgboating.org/recreational-boaters/life-jacket-wear-wearing-your-life-jacket.php
- Pool Safely (Consumer Product Safety Commission). www.poolsafely.gov

Chapter 83

Thoracic Tumors

Saumini Srinivasan, MD, MS

Introduction

- Primary pulmonary tumors are rare in infants and children and may be either benign or malignant.
- Metastatic tumor involvement is much more common than primary tumors.
- The lungs can be affected by therapies for childhood cancer; these complications may also be seen by the primary practitioner (see Chapter 84, Pulmonary Complications of Cancer Therapy).
- Primary pulmonary and thoracic tumors may arise in the lungs, the mediastinum, or the chest wall.
- These tumors may be diagnosed at any age, including at prenatal ultrasonography and incidentally on chest radiographs.

Airway Tumors

Tracheal Tumors

Papillomas

- Papillomas are proliferative lesions found on the skin or mucous membranes (Figure 83-1). (See also Chapter 49, Papillomatosis.)
- They can involve the larynx, trachea, and bronchi and are frequently multiple.
- Symptoms result from airway obstruction from the tumor.
- Pulmonary seeding has been noted in these tumors, and the human papillomavirus has a role in the pathogenesis.
- Patients present with hoarseness and stridor. Dyspnea results from progressive airway obstruction.
- These tumors are removed because of their tendency for growth and airway obstruction. However, repeat surgical procedures may be required because of their tendency to recur.

Hemangiomas

- Hemangiomas affect girls twice as often as boys.
- Hemangiomas manifest most often between 2 weeks and 2 months of age but can occur at any age.

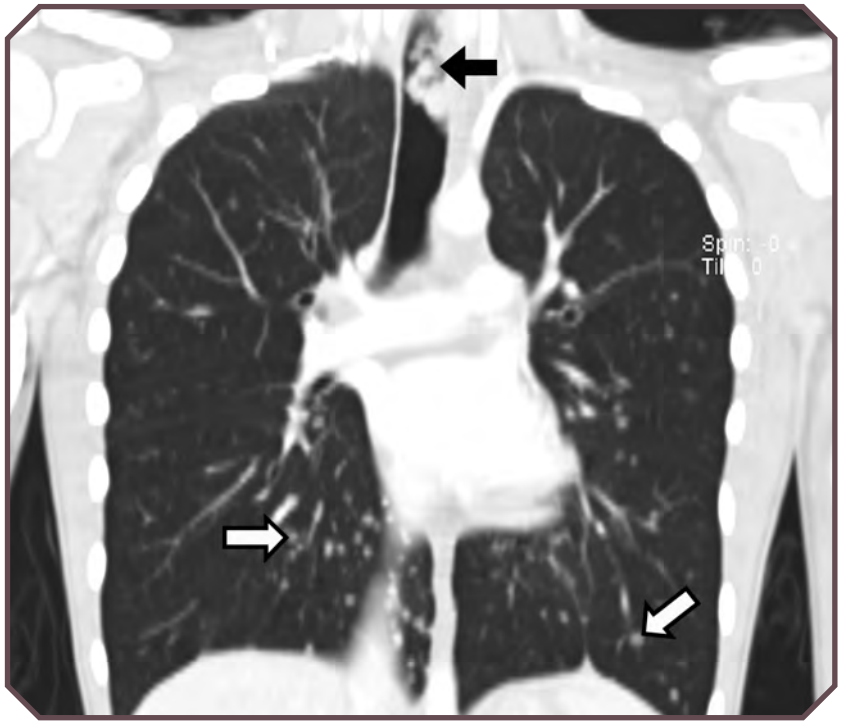

Figure 83-1. Tracheal papilloma in a 17-year-old girl. Coronal reconstructed computed tomographic image shows a lobulated tracheal papilloma (black arrow) and scattered nodules due to pulmonary seeding (white arrows) that are too numerous to count.

- The skin and the liver are the most common locations for infantile hemangiomas, which are usually treated conservatively because of their predictable course of early proliferation, followed by spontaneous involution.
- Tracheal cases are usually diagnosed by 6 months of age and manifest as recurrent croup or, less often, clinically significant bleeding.
- Cutaneous hemangiomas—particularly on the face, head, and neck—commonly coexist with tracheal lesions.
- Soft-tissue neck radiography of tracheal hemangiomas shows asymmetrical subglottic narrowing. However, lesions are better diagnosed at bronchoscopy (see Chapter 13, Subglottic Stenosis).
- Hemangiomas typically follow a predictable course of proliferation in the first year of life, followed by spontaneous involution during childhood.
- Vascular malformations have been reclassified in the past decade by the International Society for the Study of Vascular Anomalies. Those involving the chest wall, most often infantile hemangiomas and venous malformations, may manifest at any age.

- β-blockers and steroids are used to hasten the involution of hemangiomas. Rarely, complicated lesions may undergo embolization.
- The head and neck are the most common locations for venous malformations (previously termed *cavernous hemangiomas, cystic hygromas,* and *lymphangiomas*). These lesions can now be treated with percutaneous sclerotherapy and, less often, surgery.

Bronchial Adenoma

- Bronchial adenomas arise from the mucous gland of the bronchi.
- On the basis of pathologic findings, there may be 2 types:
  - — Ninety percent are of the carcinoid type but are rarely associated with the carcinoid syndrome.
  - — Ten percent are cylindromatous.
- Carcinoid tumors have malignant potential and can spread to local lymph nodes.
- Bronchial carcinoids arise in the Kulchitsky cells in the bronchial mucosa.
- Patients with both types of adenoma may present with recurrent pneumonia, chest pain, and, sometimes, hemoptysis.
- Bronchoscopy (Figure 83-2) with biopsy helps to establish the diagnosis; definitive treatment involves surgical resection.

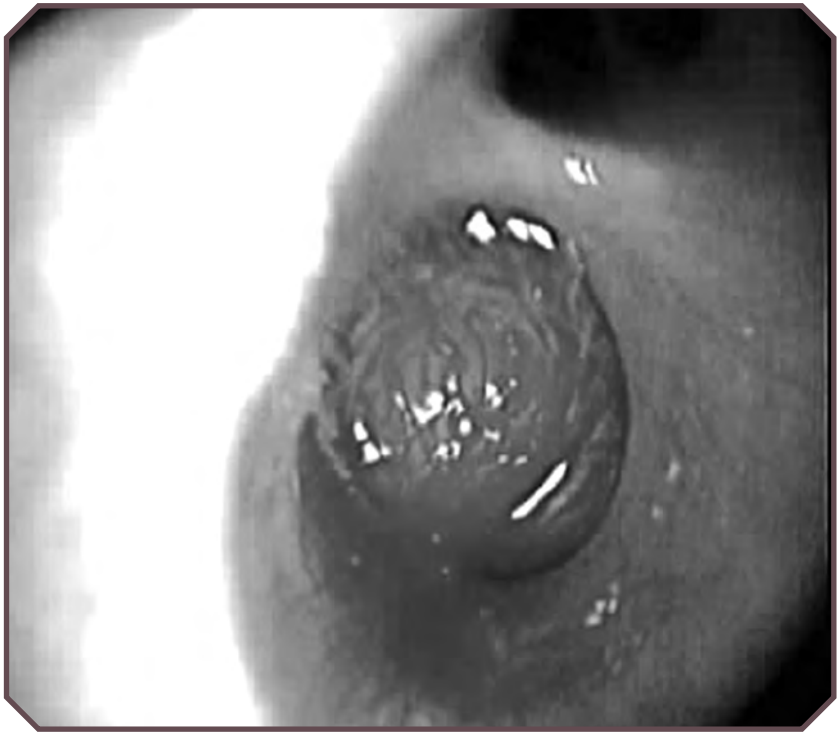

Figure 83-2. Bronchial adenoma (carcinoid) in a 15-year-old patient who presented with hemoptysis. Bronchoscopy shows a mass obstructing the right bronchus intermedius.

- Localized tumors can be resected by using a "sleeve" resection of the airway, thereby preserving the lung parenchyma.
- These tumors may spread to the surrounding airway, necessitating a lobar resection unless well localized to the airway wall.

Benign Pulmonary (Parenchymal) Tumors

- Hamartomas are tumorlike malformations formed from abnormal mixing of normal organ components.
  - Lung hamartomas are usually located in the periphery and are composed of cartilage.
  - These tumors are reported more commonly in adults with a solitary pulmonary nodule.
  - The rare form reported in infants can be large and necessitate surgical resection.
  - Differential diagnosis of hamartomas includes congenital cystic adenomatoid malformation.
- Plasma cell granulomas are also known as *inflammatory pseudotumors*, due to a polymorphic infiltrate of inflammatory cells at pathologic examination.
  - These rare tumors have been reported in patients as young as 6 years old in 1 series, in which 11% of patients were asymptomatic and 86% of the lesions were located in the lung periphery.
  - Surgical resection is the therapy of choice.

Malignant Tumors in the Lung

- Primary epithelial malignancies in the lung are rare, with 50 cases reported in the literature, mostly in adolescents and in association with respiratory papillomatosis.
  - Most patients are symptomatic, with cough, hemoptysis, and/or chest pain.
  - Malignant tumors may be misdiagnosed as pneumonia, which results in a delay in diagnosis.
- Bronchogenic carcinoma is the most frequent pulmonary malignancy in childhood and adolescence, after bronchial carcinoids.
  - These tumors have been described with several cell types in the pediatric population, with the exception of alveolar cell carcinoma, giant cell carcinoma, and carcinosarcoma.
  - Only 7 cases of squamous cell carcinoma in the pediatric population have been reported in the literature.
  - Squamous cell carcinoma is typically reported in adult men with a history of smoking; no risk factors have been identified in the pediatric population.
  - The prognosis depends on histologic findings, disease stage, and response to therapy, as in adults.

- Pleuropulmonary blastomas (PPBs) (Figure 83-3) are rare childhood tumors that develop during fetal lung development and contain both epithelial and mesenchymal elements.
  - These can be preceded by lung cysts, congenital cystic adenomatoid malformations, and congenital pulmonary airway malformations, especially in familial cases.
  - These tumors can be caused by a heterozygous mutation of the *DICER1* gene (13q32.13).
  - Twenty percent to 25% of affected children have a close relative with other neoplasias or dysplasias.
  - Although *DICER1* mutations have been reported in several different malignancies, the most common association is with PPB, cystic nephroma, and ovarian Sertoli-Leydig cell tumors.
  - PPBs are classified as type I (cystic), type II (cystic and solid), and type III (solid). Type I tumors have the best prognosis. However, transformation from type I to type II or III tumors can occur.
  - Clinically, patients with PPB present with nonspecific symptoms, including cough, respiratory distress, fever, chest pain, and anorexia. Type I tumors are seen in younger patients (median age, 9 months) as compared to types II and III (median age, 35 months).
  - Radiologically, a pulmonary or pleural mass is noted; 60% of lesions are right sided.
  - Rarely, pneumothorax or pneumomediastinum may be noted.
  - Treatment is surgical resection and chemotherapy with the use of sarcoma-targeted agents (vincristine, dactinomycin, cyclophosphamide, ifosfamide, doxorubicin, cisplatin), as well as radiation therapy.
  - Prognosis is poor, with 50% of patients dying within 2 years of diagnosis. Outcomes are poorer with mediastinal and pleural involvement.

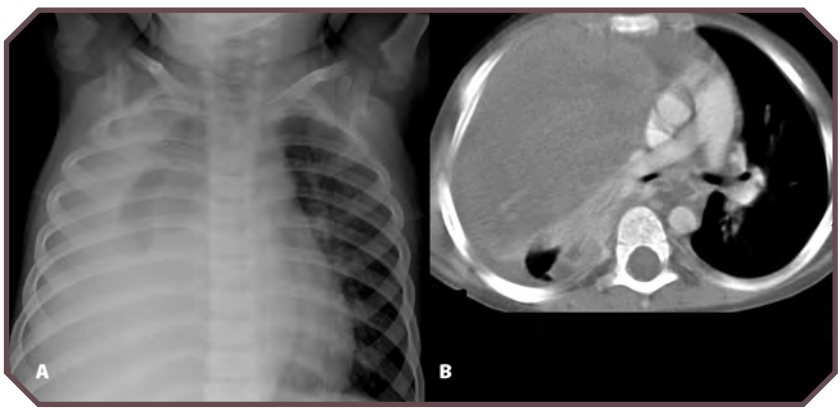

Figure 83-3. Pleuropulmonary blastoma in a 10-year-old girl with a persistent cough. A. Frontal chest radiograph demonstrates near-complete opacification of the right hemithorax, with right-to-left midline shift. B. Axial contrast-enhanced chest computed tomographic image shows a low-attenuation soft-tissue mass filling the right hemithorax.

Systemic Neoplasms Affecting the Lung: Leukemia

- Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy, with an annual incidence of 4,900 cases (2 to 5 cases per 100,000 children).
- T cell ALL is frequently seen in older boys; a mediastinal mass is present in about one-half of patients.
- Acute myeloid leukemia (AML) has an incidence of about 500 new cases each year in children aged 0–14 years.
- Clinically, bone pain results from involvement of the bone marrow and periosteum.
- Painless lymphadenopathy and hepatosplenomegaly result from extramedullary leukemia spread. Laboratory evaluation findings will be clinically significant for anemia, thrombocytopenia, and neutropenia.
- Standard therapy for ALL includes vincristine, steroids, and L-asparaginase; AML is typically treated with a regimen consisting of cytarabine, daunorubicin, and etoposide.
- Both types of malignancies require prophylaxis against *Pneumocystis jirovecii* pneumonia.
- Patients recovering from prolonged neutropenia may develop invasive pulmonary aspergillosis that can cause massive hemoptysis.
- Patients with AML and hyperleukocytosis (white blood cell [WBC] counts $>100 \times 10^9$/L) at presentation are at risk for developing pulmonary leukostasis. These patients develop tachypnea, hypoxia, pulmonary edema, or hemorrhage and may progress to respiratory failure. Therapy includes supportive measures, as well as early institution of chemotherapy and leukapheresis to decrease WBC counts.

Metastatic Pulmonary Tumors

- Metastatic pulmonary tumors comprise most malignant lesions in the lung in children. Pulmonary metastases arise from primary tumors from several sources, as summarized in Table 83-1.
- Pulmonary metastases may be solitary or multiple and are present at diagnosis or at evaluation for recurrence.
- Metastases can be diagnosed with computed tomography (CT).
- Surgical resection of metastases is considered after therapy for the primary tumor.
- Radiation therapy of the lung and/or chest may play a role in the management of lung metastases.

Mediastinal Tumors

- The mediastinum is the portion of the thorax that lies in between the lungs. It is divided into the following 4 compartments:
  - Superior mediastinum
  - Anterior mediastinum (anterior to the anterior plane of the trachea)

Table 83-1. Pediatric Tumors That Metastasize to the Lung	
Primary Site	**Tumor**
Skeletal system	Osteosarcoma Ewing sarcoma Chondrosarcoma Ameloblastoma
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 the liver Leiomyosarcoma Adenocarcinoma of the colon
Genitourinary tract	Wilms tumor Malignant rhabdoid tumor of the kidney Clear cell sarcoma of the kidney Gonadal germ cell tumor Trophoblastic choriocarcinoma
Endocrine system	Differentiated thyroid carcinoma Adrenocortical carcinoma

  - — Middle mediastinum (contains the heart and pericardium, ascending aorta, bifurcation of the pulmonary artery, trachea, the 2 mainstem bronchi, and the lower segment of the inferior vena cava)
  - — Posterior mediastinum (posterior to the anterior plane of the trachea)
- Anterior mediastinal masses are more likely to be malignant.
- Mediastinal lesions may remain asymptomatic and may be found incidentally on images.
- Respiratory symptoms result from compression of the airway, which causes narrowing of the trachea and bronchi.
- Signs at clinical examination depend on the level of partial obstruction.
  - — Stridor when the extrathoracic is partially obstructed
  - — Monophonic wheeze when the intrathoracic large airway is obstructed
- Pressure on the recurrent laryngeal nerve results in a brassy cough and hoarseness.
- Gastrointestinal symptoms can arise from pressure on the esophagus and include dysphagia and regurgitation.
- Tracheal or bronchial obstruction from a mediastinal tumor may result in dyspnea.

- Vascular symptoms may arise with compression of the great vessels, which is usually seen with malignant tumors.
- Although magnetic resonance (MR) imaging is important for evaluating the heart, great vessels, and mediastinum, CT remains the preferred modality for imaging the lungs. However, distinction of an enlarged thymus can be achieved with the use of ultrasonography or MR imaging.

Mediastinal Cysts

- Bronchogenic cysts (Figure 83-4) occur most often in the middle mediastinum (subcarinal) or lung parenchyma. They are rarely seen outside of these locations, in which case they are frequently asymptomatic.
- Subcarinal bronchogenic cysts may cause respiratory distress.
- Esophageal cysts (duplications, Figure 83-5) located in the middle mediastinum are usually right sided and are associated with the esophageal wall
- Frontal radiographs of esophageal cysts may show a well-defined, often subtle retrocardiac mass. Intracystic air is not seen because direct esophageal communication is rare.
- Neurenteric cysts lie in the posterior mediastinum against the vertebrae, free of the esophagus.
- Mediastinal cysts tend to be symptomatic (ie, cough or vomiting), due to pressure on thoracic structures.
- On radiographs, midline defects of the vertebra may occur just caudad to neurenteric cysts. When seen, they are highly suggestive of the diagnosis.
- Boys are affected more commonly than girls.

Thymic Tumors

- The thymus is located in the anterior superior mediastinum and is noted as a widened mediastinum in infants; the normal thymic shadow disappears by 1 year of age.
- Rarely, the enlarged thymus can cause respiratory obstruction.
- Thymomas, which arise from epithelial cells in the thymus, result in an anterior mediastinal mass and are rare (<2%) as a cause of mediastinal masses in children, as well as being associated with myasthenia gravis (MG).
- One-half of patients with cortical thymoma develop MG, while 15% of patients with MG have thymomas.

Teratoid and Germ Cell Tumors

- Teratoid tumors make up one-fifth of all mediastinal neoplasms in the pediatric age group; teratoma is the most common anterior mediastinal tumor in children.
- Teratomas are germ cell tumors that exhibit differentiation to somatic tissues of endodermal, mesodermal, and/or ectodermal tissue.

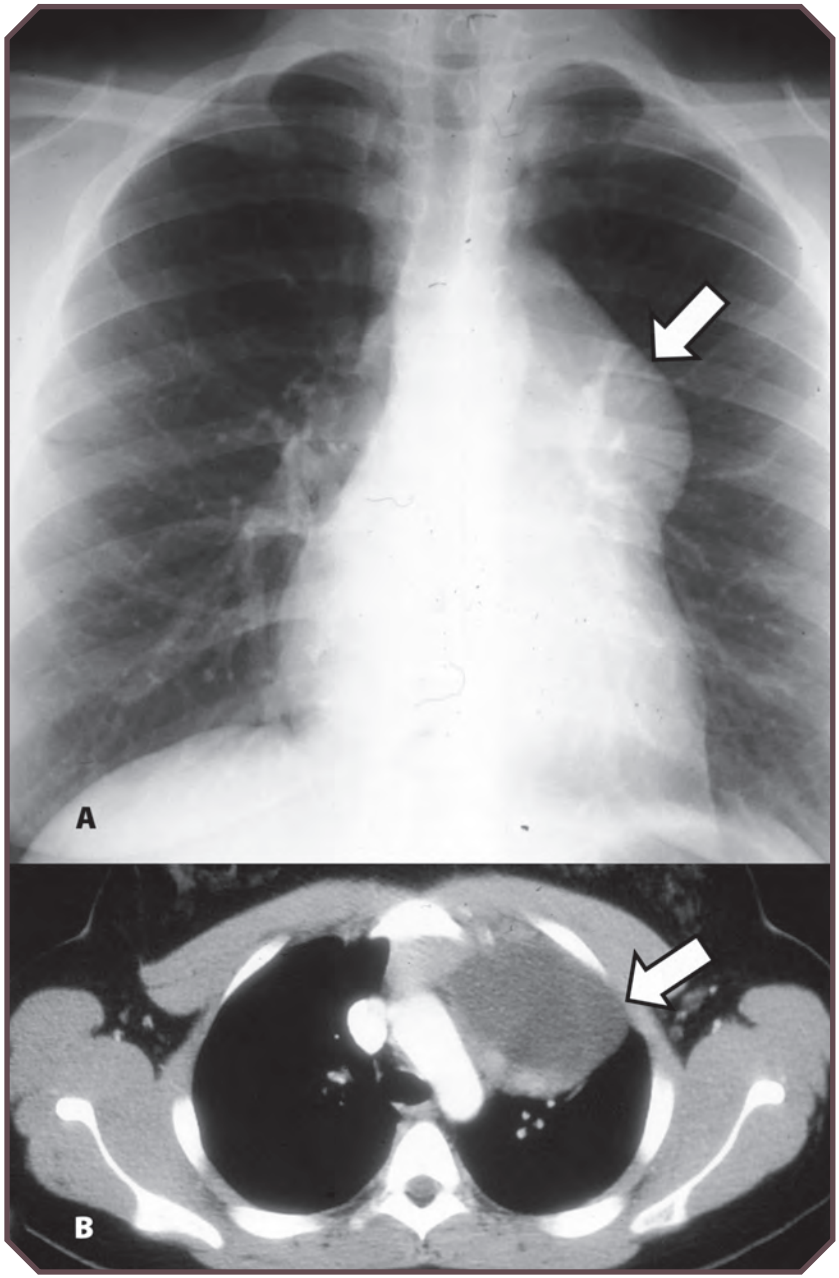

Figure 83-4. Bronchogenic cyst in a 12-year-old boy discovered incidentally. A. Frontal chest radiograph demonstrates a mass (arrow) overlying the left hilum, which is known as the "hilum overlay sign." B. Axial contrast-enhanced chest computed tomographic image shows a unilocular, fluid-attenuated, anterior mediastinal mass (arrow) at the level of the aortic arch, adjacent to the thymus.

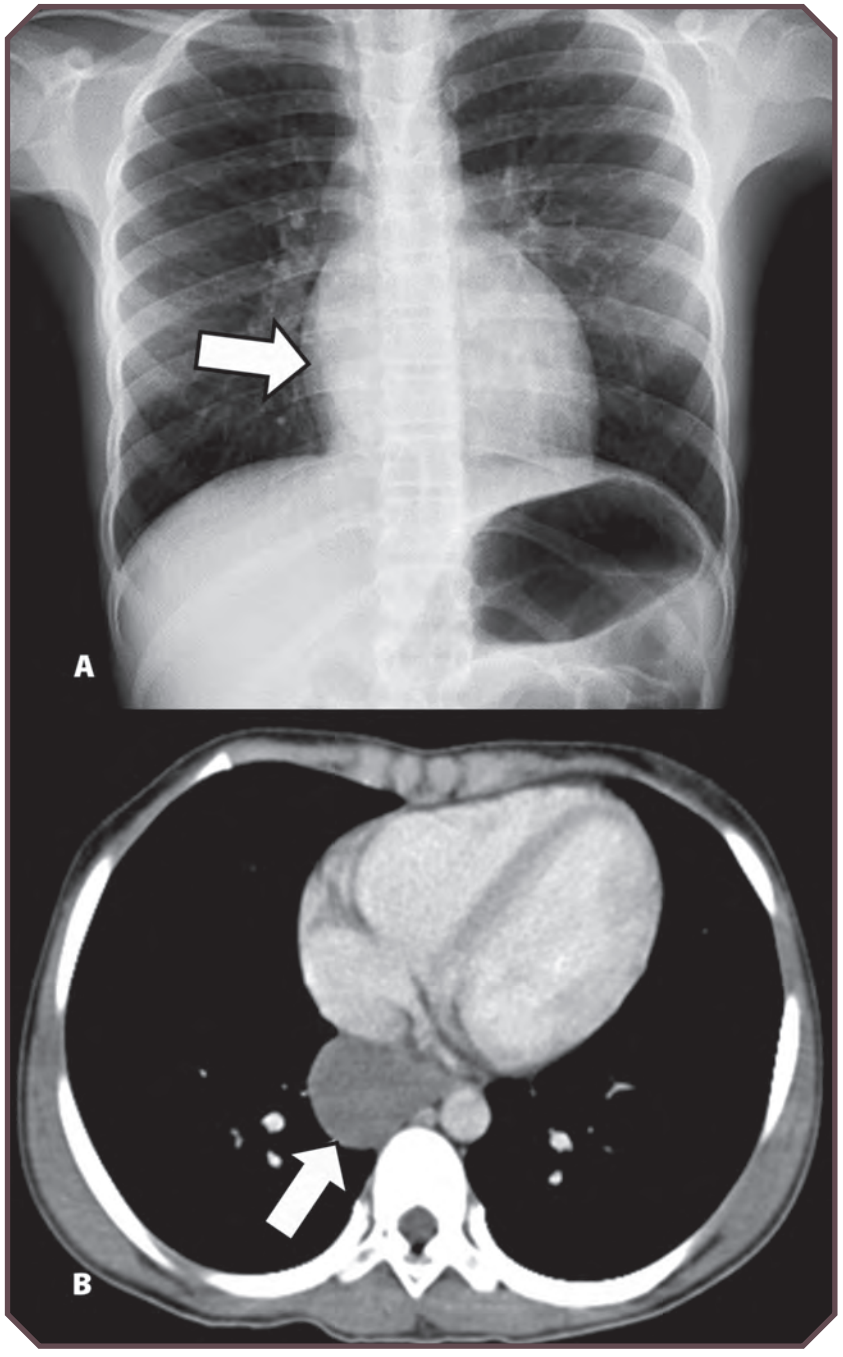

Figure 83-5. Esophageal duplication cyst in a 10-year-old girl with recurrent pneumonia. A. Frontal chest radiograph shows a well-defined retrocardiac mass (arrow). B. Axial chest computed tomographic image demonstrates a unilocular, fluid-attenuated (cystic), posterior mediastinal mass (arrow).

- Mediastinal teratomas are located in the anterior mediastinum. In the prepubertal age group, the tumor is more common in girls, with predominance in boys after puberty.
- Patients typically present with dyspnea, with evidence of a mediastinal mass on radiographs (Figure 83-6).
- There is an association with Klinefelter syndrome.
- Treatment is surgical resection after chemotherapy.
- Patients are at increased risk for developing hematopoietic malignancies.

Neurogenic Tumors

- Neurogenic tumors make up 25%–35% of all mediastinal tumors. They are generally located in the posterior mediastinum and include rare lesions, such as benign neurofibromas and neurilemmomas, as well as neuroblastomas, which are the most common extracranial solid tumors in children.
- Neuroblastomas arise in the adrenal medulla or from the ganglia of the sympathetic nervous system.
- Although these tumors may regress spontaneously in infants, older children often present with unresectable or metastatic disease.
- Seventy-five percent of neuroblastomas arise in the abdomen.
- The prevalence of thoracic and cervical tumors is higher in infants. These tumors predominantly affect young children, with most receiving diagnoses by 5 years of age.

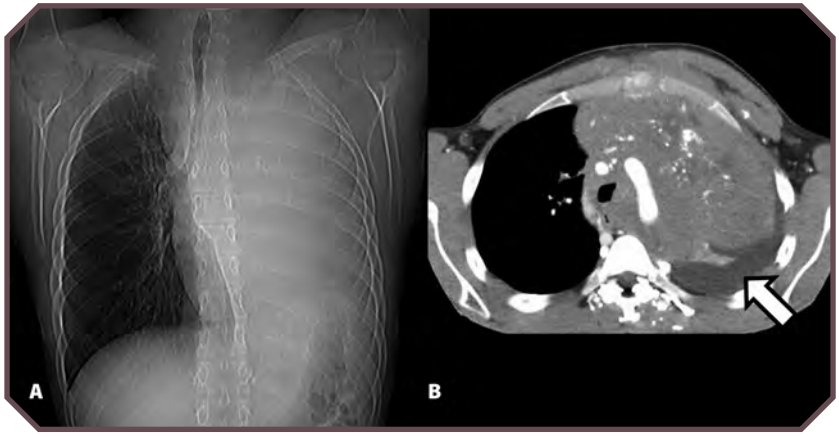

Figure 83-6. Germ cell tumor in a 16-year-old boy with dyspnea. A. Frontal chest radiograph shows complete opacification of the left hemithorax. B. Axial contrast-enhanced chest computed tomographic image demonstrates a large anterior mediastinal mass encasing the aortic arch and compressing the mediastinal veins. Numerous enhancing collateral veins posterior to the spine are noted, along with a left pleural effusion (arrow).

- Symptoms from thoracic tumors can be caused by superior vena cava syndrome from venous obstruction or from Horner syndrome, but these tumors may be discovered incidentally at chest radiography (Figure 83-7).
- Localized tumors are treated with surgical resection.
- Chemotherapeutic agents used include vincristine, doxorubicin, cyclophosphamide, cisplatin, and etoposide.
- Despite aggressive therapies, 5-year survival continues to be poor (40%) when compared to that for other childhood cancers.

Chest Wall Tumors

- Chondroma and chondrosarcoma are the main bone tumors of the chest wall, with 80% occurring in the ribs or sternum.
- Ewing sarcoma (also termed *Askin tumor* when involving the chest wall) is the second most common primary bone tumor after osteosarcoma. Up to 23% of Ewing sarcomas occur in the chest wall (Figure 83-8). Therapy is multimodal and includes chemotherapy, radiation therapy, and surgical resection. Recurrence is common and has a poor prognosis.
- Rhabdomyosarcoma of the chest wall may have metastatic disease at presentation and has a poor prognosis.
- Most chest wall tumors manifest with local pain and swelling.
- Osler-Weber-Rendu syndrome, a disorder of multiple arteriovenous malformations (AVMs), should be considered in patients with AVMs of the lung. Modern treatment of AVMs includes embolization and, less often, surgical resection, chemotherapy, or radiation therapy.

Resources for Families

- Patient/Family Education Materials (St Jude Children's Research Hospital). www.stjude.org/treatment/patient-resources/caregiver-resources/patient-family-education-sheets.html
- Patients and Families (Children's Oncology Group). childrensoncologygroup.org/index.php/patients-and-families
- Children's Neuroblastoma Cancer Foundation. www.cncfhope.org
- Children With Cancer: A Guide for Parents (National Cancer Institute). www.cancer.gov/publications/patient-education/guide-for-parents
- Childhood Cancer Resources (American Society of Clinical Oncology). www.cancer.net/navigating-cancer-care/children/childhood-cancer-resources
- International Society for the Study of Vascular Anomalies. www.issva.org

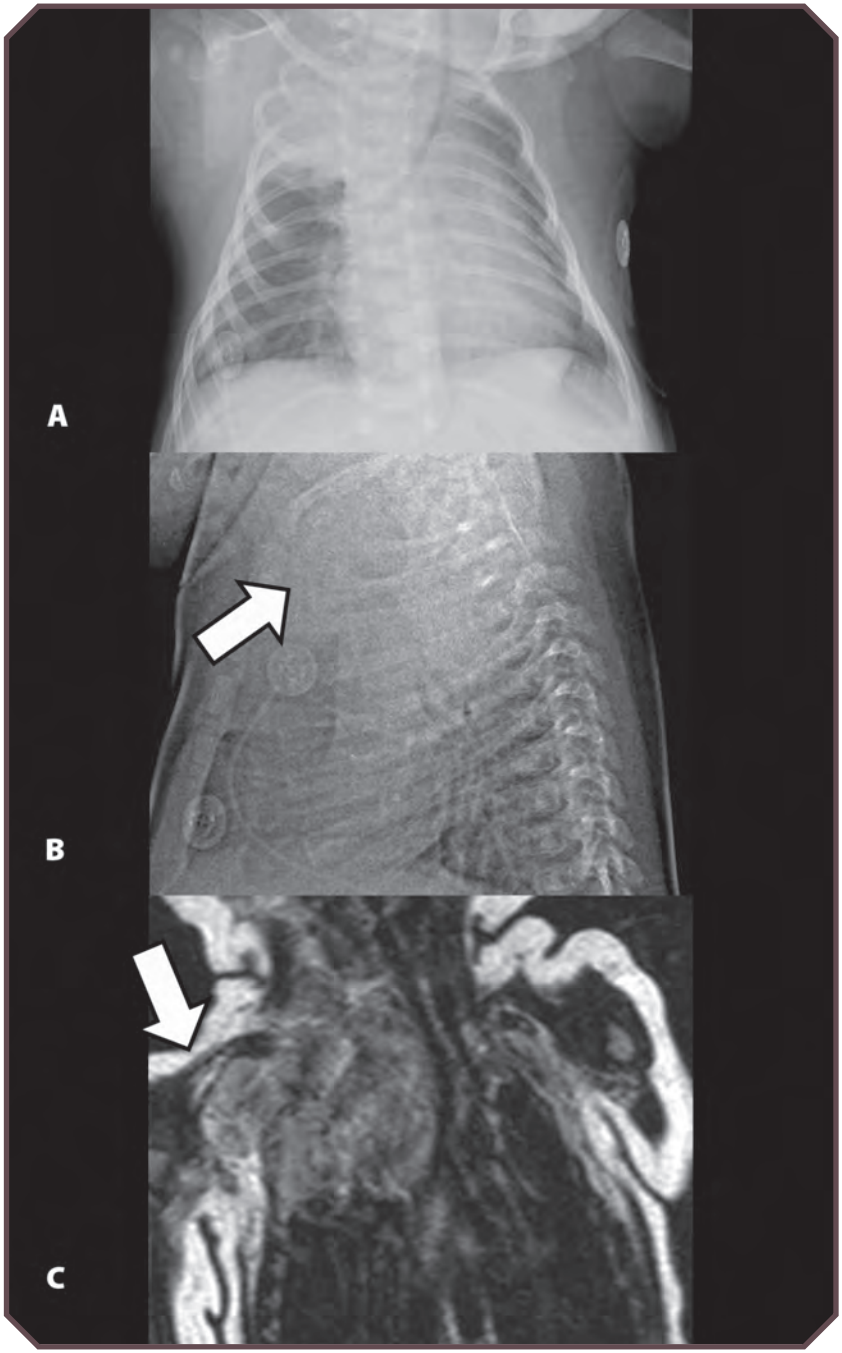

Figure 83-7. Neuroblastoma in an 18-month-old boy with opsomyoclonus. A. Frontal and B. lateral chest radiographs demonstrate a right apical chest mass. Note anterior displacement of the trachea on the lateral view (arrow). C. Coronal T2-weighted magnetic resonance image confirms a heterogeneous, hyperintense mass (arrow).

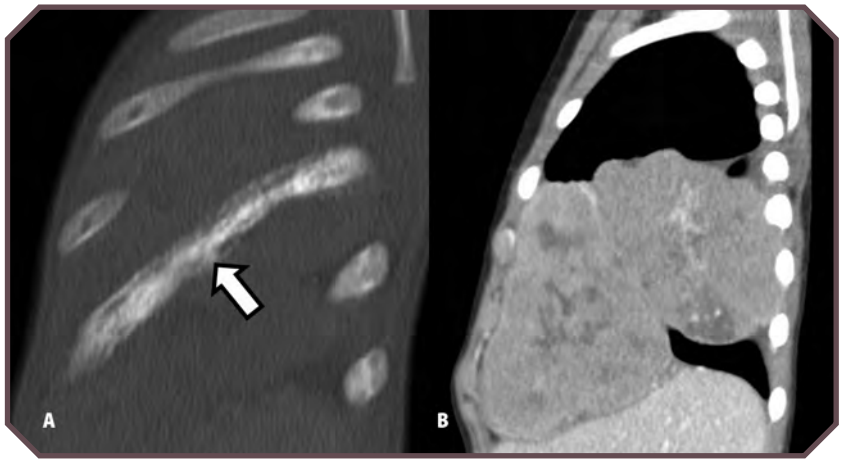

Figure 83-8. Ewing sarcoma (also termed *Askin tumor*) in a 10-year-old girl with a palpable lump. Sagittal A. reconstructed bone and B. soft-tissue windows from a contrast-enhanced chest computed tomographic examination show a heterogeneous, enhancing mass arising from the fifth rib. Note the extensive periosteal reaction and the moth-eaten appearance of the rib (arrow on A).

Chapter 84

Pulmonary Complications of Cancer Therapy

Saumini Srinivasan, MD, MS

Introduction

- Treatment of malignancies involves administration of chemotherapy and radiation therapy and/or the need for hematopoietic stem cell transplantation (HSCT).
- With the introduction of chemotherapy more than 60 years ago, prognosis in all childhood cancers has improved. Overall 5-year survival rates have increased from <30% in 1960 to >80% for all childhood cancers.
- Increased survival after childhood malignancies has resulted in increasing emergence and recognition of the pulmonary complications of these treatments.

Diagnostic Considerations

- Patients with radiation pneumonitis most commonly present with fever, cough, and shortness of breath. At examination, they are tachypneic with audible crackles.
- Kyphosis and/or scoliosis can result from radiation involving the chest, abdomen, or spine, as well as from spinal tumors. Severe deformities require surgical correction.
- Plain chest radiographs are only useful when pulmonary involvement is extensive. Computed tomography (CT) can be used to detect small areas of fibrosis, as well as infiltrates, and demonstrates the mosaic pattern characteristic of obliterative bronchiolitis (bronchiolitis obliterans).
- Pulmonary function testing helps to identify the presence of obstructive or restrictive defects. Serial lung function testing is useful in monitoring pulmonary toxicity. In the growing child undergoing therapy for cancer, lung function testing can also be useful in detecting abnormal lung growth.

Lung Injury Due to Infection

- Infections are a major cause of morbidity and mortality in children undergoing therapy for cancers.
- Several factors increase susceptibility to infections.
  - — Disruptions of mucocutaneous barriers provide a portal of entry for pathogens.
    - ▪ Indwelling catheters, endotracheal tubes and/or chest tubes
    - ▪ Chemotherapeutic agents, such as cytosine arabinoside and anthracyclines
    - ▪ Radiation delivered to the thorax and abdomen
    - ▪ Graft versus host disease in stem cell transplantation
  - — Depleted or abnormally functioning phagocytic cells occur from the malignancy or result from therapies.
    - ▪ Neutropenia results in increased susceptibility to bacterial infections (*Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa,* and several resistant gram-negative organisms).
    - ▪ Fungal infections (caused by *Candida* species, *Aspergillus, Fusarium,* and *Zygomycetes*) can also occur because of neutropenia.
    - ▪ The use of infliximab to treat graft versus host disease increases the risk of reactivation of *Mycobacterium tuberculosis* infection and the development of invasive aspergillosis.
    - ▪ Effect of impaired humoral and/or cell-mediated immunity: Hypogammaglobulinemia increases the susceptibility to infection by encapsulated bacteria, including *Streptococcus pneumoniae*, *Haemophilus influenzae,* and *Neisseria meningitidis*.
  - — Impaired cell-mediated immunity in patients with Hodgkin disease and in non-Hodgkin lymphoma makes patients more prone to fungal and viral infections, as well as intracellularly replicating bacteria like *M tuberculosis* and *Listeria*.
  - — Herpes simplex virus infections are commonly seen after allogeneic stem cell transplantation.
  - — The use of T cell–depleted marrow increases the risk for cytomegalovirus infection.
  - — Prolonged T cell depletion results in opportunistic infections like herpes zoster and *Pneumocystis jirovecii* pneumonia.
  - — Altered central nervous system function from tumors themselves or from opioid administration increases the risk of aspiration pneumonia. Aspirated organisms colonize, invade, and disseminate from the lungs. Reduced mucosal clearance from damage caused by antineoplastic therapy facilitates invasion and dissemination.

Immunizations

- Patients ≥6 months of age need to be immunized with the killed influenza vaccine once they have completed chemotherapy. For those who cannot receive this vaccine, everyone who comes into the home needs to be immunized.
- The routine childhood vaccine schedule should be started or resumed 3 months after the completion of chemotherapy.

Infectious Complications and the Upper and Lower Respiratory Tracts

Ear Infections

- Anatomic alteration from radiation damage increases the susceptibility to ear infections.
- Treatment involves the use of broad-spectrum antibiotics for 10–14 days.
- Prolonged neutropenia increases the risk for fungal mastoiditis.

Sinusitis

- Infections are usually bacterial or fungal.
- Acute sinusitis is usually caused by *S pneumoniae*, *Moraxella catarrhalis*, or *H influenzae*.
- Chronic sinusitis is usually caused by gram-negative bacteria (mainly *P aeruginosa*) or anaerobes. This is seen more commonly in nasopharyngeal carcinomas and in Burkitt lymphomas.
- Fungal sinusitis is seen in patients with acute leukemias, those with aplastic anemias, and stem cell transplant recipients. Causative organisms include *Aspergillus*, *Zygomycetes*, and *Fusarium* species.

Lower Respiratory Tract Infections

- Bacterial colonization of the upper respiratory tract serves as a source of pathogenic organisms for the lower respiratory tract.
- Pulmonary infiltrates on images can be infectious or noninfectious, as detailed in Table 84-1.
- Diagnosing pneumonia in an immunocompromised child is as follows.
  - — Imaging studies include chest radiography and chest CT. The latter is more sensitive. The presence of a halo sign (nodular or consolidated opacities surrounded by ground-glass attenuation) at chest CT indicates the possibility of infection by an invasive filamentous fungus, such as *Aspergillus*, *Fusarium*, or *Scedosporium* species.
  - — Nasopharyngeal aspirate samples are important in diagnosing viral infections.
  - — Bronchoscopy and bronchoalveolar lavage are highly sensitive for the diagnosis of *P jirovecii* pneumonia but are less so for other fungal infections.

Table 84-1. Differential Diagnosis of Pulmonary Infiltrates During Therapy for Childhood Malignancies

	Localized Infiltrates	Diffuse Infiltrates
Non-neutropenic Patients		
Bacteria	*Streptococcus pneumoniae, Moraxella* species, *Legionella, Mycobacteria, Nocardia*	*Mycobacteria, Chlamydia, Mycoplasma*
Fungi	*Cryptococcus, Histoplasma, Coccidioides, Aspergillus*	*Pneumocystis jirovecii, Cryptococcus, Histoplasma*
Viruses	RSV, adenovirus, influenza, CMV	RSV, adenovirus, CMV, influenza, HSV, VZV
Drugs		Bleomycin, busulfan, cyclophosphamide, methotrexate, cytosine arabinoside
Radiation-induced conditions		Radiation pneumonitis
Neutropenic Patients		
Bacteria	Gram-positive and gram-negative organisms, *Mycobacteria, Legionella, Nocardia*	Gram-positive and gram-negative organisms, *Mycobacteria, Mycoplasma, Chlamydia, Legionella, Nocardia*
Fungi	*Pneumocystis jirovecii, Cryptococcus, Histoplasma*	*Aspergillus, Zygomycetes, Fusarium, Scedosporium*
Neutropenic Patients		
Viruses	RSV, adenovirus, influenza virus	RSV, adenovirus, influenza, HSV, VZV, CMV
Protozoa		*Toxoplasma gondii*
Radiation		Radiation pneumonitis

CMV, cytomegalovirus; HSV, herpes simplex virus; RSV, respiratory syncytial virus; VZV, varicella zoster virus.

— In *P jirovecii* pneumonia:
  - Patients present with fever, dry cough, and dyspnea and are tachypneic and hypoxic at examination.
  - Bronchoscopy and bronchoalveolar lavage are highly sensitive for detecting the causative organism.

Treatment of Infectious Complications

- Treatment is based on underlying etiologic origins.
- A neutropenic patient should be started on broad-spectrum antibiotic therapy.

  - If improvement is seen at 48–72 hours, this therapy should be continued for 10–14 days.
  - Nonresponsive patients require further evaluation, including bronchoscopy and bronchoalveolar lavage, followed, if needed, by lung biopsy.
  - Patients too sick to undergo an invasive procedure require the addition of antifungal therapy, macrolide antibiotics, and sulfamethoxazole-trimethoprim.
- For *P jirovecii* pneumonia:
  - Therapy consists of sulfamethoxazole-trimethoprim.
  - Alternative treatments for nonresponsive patients include a combination of clindamycin and primaquine or intravenous pentamidine.

Lung Injury Due to Chemotherapeutic Agents

- Current therapies for childhood malignancies include surgery and radiation therapy to control local disease, with chemotherapy administered to eradicate systemic disease.
- Drugs used to treat diverse conditions such as seizures (diphenylhydantoin, carbamazepine, levetiracetam), as well as antibiotics (nitrofurantoin, minocycline), can cause pulmonary toxicity. However, it is most often seen with chemotherapeutic agents.
- Direct lung cell injury is the likely cause of lung damage with most drugs, and changes may be irreversible. In some cases, injury is related to the oxidative damage and the glutathione synthetase reactions.
- Risk factors for pulmonary damage include cumulative drug dose, age of the patient, use of multiple chemotherapeutic agents, surgery for removal of a primary pulmonary tumor or pulmonary metastases, and combination therapy with the use of a pulmonary toxic drug, along with radiation therapy.
- Up to 40% of patients who receive bleomycin experience lung damage, but pulmonary complications are rare with fludarabine and cyclophosphamide.
- Pulmonary toxicity occurs in specific patterns.
  - Acute hypersensitivity (inflammatory interstitial pneumonitis)
    - Symptoms include fever, dyspnea, and malaise
  - Noncardiogenic pulmonary edema
  - Pulmonary fibrosis
    - Manifests with dry cough, exercise intolerance, and hypoxemia
- Pulmonary function abnormalities that consist of restrictive or obstructive disease, as well as reduction in the single-breath diffusing capacity for carbon monoxide (DLCO), may be present prior to radiologic changes.
  - Pulmonary function testing, including spirometry, lung volumes, and diffusing capacity, is most useful in fibrosis that results in a restrictive abnormality, as well as reduction in DLCO.
  - Interstitial pneumonitis may have a mixed obstructive and restrictive pattern.

- Plain chest radiographic and CT findings demonstrate involvement of the airways, alveolar spaces, and/or interstitium (Figures 84-1 and 84-2).
  - — Interstitial pneumonitis can be seen with several agents, including bleomycin, cyclophosphamide, busulfan, melphalan, carmustine, chlorambucil, methotrexate, gemcitabine, cytosine arabinoside, and fludarabine.
  - — Fibrosis can result from the use of bleomycin, cyclophosphamide, busulfan, chlorambucil, methotrexate, cytosine arabinoside, and fludarabine.
  - — Pulmonary edema may be present with the use of imatinib, gemcitabine, cyclophosphamide, and methotrexate.
- Treatment consists of cessation of the drug, as well as supportive measures.

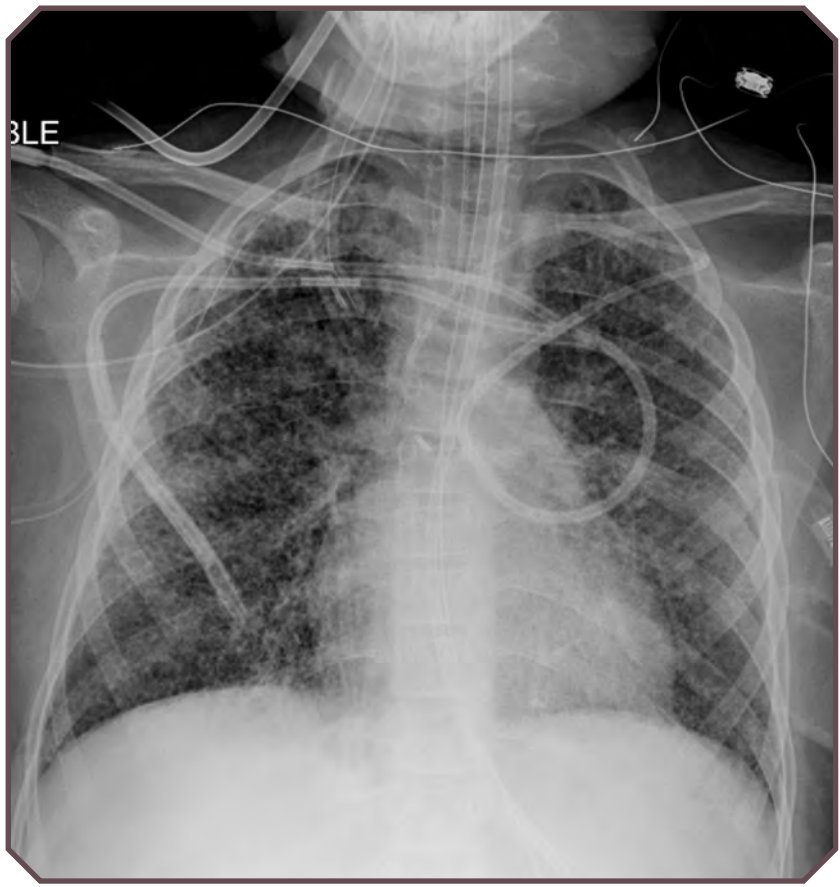

Figure 84-1. Busulfan and melphalan pulmonary toxicity in a child with acute respiratory failure. Frontal chest radiograph demonstrates diffuse interstitial markings and bilateral diffuse hyperlucent linear markings due to interstitial disease and interstitial emphysema. Extensive support tubing is noted, including an endotracheal tube, 2 orogastric tubes, and a central line in the superior vena cava.

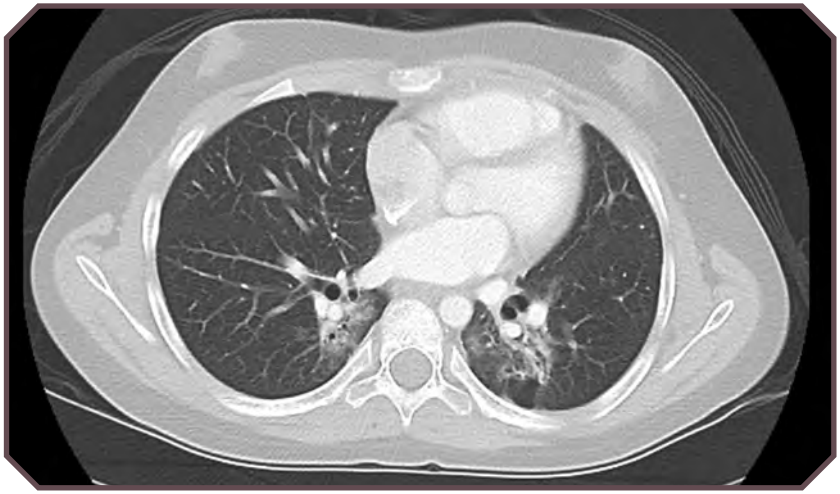

Figure 84-2. Combined pulmonary toxicity after combined chemotherapy with bleomycin, carmustine, cytarabine, doxorubicin, and radiation therapy. Axial computed tomographic image demonstrates coarse, bilateral, paramediastinal interstitial thickening, bronchiectasis, and scarring.

- Table 84-2 provides an overview of drugs, with pulmonary toxicity, indications for use, and the type of lung damage they may cause.
- Signs and symptoms of toxicity may not manifest for ≥5 years after therapy.

Table 84-2. Chemotherapeutic Agents and Pulmonary Toxicity

Drug	Indication	Pulmonary Toxicity
Alkylating Agents		
Cyclophosphamide	Lymphoma, leukemia, sarcoma, neuroblastoma	Interstitial pneumonitis, pulmonary fibrosis, noncardiogenic pulmonary edema, bronchospasm
Melphalan	Sarcoma, neuroblastoma, leukemia	Interstitial pneumonitis, pulmonary fibrosis
Carmustine	Brain tumors, lymphoma, Hodkgin disease	Interstitial pneumonitis, pulmonary fibrosis
Busulfan	CML, leukemia, conditioning in stem cell transplantation	Interstitial pneumonitis, pulmonary fibrosis, pleural effusion
Antimetabolites		
Methotrexate	Leukemia, lymphoma, osteosarcoma	Interstitial pneumonitis, pulmonary fibrosis, noncardiogenic pulmonary edema, hypersensitivity, pleural effusion

Continued

Table 84-2. Chemotherapeutic Agents and Pulmonary Toxicity, *continued*

Drug	Indication	Pulmonary Toxicity
Antimetabolites, *continued*		
Mercaptopurine	Leukemia (ALL, CML)	Interstitial pneumonitis, pulmonary fibrosis
Fludarabine	Leukemia (ALL, CML), indolent lymphoma	Interstitial pneumonitis, pulmonary fibrosis
Cytarabine (cytosine arabinoside)	Leukemia, lymphoma	Interstitial pneumonitis, pulmonary fibrosis, noncardiogenic pulmonary edema, cryptogenic organizing pneumonia, diffuse micronodular disease
Gemcitabine	Hodgkin disease	Interstitial pneumonitis, bronchospasm, noncardiogenic pulmonary edema
Topoisomerase Inhibitors		
Paclitaxel	Limited use in pediatrics	Hypersensitivity reactions with bronchospasm
Docetaxel	Ewing sarcoma	Interstitial pneumonitis
Small Molecule Pathway Inhibitors		
Imatinib	CML	Pleural effusion, noncardiogenic pulmonary edema
Tubulin Inhibitors		
Vincristine	Leukemia, lymphoma, most solid tumors	Interstitial pneumonitis
Vinblastine	Histiocytosis, Hodgkin disease	Interstitial pneumonitis, bronchospasm, noncardiogenic pulmonary edema, bronchospasm
Miscellaneous		
Bleomycin	Lymphoma, other germ cell tumors	Interstitial pneumonitis, pulmonary fibrosis, hypersensitivity lung reaction,[a] pleural effusion, eosinophilic pneumonia
All-trans retinoic acid	Acute promyelocytic leukemia	Interstitial pneumonitis, pleural effusion, noncardiogenic pulmonary edema

AML, acute myeloid leukemia; CML, chronic myeloid leukemia.

[a] Bleomycin can generate production of inflammatory mediators by lung cells. Inflammatory cells may participate in further oxidant and proteolytic damage to lungs. Eosinophilic pneumonia secondary to bleomycin has also been reported.

Postoperative Sequelae Affecting the Lung

- Resection of primary tumors or pulmonary metastases results in loss of lung parenchyma.
- Pulmonary function testing shows a restrictive ventilatory defect. Although the DLCO may be decreased, values are usually normal when corrected for lung volume.
- Lobectomy and/or pneumonectomy can result in scoliosis.

Radiation-Induced Lung Injury

- Lung injury after radiation therapy is seen in pediatric patients undergoing whole-lung irradiation and total-body irradiation, as well as those undergoing wide-field irradiation for thoracic sarcomas.
- The growing and developing tissues in the child are more sensitive to late effects of irradiation, as compared to the mature tissues in an adult. Therefore, delivering adequate radiation doses must be balanced with potential toxicity related to this treatment.
- The lung is a very radiosensitive organ that is susceptible to damage at relatively low radiation doses. Therefore, the maximum dose tolerated decreases quickly as a larger percentage of the lung is irradiated. Fields >50% require no more than 15 Gy in most pediatric protocols.
- Radiation affects both skeletal development and the lung parenchyma (Figure 84-3).
  - Growth restriction in small children may alter the shape and size of the rib cage, resulting in chest wall restrictive diseases.
  - Radiation results in the release of proinflammatory cytokines, growth factors, and reactive oxygen species, which can cause tissue damage. Injury affects type I and II pneumocytes, as well as endothelial cells and stromal fibroblasts.
- Ionizing radiation has a direct effect on DNA. Moreover, free radicals generated from the ionization of water yield free hydroxyl radicals, which also damage DNA.
- Acute pneumonitis occurs within 1–4 months after irradiation.
- Clinically, the patient may present with cough, dyspnea, and hypoxia with decreased DLCO.
- Pathologic studies demonstrate type II cell hyperplasia and inflammatory cell infiltration.
- Progressive pulmonary fibrosis can occur within 6–12 months or several years after radiation therapy. In this condition, there is thickening of interstitial tissue and accumulation of fibrin and atypical fibroblasts.
- Childhood cancer survivors have been reported to have a higher relative risk of developing late pulmonary complications, including lung fibrosis, recurrent pneumonia, chronic cough, shortness of breath, and abnormal chest wall development.
- Treatment remains supportive, with the use of supplemental oxygen for relief of symptoms.

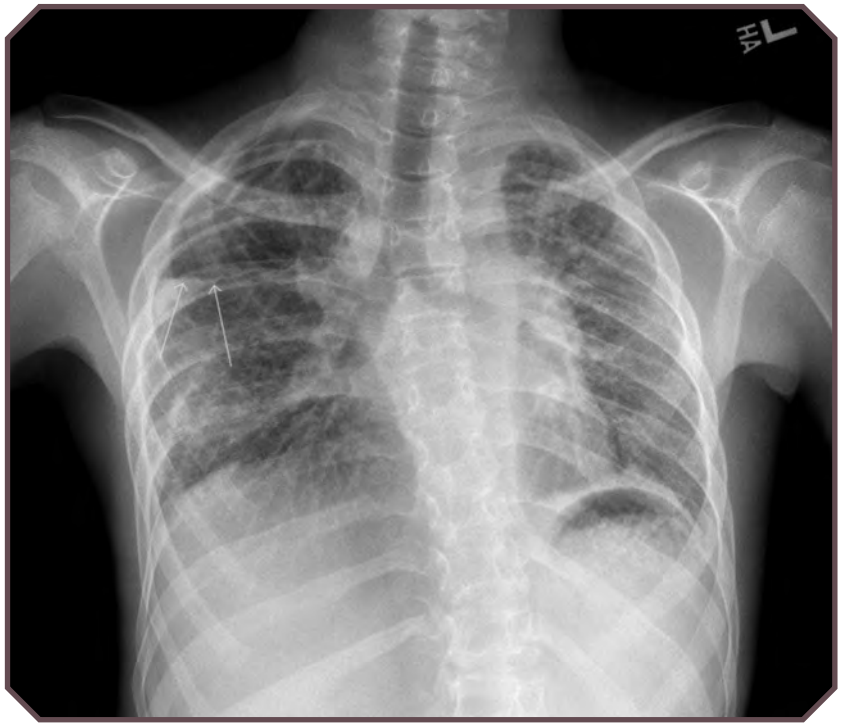

Figure 84-3. Frontal chest radiograph in a 15-year-old boy treated with chemotherapy and radiation therapy during infancy for a paraspinal embryonal rhabdomyosarcoma. Interstitial changes are shown, with bronchiectasis and small right apical pneumothorax, as well as kyphoscoliosis. (Arrows do not indicate a relevant finding.)

- Severe pneumonitis that results in respiratory failure requires intubation and mechanical assisted ventilation.
- Patients with acute pneumonitis may benefit from short-term therapy with corticosteroids.
- Severe scoliosis that results from radiation therapy for spinal and/or paraspinal tumors requires surgical correction.

Pulmonary Complications From HSCT

- HSCT is used for children with hematologic malignancies, as well as those with immunodeficiency.
- Stem cell transplants are allogeneic (not obtained from the same patient) or autologous. Bone marrow, peripheral blood, and umbilical cord blood can all be used as sources of stem cells for allogeneic transplantation.
- Infectious complications can be bacterial, fungal, or viral, with bacterial and fungal infections more prevalent during the early posttransplant period (before day 100) and viral infections more common in the late posttransplant period (beyond day 100).

- Noninfectious pulmonary complications are also classified as "early" if they occur within the first 100 days and "late" if they occur beyond this period (see Figure 84-4).

Early Noninfectious Posttransplant Complications

- Oral mucositis occurs within the first 2 weeks after transplantation and can result in sinusitis, upper-airway obstruction, and aspiration pneumonia due to impaired mucociliary clearance.
- Pulmonary edema and capillary leak syndrome
  - These occur within 2–3 weeks after transplantation and are characterized by dyspnea, hypoxemia, and crackles on auscultation.
  - Chest radiographs may show bilateral infiltrates and/or pleural effusion.
  - Treatment consists of vigorous diuresis.
- Periengraftment respiratory distress syndrome
  - Occurs at a time when neutrophil engraftment is occurring.
  - Patients present with hypoxemia and respiratory distress.
  - Diffuse edema and infiltrates may be present on chest radiographs, with bronchoalveolar lavage fluid at bronchoscopy having negative findings for pathogens.
- Idiopathic pneumonia syndrome
  - It affects 5%–10% of adult patients undergoing HSCT and has been reported in 23.3% of children in 1 study.
  - The condition occurs a median of 21 days after transplantation and can have a mortality rate of >70%.

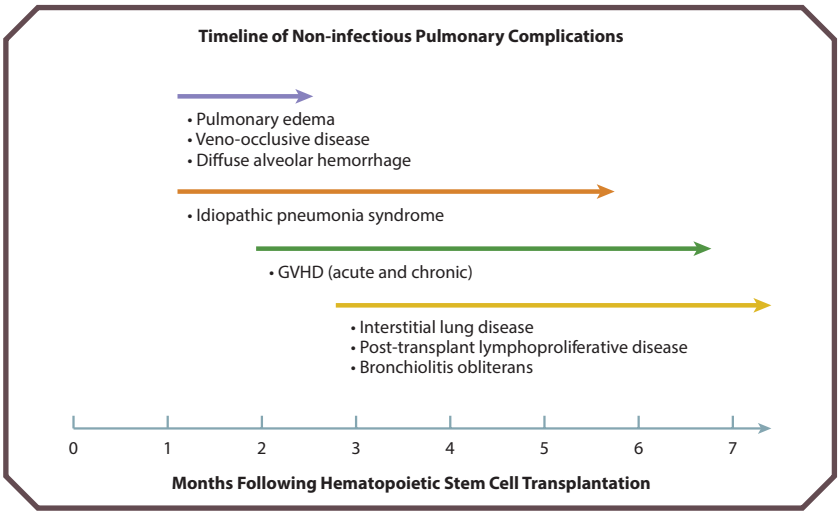

Figure 84-4. Timeline of pulmonary complications after hematopoietic stem cell transplantation. GVHD = graft versus host disease. From Spahr J, Weiner DJ, Stokes DC, Kurland G. Pulmonary disease in the pediatric patient with acquired immunodeficiency states. In: *Kendig and Chernick's Disorders of the Respiratory Tract in Children*. 8th ed. Philadelphia, PA: Elsevier; 2012:899–919. Copyright 2012, with permission from Elsevier.

  - Symptoms include dyspnea and nonproductive cough with audible crackles.
  - Diffuse infiltrates are seen on chest radiographs, and bronchoalveolar lavage is indicated to rule out infectious etiologic origins.
  - Treatment is supportive; steroids have not been shown to be beneficial.
  - The need for mechanical assisted ventilation is associated with a poor prognosis.
- Diffuse alveolar hemorrhage
  - This is reported in ≤21% of adult HSCT recipients but is less common in children, with an incidence rate of 5% in 1 series. It is more prevalent in patients receiving allogeneic transplants and is usually associated with a poor prognosis.
  - It occurs within 30 days of HSCT, with rapid onset of dyspnea and hypoxemia, and coincides with white blood cell engraftment.
  - At bronchoalveolar lavage, the fluid is progressively more blood-stained with each lavage.
- Sinusoidal obstructive syndrome
  - This was formerly called *pulmonary and hepatic veno-occlusive disease (VOD)*.
  - It is seen more commonly in children than in adults.
  - Patients present with dyspnea and signs of right-sided heart failure.
  - Intimal fibrosis occludes the small veins and venules in both hepatic and pulmonary VOD.
  - Defibrotide has been used to treat hepatic VOD, but pulmonary VOD has few treatment options.

Late Noninfectious Posttransplant Complications

- Obliterative bronchiolitis (bronchiolitis obliterans)
  - Most commonly associated with chronic graft versus host disease.
  - Patients present with dyspnea, nonproductive cough, and wheezing, with symptoms starting 12–24 months after HSCT.
  - Areas of mosaic perfusion are often present on thin-section chest CT images.
  - Pulmonary function testing shows an obstructive pattern with decreased forced expiratory volume in 1 second (FEV_1), as well as ratio of FEV_1 to forced vital capacity.
  - Therapy requires increased immunosuppression.
  - Improved lung function has been reported with the use of azithromycin and, in pediatric patients, pulse methylprednisolone.
- Interstitial lung disease
  - Progressive onset of a restrictive defect is noted at serial pulmonary function testing in a patient who may otherwise be asymptomatic.
  - Pre–stem cell transplant exposure to chemotherapeutic agents (carmustine, busulfan, cyclophosphamide, and methotrexate) and to radiation is an important etiologic factor.

- Cryptogenic organizing pneumonia, characterized by organizing connective tissue in the respiratory bronchioles and alveolar ducts, results in a restrictive defect at pulmonary function testing.
- Definitive diagnosis is established by means of lung biopsy.
- This condition is responsive to steroids.

Therapy for Established Toxicity

- Corticosteroids are important in the relief of symptoms from radiation therapy and chemotherapy-induced pneumonitis.
- Clinically significant hypoxemia necessitates the use of supplemental oxygen; a subset of patients may require noninvasive ventilation.
- Severe irreversible lung damage may necessitate referral for lung transplantation.

Resources for Families

- Patients & Families (Children's Oncology Group). childrensoncologygroup.org/index.php/patients-and-families
- Children's Neuroblastoma Cancer Foundation. www.cncfhope.org
- Children With Cancer: A Guide for Parents (National Cancer Institute). www.cancer.gov/publications/patient-education/guide-for-parents
- Childhood Cancer Resources (American Society of Clinical Oncology). www.cancer.net/navigating-cancer-care/children/childhood-cancer-resources

Clinical Pearls

- Pulmonary sequelae from therapy for childhood cancers are common and may include infection or damage from radiation and/or chemotherapeutic agents.
- Respiratory infections are caused by a wide variety of bacteria, viruses, and fungi.
- Bronchoscopy and bronchoalveolar lavage are essential to rule out infectious complications and are diagnostic for diffuse alveolar hemorrhage after stem cell transplantation.
- Chemotherapeutic agents and radiation can cause lung damage during therapy and for several years after treatment.
- Pulmonary function testing, including spirometry, diffusing capacity, and lung volumes, should be performed routinely in all children prior to and after radiation therapy, especially thoracic radiation therapy, as well as stem cell transplantation.
- Lung involvement can result in chronic respiratory failure; patients may require referral for lung transplantation.

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Chapter 85

Children's Diffuse and Interstitial Lung Disease

Timothy J. Vece, MD

Introduction/Epidemiology/Pathophysiology

The Basics

- Children's diffuse and interstitial lung disease (hereafter referred to as "children's ILD") is a heterogeneous group of individually rare disorders of the lung that can manifest at any age during childhood.
- *Interstitial lung disease* and *diffuse lung disease* are often used interchangeably to describe these disorders.

Epidemiology

- Disease prevalence ranges from 0.13 to 16.2 cases per 100,000 children. The range is large because there is no agreed-upon list of children's ILD disorders. The classification schemes proposed by Deutsch et al in 2007 and Fan et al in 2015 are the most widely accepted (Box 85-1).
- There is no known racial or ethnic predisposition for any of the common children's ILD disorders.
- The prevalence of specific disorders varies by age group.

Pathophysiology

- Alveoli and supporting cells of the lungs (interstitium) are most often affected. Exceptions are neuroendocrine cell hyperplasia of infancy (NEHI) and bronchiolitis obliterans, which affect the small airways.
- Gas exchange of the lung is compromised—most commonly oxygen transfer, which can lead to hypoxemia.
- Most disorders are inflammatory and lead to fibrosis of the interstitium and chronic lung disease.
- Lung involvement is usually diffuse at imaging (including chest computed tomography [CT]). Some disorders have specific patterns at imaging.

General Clinical Features

- Chronic and progressive tachypnea and increased work of breathing are typical.
- In infants, failure to thrive may be seen because of the increased caloric demand from the increased work of breathing.

Box 85-1. Children's Diffuse and Interstitial Lung Disease Classification Scheme

Age 0–2 classification

Disorders more prevalent in infancy
- *Diffuse developmental disorders*
  - Alveolar capillary dysplasia with misalignment of the pulmonary veins
- *Growth abnormalities*
  - Alveolar simplification
- *Conditions of undefined etiologic origin*
  - Neuroendocrine cell hyperplasia of infancy
  - Pulmonary interstitial glycogenosis
- *Disorders of surfactant metabolism*

Disorders prevalent throughout childhood
- *Disorders of systemic disease*
  - Diffuse alveolar hemorrhage
  - Rheumatologic disease–related lung disease
- *Disorders of the normal host*
  - Postinfectious lung disease
- *Disorders of the immunocompromised host*
  - Opportunistic infections
  - Damage related to chemotherapy or radiation therapy

Age 2–18 classification

Disorders in clinically immunocompetent patients
- *Disorders of infancy*
  - Disorders of surfactant metabolism
  - Neuroendocrine cell hyperplasia of infancy
- *Disorders of the immunocompetent host*
  - Postinfectious lung disease
- *Disorders of systemic diseases*
  - Diffuse alveolar hemorrhage
  - Rheumatologic disease–related lung disease

Disorders in clinically immunocompromised patients
- *Opportunistic infections*
- *Related to treatment*
  - Chemotherapy
  - Radiation therapy
- *Related to transplant rejection*
- *Diffuse alveolar damage*
- *Lymphoid infiltrates*
  - Lymphocytic interstitial lung disease
  - Lymphoprolific interstitial lung disease

Adapted from *(a)* Deutsch GH, Young LR, Deterding RR, et al. Diffuse lung disease in young children: application of a novel classification scheme. *Am J Respir Crit Care Med.* 2007;176(11):1120–1128 and *(b)* Fan LL, Dishop MK, Galambos C, et al. 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.

- Older children often experience shortness of breath that is worse with exercise and progressive in nature.
- Hypoxemia is common.
- Physical examination often reveals crackles or rales on inspiration. Wheezing is an uncommon finding in most children's ILD disorders.
- Digital clubbing can be present and denotes chronic hypoxemia.
- Routine laboratory testing is generally nonspecific in children's ILD.
- Pulmonary hypertension is seen in advanced, severe cases and is a poor prognostic indicator, with up to a fourfold increase in mortality shown in some studies.

General Diagnostic Considerations

- A family history of interstitial lung disease or early death is important because a number of children's ILDs are genetic.
- Timing of studies is based on severity of illnesses and age at presentation, with a more aggressive approach advocated for more severe forms of children's ILD, where a quick diagnosis is needed for medical decision-making.

Imaging

- Chest imaging is the first step in evaluation and usually leads to the suspicion of an interstitial lung process. However, chest CT is preferable to chest radiography because CT (usually thin-section CT) is more sensitive and shows specific patterns that may be helpful in classification.
- Patterns at CT may indicate specific diseases (NEHI, bronchiolitis obliterans) or can be suggestive but nonspecific, such as in disorders of surfactant metabolism.

Additional Diagnostic Testing

- Lung biopsy is often required for diagnosis.
  - Certain disorders can be diagnosed without lung biopsy, including NEHI, bronchiolitis obliterans, disorders of surfactant metabolism if genetic changes are present, and alveolar hemorrhage syndromes if there are positive auto-antibodies and a compatible clinical picture.
- Genetic testing is becoming increasingly important for diagnosis, particularly in disorders of surfactant metabolism and immune dysregulation.
- A screening echocardiogram is recommended because some children's ILD disorders can manifest with pulmonary hypertension at presentation. In addition, there are cardiac disorders, such as total anomalous pulmonary venous return and pulmonary veno-occlusive disease, that can mimic children's ILD and need to be ruled out.
- Patients with children's ILD who require supplemental oxygen should undergo yearly echocardiography for evaluation of potential pulmonary hypertension.

Specific Children's ILDs

Neuroendocrine Cell Hyperplasia of Infancy

History and Symptoms

- Specific to young children, with all known cases manifesting symptoms <2 years of age.
- Patients generally present <1 year of age, with a typical onset of first symptoms at 2–4 months of age.
- Symptoms are often first recognized during a viral respiratory infection; however, the tachypnea and hypoxemia do not resolve after the infection.

Physical Examination

- Findings are nonspecific and demonstrate retractions, crackles, and increased diameter of the chest. Digital clubbing is not found, and wheezing is rare and intermittent.
- Failure to thrive is often seen because of increased work of breathing.

Imaging

- Chest CT shows ground-glass opacities in the right middle lobe, lingula, and medial portion of the upper and lower lobes (see Figure 85-1). This pattern on CT images can be diagnostic in the correct clinical setting and can obviate the need for lung biopsy.

Lung Biopsy

- Lung biopsy, when required for diagnosis in atypical cases, shows increased neuroendocrine cells surrounding the small airways.

Treatment

- Treatment is supportive because there are no known effective therapies for NEHI.

Prognosis

- Long-term prognosis is excellent—there are no reported deaths caused by NEHI.
- Significant morbidity is associated with chronic hypoxemia and exercise intolerance in children with NEHI that generally improves over time.

Disorders of Surfactant Metabolism

For a full discussion, see Chapter 66, Surfactant Metabolism Disorders, Including Surfactant Protein Deficiencies.

General Surfactant Biology

- Surfactant lines the alveoli and reduces surface tension, allowing for easier maintenance of patency of the alveoli and decreased work of breathing.

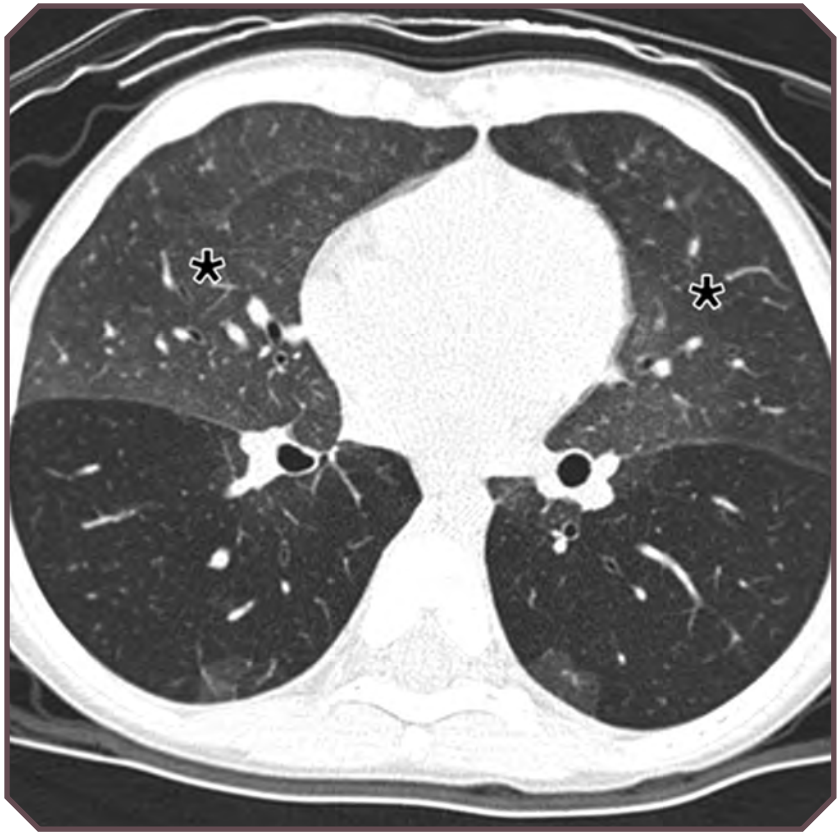

Figure 85-1. Axial computed tomographic (CT) image from a 3-year-old girl with neuroendocrine cell hyperplasia of infancy (NEHI). Note the ground-glass opacities in the right middle lobe and lingual (asterisks)—a finding consistent with NEHI in the proper clinical picture. Image from Brody AS, Guillerman RP, Hay TC, et al. Neuroendocrine cell hyperplasia of infancy: diagnosis with high-resolution CT. *AJR Am J Roentgenol.* 2010;194(1):238–244. Reprinted with permission from the American Journal of Roentegenology.

- Surfactant is composed primarily of phospholipids and specific proteins that either aid in surfactant structure or are part of the innate immunity of the lung.
- Surfactant proteins B and C, along with a trafficking protein called *member A3 of the adenosine triphosphate–binding cassette family (ABCA3)*, as well as a transcription factor called *thyroid transcription factor 1 (TTF-1)*, are implicated in children's ILD disorders.
- ABCA3 likely plays a role in packaging and delivering surfactant into the apical membrane of the alveolar cells.

Specific Disorders of Surfactant Metabolism

- Surfactant protein B (SPB) is encoded by the *SFTPB* gene. Surfactant protein deficiency is inherited in an autosomal recessive pattern.

- Deficiency results in severe disease, with onset of symptoms in the neonatal period. Most patients die or require lung transplantation by 1 month after birth.
- Surfactant protein C (SPC) is encoded by the *SFTPC* gene and is inherited in an autosomal dominant fashion.
  - SPC deficiency has a variable presentation, with patients presenting from infancy to adulthood. There is also a variable outcome, with some patients progressing to severe chronic lung disease in early childhood.
- ABCA3 disease is inherited in an autosomal recessive pattern.
  - ABCA3 disease has a variable prognosis, with some patients having a severe SPB deficiency–like presentation, while others have a more chronic course, such as in SPC deficiency.

Diagnostic Considerations: Imaging

- Imaging patterns are nonspecific but can be suggestive of a disorder of surfactant metabolism. Chest CT is preferred to chest radiography.
- Young children often have diffuse ground-glass opacities with septal thickening (see Figure 85-2).
- Older children have fewer areas of ground-glass opacities and have increased areas of fibrosis on chest CT images.

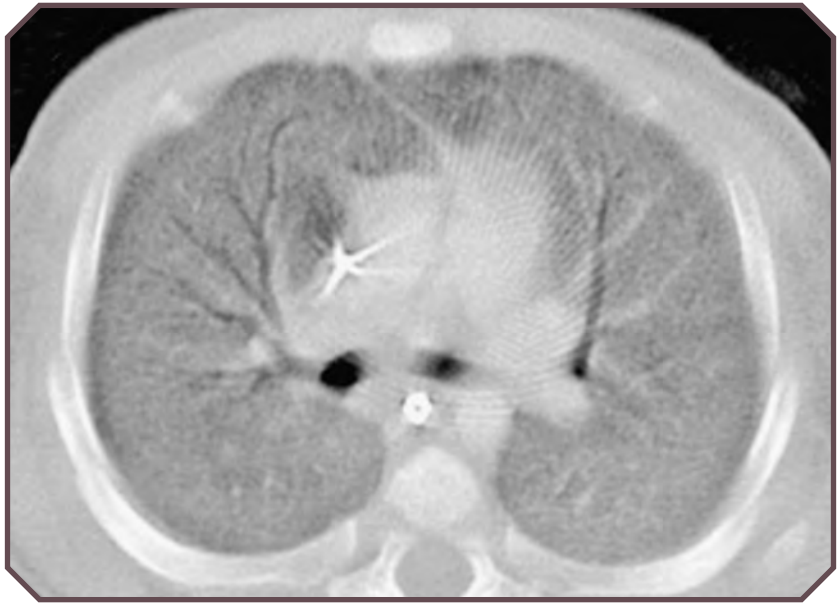

Figure 85-2. Axial chest computed tomographic image from full-term infant with ABCA3 deficiency. Note the diffuse ground-glass opacities. Septal thickening is present but less obvious. From Guillerman RP. Imaging of childhood interstitial lung disease. *Pediatr Allergy Immunol Pulmonol.* 2010;23(1):43–68. The publisher for this copyrighted material is Mary Ann Liebert, Inc. publishers.

Table 85-1. Known Genetic Causes of Disorders of Surfactant Metabolism

Disease	Associated Gene	Inheritance Pattern	Age at Presentation	Prognosis
Surfactant protein B deficiency	*SFTPB*	Autosomal recessive	Neonatal	Poor
Surfactant protein C deficiency	*SFTPC*	Autosomal dominant	Infancy to adulthood	Variable
ABCA3 deficiency	*ABCA3*	Autosomal recessive	Neonatal to infancy	Variable
Thyroid transcription factor 1 deficiency	*NKX2.1*	Autosomal dominant	Neonatal to adulthood	Variable

ABCA3, member A3 of the adenosine triphosphate–binding cassette family.

Diagnostic Considerations: Genetics

- Genetic testing is available for SPB, SPC, ABCA3, and *NKX2.1,* a newer gene that encodes TTF-1 (Table 85-1).
- Results are generally available in 2–4 weeks and can provide prognostic information in some cases.
- Genetic testing is preferred if there is a family history of a disorder of surfactant metabolism.
- Results are only positive in 70%–80% of surfactant cases. A lung biopsy may still be necessary.

Diagnostic Considerations: Lung Biopsy

- Lung biopsy findings have specific patterns that are associated with disorders of surfactant metabolism.
- Electron microscopy should be performed on all lung biopsy samples for which a disorder of surfactant metabolism is suspected, because it can have specific defects in SPB and ABCA3.
- All lung biopsy findings should be reviewed by a pediatric pathologist with experience in children's ILD disorders.

Treatment

- No treatment has been well studied for any of the disorders of surfactant metabolism.
- Systemic steroids (typically administered as monthly pulse steroids), chronic azithromycin, hydroxychloroquine, or some combination have been tried with varying degrees of success.

When to Refer

- All patients with a suspected children's ILD disorder should be referred to a pediatric pulmonologist who has experience in treating these disorders.

When to Admit

- Patients should be admitted for worsening respiratory symptoms or increased supplemental oxygen requirement.
- In general, these patients have chronic, severe lung disease and require frequent hospitalizations.
- Often, patients require hospitalization to establish the diagnosis.

Resources for Families

- Children's Interstitial and Diffuse Lung Disease Foundation. www.child-foundation.com
- What Is Childhood Interstitial Lung Disease? (National Heart, Lung, and Blood Institute). www.nhlbi.nih.gov/health/health-topics/topics/chld
- What Is Interstitial Lung Disease in Children? (American Thoracic Society). www.thoracic.org/patients/patient-resources/resources/interstitial-lung-disease-in-children.pdf

Clinical Pearls

- Children with NEHI often appear much more ill than their image findings suggest.
- Oxygen saturation levels are often on the low side of normal (92%–95%), which should raise suspicion for NEHI.
- Most children with disorders of surfactant metabolism present in the first 12 months of life.

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Part VII. Respiratory Disease in Association With Other Systemic Diseases

Associate Editor: Michael S. Schechter, MD, MPH, FAAP

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Chapter 86

Pulmonary Complications of Immune Deficiencies

Girish Vitalpur, MD, FAAP, and Clement L. Ren, MD, MS

Introduction

- More than 200 primary immune deficiency disorders (PIDDs) are recognized.
- PIDDs affect 1 in 2,000 children in the United States and 1 in 1,200 children worldwide.
- More than 60% of PIDDs are diagnosed in childhood.
- Many PIDDs are caused by X-linked recessive disorders: They are ≤4 times more common in boys <16 years of age.
- PIDDs are detected in 16% of non–cystic fibrosis bronchiectasis cases in children.

Etiology

- See Figure 86-1 for the etiologic origins of PIDDs.
- B cell defects and/or antibody disorders (50%–60% of PIDD cases)
  - — Common variable immune deficiency (CVID)
    - ▪ This is a heterogeneous group of disorders characterized by low immunoglobulin (Ig) levels, with normal or decreased levels of B cells.

Although some gene mutations have been associated with CVID (eg, mutations in the gene for transmembrane activator and calcium-modulating cyclophilin ligand interactor, or TACI), the genetic basis for most CVID is unknown.

  - — X-linked agammaglobulinemia (XLA)
    - ▪ About 85% of cases are caused by a mutation in the Bruton tyrosine kinase *(BTK)* gene, leading to a lack of BTK and a block in B cell maturation at the pre–B cell stage.
  - — Selective IgA deficiency (polygenic)
    - ▪ This is defined as a serum IgA level <5 or7 mg/dL (<50 or 70 g/L), with normal levels of other Igs, at ≥4 years of age.
    - ▪ It is the most common antibody defect, occurring in 1 in 400–600 births in the U.S. population.
    - ▪ Ninety percent of cases are asymptomatic.
    - ▪ Patients may have enough secretory IgA or IgG to compensate for low serum IgA levels.

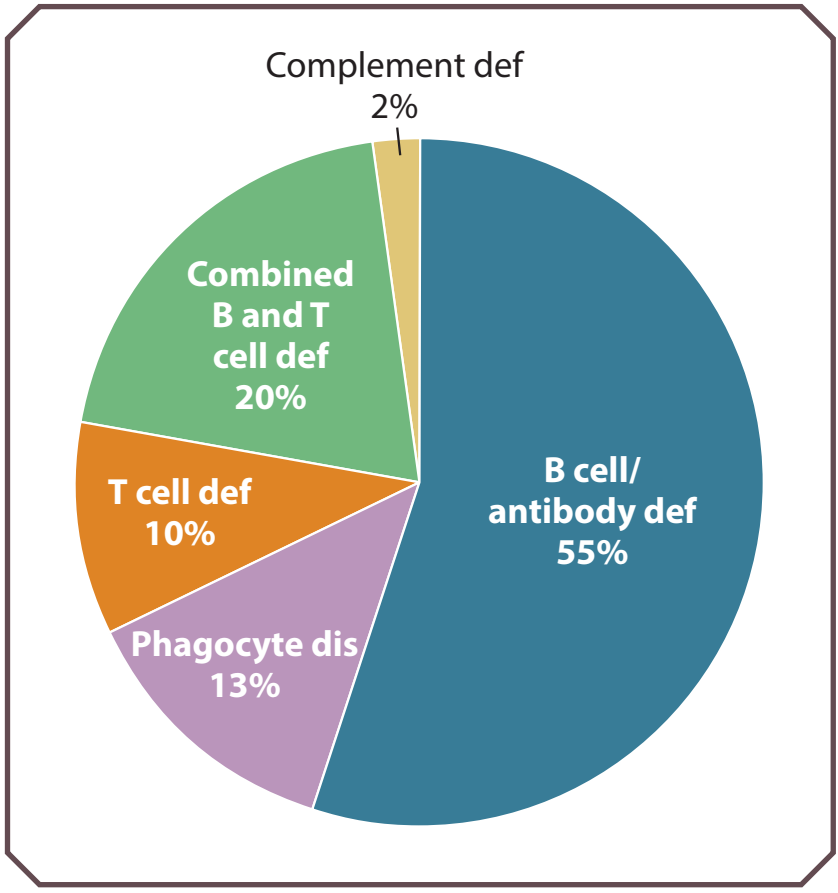

Figure 86-1. Etiologic origins of primary immune deficiency disorders.

- The deficiency can resolve over time and can be associated with development of normal IgA levels but may also precede the onset of CVID.

— Specific antibody deficiency (usually pneumococcal antibody deficiency)

— Transient hypogammaglobulinemia of infancy (THI)
- Commonly observed
- Usually not associated with clinically significant immune dysfunction
- Resolves on its own by 2–4 years of life

— IgG subclass deficiency
- Low levels of IgG subclasses IgG1, IgG2, and/or IgG3 or IgG4, with normal total IgG levels
- Can be associated with IgA deficiency and/or autoimmunity
- Subclass levels vary with age; may be asymptomatic

- Phagocyte disorders (10%–15% of PIDDs)
  - — Chronic granulomatous disease (CGD)
    - ▪ More than 50% of cases are caused by X-linked recessive deficiency; otherwise, CGD is autosomal recessive.
    - ▪ A defect in nicotinamide adenine dinucleotide phosphate oxidase production leads to defective microbicidal function.
  - — Chédiak-Higashi disease
    - ▪ Autosomal recessive
    - ▪ Caused by a mutation in the *LYST* gene
    - ▪ Results in impaired bacteriolysis in lysosomes
  - — Leukocyte adhesion defects (LADs)
    - ▪ Because of a lack of adhesive proteins (CD11/CD18) on white blood cell (WBC) surfaces, WBCs cannot adhere to the endothelium or travel to sites of infection.
    - ▪ Bacterial and fungal skin infections, delayed umbilical cord separation, recurrent pneumonias, and ear infections
    - ▪ Autosomal recessive; 3 forms
  - — Severe neutropenia ($<0.5 \times 10^9$/L)
    - ▪ Congenital (Kostmann syndrome, severe congenital neutropenia)
    - ▪ Associated with other PIDDs (severe combined immune deficiency [SCID], CVID, Chédiak-Higashi disease, etc)
    - ▪ Associated with other disorders (Schwachman-Diamond syndrome, glycogen storage disease, etc)
    - ▪ Acquired by infection, drug effect, or vitamin B_{12} or folate deficiency
- T cell defects (5%–10% of PIDDs)
  - — Wiskott-Aldrich syndrome
    - ▪ X-linked recessive
    - ▪ A defect in Wiskott-Aldrich syndrome protein causes impaired B cell and T cell signaling
  - — DiGeorge syndrome
    - ▪ Mutations in genes on 22q11, 10p13, or others
    - ▪ Thymic hypoplasia; associated with hypoparathyroidism and conotruncal heart defects
    - ▪ Inheritance usually sporadic
  - — Interleukin-12 receptor *(IL12R)* mutations cause lack of interleukin-12 activity, leading to lack of interferon-γ production from T cells and natural killer cells.
  - — Hyper-IgM syndrome
    - ▪ If X-linked—CD40 ligand defect
    - ▪ If autosomal recessive—CD40 defect
    - ▪ Both lead to failure of B cells to switch from making IgM to making IgG and other Ig isotypes
    - ▪ IgM levels increased; IgG, IgA, and IgE levels decreased or absent

- Combined B cell and T cell defects (20% of PIDDs)
  - SCID
    - Affects 1 in 58,000 live births in the United States
    - More than 14 genetic causes have been identified. Common examples include
      - ~ Adenosine deaminase deficiency
        - Autosomal recessive
        - Adenosine and deoxyadenosine accumulates in T cells, leading to their death
      - ~ Interleukin-2 receptor γ chain deficiency
        - X-linked recessive
        - T cells cannot respond to interleukin-2, a cytokine critical for T cell activation
    - Defects in T cell precursors or T cell maturation cause a lack of T cells, with lack of or nonfunctioning B cells (with or without natural killer cells).
  - Ataxia telangiectasia
    - Autosomal recessive
    - A defect in the ataxia telangiectasia mutated *(ATM)* gene causes impaired DNA repair and regulation of cell growth.
- Complement defects, innate immunity defects, inflammasome defects (<2% of PIDDs)—complement component 2 and mannose-binding lectin deficiencies can result in recurrent lower respiratory tract infections.

Clinical Features

The clinical features of PIDDs are provided in Table 86-1.

Diagnostic Considerations

- History
  - Number, type, site, and severity of infections
  - Frequent diarrhea
  - Family history of severe infections or immune disorders
  - Delayed umbilical cord separation (suggestive of LAD)
  - Response to antibiotics or otolaryngological procedures
- Physical examination
  - Assess growth parameters (often subnormal with PIDDs)
  - Absence of tonsils (suggestive of XLA)
  - Crackles, wheezes, clubbing
  - Severe eczema
- Laboratory studies
  - Initial assessment is shown in Table 86-2. Secondary assessment is shown in Box 86-1.

Table 86-1. Clinical Features of Primary Immune Deficiency Disorders

Immune Defect	Infectious Complications	Noninfectious Complications
B cell defects (often may not present in the first 6 months of life, as maternal antibodies are still offering protection the first 6 months of life)	Recurrent pneumonias, sinusitis, upper respiratory infections due to • Encapsulated organisms (eg, *Streptococcus pneumoniae, Haemophilus influenzae*) • *Mycoplasma* • Enteroviruses (mainly with CVID and XLA) Patients with XLA are also more susceptible to *Pneumocystis jirovecii* pneumonia	Obstructive lung disease (bronchiectasis, asthma), ILD, lymphoma, and autoimmunity (mainly with CVID)
Phagocyte defects	• Necrotizing pneumonia • Lung abscess • Empyema • Associated with *Aspergillus* spp and/or catalase-producing bacteria — *Staphylococcus aureus* — *Nocardia* — *Serratia marcescens* — *Klebsiella* — *Burkholderia cepacia*	ILD, mainly with CGD
T cell defects (often present within the first 6 months after birth) Most patients with SCID present with chronic cough, pneumonia, failure to thrive, and/or diarrhea	Bacteria • *Pseudomonas* spp • *H influenzae* • *S pneumoniae* • *Mycobacteria* Fungi • *P jirovecii* • *Candida* spp • *Aspergillus* spp • *Coccidioides* Viruses • Cytomegalovirus • Herpes simplex virus • Epstein-Barr virus • Varicella-zoster virus	Bronchiectasis Bronchiolitis with organizing pneumonias Lymphoma
Combined B cell and T cell defects	Those due to B cell and T cell defects as noted	Due to treatments of SCIDs, as discussed ILD Leukemias and lymphomas (especially with ataxia telangiectasia) Thrombocytopenia (WAS)
Complement defects	Encapsulated bacteria With mannose-binding lectin deficiency: URIs and pneumonia	

CGD, chronic granulomatous disease; CVID, common variable immune deficiency; ILD, interstitial lung disease; SCID, severe combined immune deficiency; URI, upper respiratory infection; WAS, Wiskott-Aldrich syndrome; XLA, X-linked agammaglobulinemia. Adapted from Nonas S. Pulmonary manifestations of primary immunodeficiency disorders. *Immunol Allergy Clin N Am.* 2015;35(4):753–766. Copyright 2015, with permission from Elsevier.

Table 86-2. Laboratory Studies for Initial Assessment in the Diagnosis of Primary Immune Deficiency Disorders

Initial Assessment	PIDD
Complete blood count with differential	B cell, T cell, B cell and T cell, neutropenias
Quantitative Ig levels (IgG, IgA, IgM, IgE)[a]	B cell, T cell, B cell and T cell
Specific antibody titers (pneumococcal antibody titers, to 14 or 23 serotypes)[b]	B cell, T cell, B cell and T cell
Specific antibody titers (diphtheria and tetanus antigens)[b]	B cell, T cell, B cell and T cell
IgG subclass levels	Role in PIDD assessment is controversial, and interpretation of results may be difficult
HIV[c]	
Oxidative burst assays[c]	Phagocyte defects (eg, CGD): flow cytometry assays with nitroblue tetrazolium or dihydrorhodamine dyes to test for the ability to generate an oxidative burst
Total complement hemolytic activity (CH50); mannose-binding lectin level[c]	Complement defects (CH50 is used to assess the presence of a classic pathway)

CGD, chronic granulomatous disease; Ig, immunoglobulin; PIDD, primary immune deficiency disorder.

[a] Values vary with age.
[b] Values vary with age and immunization status.
[c] Tests are indicated by specific histories or concerns.

Box 86-1. Laboratory Studies for Second Assessment in the Diagnosis of Primary Immune Deficiency Disorders

Secondary Assessment

Vaccinate with polysaccharide pneumococcal vaccine and assess pneumococcal titers 4 weeks later to assess immune responses and antibody production.

Use flow cytometry to assess lymphocyte subsets.

Perform lymphocyte stimulation assays to mitogens and antigens.

Genetic testing is available for specific PIDDs, such as interleukin-2 receptor deficiency and leukocyte adhesion defects.

Nutritional deficiencies are associated with PIDD: vitamins A, B_6, B_{12}, C, and E; copper; folic acid; iron; selenium; and zinc.

Imaging

- Plain chest radiography
  - — Thymic shadow is absent in infants and teenagers with DiGeorge syndrome (Figure 86-2).
  - — Tram-track lines are suggestive of bronchiectasis.
  - — Evidence of pneumonia (recurrent pneumonias in the same site) suggests bronchial obstruction.
  - — Hyperinflation is suggestive of obstructive airway disease.
- Thin-section chest computed tomography
  - — More sensitive than plain radiography in the detection of bronchiectasis
  - — "Tree-in-bud" pattern indicates bronchiolar inflammation
  - — Ground-glass opacities, adenopathy, and fibrosis can be seen in interstitial lung disease

Spirometry

- Obstructive lung defects are associated with bronchiectasis.
- Restrictive lung defects are associated with interstitial lung disease.

Bronchoscopy and Bronchoalveolar Lavage

- These should be used to recover lower respiratory tract pathogens in patients who do not expectorate sputum.
- These should be used to evaluate the presence of any bronchial obstruction if the pneumonias recur in the same site.

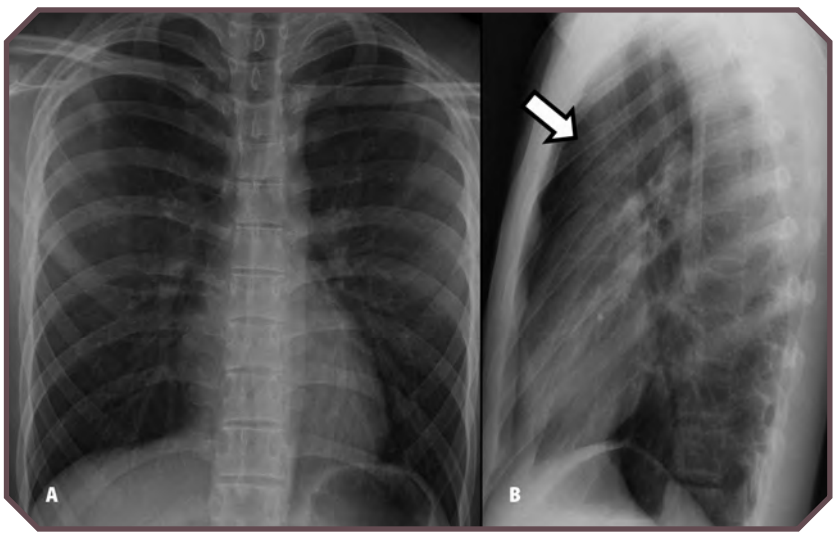

Figure 86-2. Chest radiograph in a 13-year-old boy with a history of DiGeorge syndrome. A. Frontal radiograph shows a narrow mediastinum with no thymus. B. Lateral radiograph demonstrates the absence of normal thymic shadow behind the sternum (arrow).

Differential Diagnosis

The differential diagnosis for PIDDs includes but is not limited to

- HIV
- Asplenia
- Autoimmunity (systemic lupus erythematosus)
- Nutrient deficiency (vitamins A, B_6, B_{12}, C, and E; copper; folic acid; iron; selenium; and zinc)
- Malignancy (lymphomas and leukemias, as noted earlier)
- Chronic use of oral corticosteroids (or other immunosuppressive medication)
  - — Increased Ig catabolism
  - — Decreased Ig synthesis
  - — May still have normal responses to vaccines and may *not* require Ig replacement

Management

- Antibiotic prophylaxis
  - — THI, IgA deficiency: Judicious, temporary use, depending on patient history
  - — XLA, CVID, with chronic sinusitis and/or bronchiectasis: Daily prophylaxis with amoxicillin, trimethoprim-sulfamethoxazole
  - — Other PIDDs: Depending on the type and severity of infection
- Gammaglobulin replacement (XLA, CVID, select cases of specific antibody deficiency): The role in IgG subclass deficiency is controversial.
  - — Intravenous Ig (IVIg)—400–600 mg/kg/mo
  - — Subcutaneous Ig
    - ▪ Administered at home
    - ▪ Doses vary from daily to twice a month
    - ▪ Fewer systemic side effects than IVIg
- Hematopoietic stem cell transplantation—most commonly used with SCIDs and Wiskott-Aldrich syndrome; also considered with CGD and other PIDDs

Treating Associated Conditions

- Obstructive airway disease
- Bronchiectasis
- Interstitial lung disease
- Graft versus host disease after stem cell transplantation

Prevention of PIDDs and Complications

- Prenatal diagnosis is available for certain forms of SCID, CGD, LAD, and XLA.
- Newborn screening for SCID was available in 11 U.S. states in 2015.
  - — Early detection improves immune reconstitution and survival.

- Vaccinations
  - — Live virus vaccines can potentially cause disease in patients with severe T cell and humoral deficiencies, and caution should be exercised regarding their use in patients with these disorders or their household contacts.
  - — According to the U.S. Centers for Disease Control and Prevention, patients with "less severe antibody deficiencies," such as selective IgA deficiency, should avoid vaccination with bacillus Calmette-Guerin, or BCG, and yellow fever, but "other live vaccines appear to be safe."
  - — Yearly inactivated influenza vaccination should be administered.
  - — Pneumococcal vaccination should be administered, as indicated.
- Avoid smoking and secondhand smoke exposure.
- Patients with absent IgA findings may have increased risk of transfusion reactions.

When to Refer

The following are criteria for referral to an immunologist.

- Two or more pneumonias in 1 year
- Two or more months on antibiotics with little effect
- Need for intravenous antibiotics to clear infections
- Presence of sepsis or meningitis, depending on age
- Family history of PIDDs
- Uncommon infections or opportunistic infections
- Chronic lung disease or bronchiectasis without clear etiologic origin, such as cystic fibrosis
- Abnormal immunologic laboratory results

Resources for Families

- Immune Deficiency Foundation. www.primaryimmune.org
- Jeffrey Modell Foundation. www.info4pi.org
- International Patient Organization for Primary Immunodeficiencies. www.ipopi.org
- American Academy of Allergy, Asthma, and Immunology. www.aaaai.org

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Chapter 87

Respiratory Disorders Associated With Sickle Cell Disease

Robyn T. Cohen, MD, MPH

Introduction

- Sickle cell disease (SCD) affects 100,000 individuals in the United States and is the most common genetic disease among African Americans.
- SCD is caused by a single gene mutation in the β-globin chain of the heme molecule, leading to production of hemoglobin S.
  - In a deoxygenated state, hemoglobin S forms polymers that lead to rigid, "sickle-shaped" erythrocytes.
  - Increased adhesion, inflammation, and oxidative stress lead to acute vaso-occlusion of the microvasculature, hemolytic anemia, chronic progressive vasculopathy, and eventual end-organ complications.
- SCD is a progressive, life-limiting condition with an average life expectancy in the fifth decade.
- The most severe form, in which patients are homozygous for the *HbS* mutation, is referred to as *sickle cell anemia (SCA)*.
- Only 1 pharmacological agent is approved by the U.S. Food and Drug Administration to treat SCA: hydroxyurea (hydroxycarbamide).
  - A once-daily oral medication that inhibits the production of hemoglobin S and promotes the bone marrow production of fetal hemoglobin
  - Well tolerated in infants and children with SCA, with randomized controlled trial–proven benefits seen in children as young as 9 months of age
- Pulmonary abnormalities are common and are associated with an increased risk of death in patients with SCD, but data on prevalence, etiologic origins, and treatment for pulmonary complications are lacking.

Acute Chest Syndrome

- An acute complication of SCD, acute chest syndrome (ACS), is a clinical syndrome characterized by a new pulmonary infiltrate (not atelectasis) accompanied by acute-onset fever and typically associated with oxygen desaturation and respiratory symptoms, including tachypnea, retractions, and shortness of breath.

- The second most common cause of hospitalization (after vaso-occlusive pain episodes), it leads to prolonged hospitalizations.
- It can develop acutely or subacutely, during hospitalization for a vaso-occlusive pain episode, or after a surgical procedure.
- It can progress to respiratory failure, neurological complications, and right-sided heart failure.
- It accounts for 15%–25% of SCD deaths.
- ACS in the preschool age group is associated with increased risk of future ACS episodes.
- The effect of ACS on long-term lung function in children has not been proven, although repeated ACS episodes seem to be associated with decreased lung capacity in adults.
- Although ACS is nonspecific on plain radiographs, typical findings include patchy, scattered air space opacity (Figure 87-1).
  - — Acute infarction, although rare, demonstrates focal, wedge-shaped opacities.
- Guidelines-based care includes
  - — Broad-spectrum antibiotics with a cephalosporin and a macrolide
  - — Pulse oximetry with supplemental O_2 as needed
  - — Monitoring the patient for bronchospasm and acute anemia, with treatment as indicated

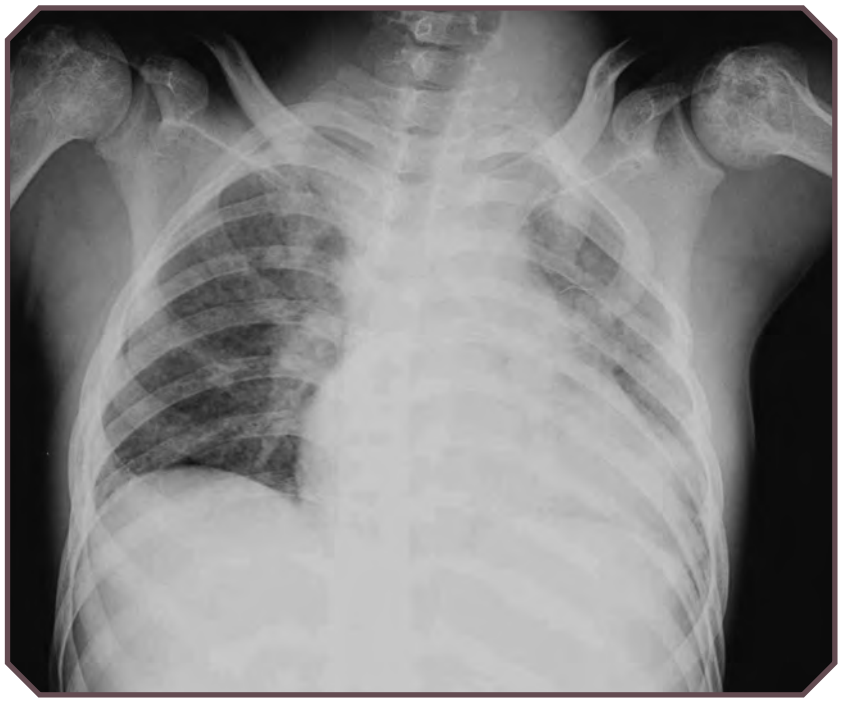

Figure 87-1. Frontal radiograph shows acute chest syndrome in a 15-year-old boy with sickle cell disease. Cardiomegaly is also noted.

  - Consideration of blood transfusion if the hemoglobin level decreases >1 g/dL (>10 g/L) below baseline
  - Incentive spirometry
- Early detection and prevention
  - There are no evidence-based biomarkers to predict which patients hospitalized for vaso-occlusive pain episodes will develop ACS.
  - Incentive spirometry performed on admission for pain has been shown to reduce the incidence of ACS.
  - Hydroxyurea initiated in infancy reduces the future risk of ACS events.
  - Preoperative transfusion performed to increase hemoglobin levels and reduce the hemoglobin S percentage may reduce the postoperative risk of ACS.

Asthma as a Comorbidity or Complication

- Given the burden of asthma among African Americans, a substantial percentage of children with SCD will also have asthma.
- Children with SCD and asthma have increased rates of hospitalization for pain and ACS and increased risk of mortality when compared to children with SCD and no asthma.
- Asthma is challenging to diagnose in children with SCD because several features of asthma (wheezing, an obstructive pattern at spirometry, and/or airway hyperresponsiveness) are common but may exist in the absence of asthma among children with SCD.
  - Recurrent wheezing alone (with or without a clear diagnosis of asthma) is associated with increased rates of ACS.
  - Airway hyperresponsiveness to methacholine is highly prevalent but not necessarily associated with asthma among children with SCD; it may be associated with hemolysis.
  - Lower-airway obstruction is seen in some children without asthma; while not necessarily associated with increased rates of pain or ACS, it has been associated with measures of increased cardiac output.
- History of recurrent wheezing, along with family history of asthma and history of atopy, should raise the index of suspicion for asthma in a child with SCD.
- Patients for whom a diagnosis of persistent asthma seems appropriate should receive treatment with anti-inflammatory controller therapy according to National Asthma Education and Prevention Program guidelines.
- Optimization of SCD management, including consideration of hydroxyurea, should be considered for patients with any of the above asthma-related features, because they may be markers of SCD severity.
- Further research is needed to differentiate asthma from “recurrent wheezing in SCD” so that therapy may be optimized for these patients.
- Systemic steroids are of clear benefit for acute asthma exacerbations but should be used judiciously in children with sickle cell disease owing to reports of an association with vaso-occlusive crises.

Sleep-Disordered Breathing

- Nocturnal oxygen desaturation is common among children with SCD.
- Nocturnal hypoxemia is associated with increases in biomarkers of vascular adhesion and inflammation and may be associated with vaso-occlusive episodes.
- Obstructive sleep apnea is more prevalent among children with SCD than the general population.
  - — Historically, this has been attributed to compensatory adenotonsillar hyperplasia after splenic infarction.
- Have a high index of suspicion for sleep-disordered breathing in children with SCD who snore or have baseline daytime oxygen saturations of <94%, nocturnal enuresis, and/or recurrent priapism.
  - — Full polysomnography (rather than simple overnight oximetry) is the test of choice for children with SCD to determine the nature of the sleep-disordered breathing and whether supplemental oxygen, adenotonsillectomy, or positive pressure therapy (continuous positive airway pressure or bilevel positive airway pressure) are indicated.
- Many children have isolated gas exchange abnormalities (nocturnal hypoxemia or nonobstructive hypoventilation) in the absence of OSA.

Lung Function and SCD

- Although several cohort studies have shown that children with SCD have significantly lower levels of lung function when compared to healthy age-, race-, and sex-matched control subjects, most pediatric patients with SCD have lung function that is within the normal range.
- The most common lung function abnormality in children is lower-airway obstruction, with or without bronchodilator responsiveness.
  - — Some studies indicate that lower-airway obstruction may be related to increased pulmonary blood flow.
- Eight percent to 10% of children with SCA have evidence of restriction.
- While the significance of abnormal pulmonary function in children is unknown, lower forced expiratory volume in 1 second has been associated with an increased risk of mortality among adults.
- Six-minute walk test (6MWT) distances are reduced in patients with SCD and can worsen over time.
- 6MWT abnormalities are associated with dyspnea and decreased exercise capacity and may be associated with echocardiographic abnormalities (ie, increased tricuspid regurgitation jet velocity [TRV]).

Measuring Blood Oxygen Content in SCD

- The standard of reference for measuring blood oxygen content in individuals with SCD is arterial blood gas analysis with co-oximetry.
- Pulse oximetry may lead to underestimation of arterial oxygen saturation, but the difference is rarely clinically significant, except during times of acute illness.

- Owing to intrinsic properties of hemoglobin S, anemia, and increased 2,3-diphosphoglyceric acid, or 2,3-DPG, concentrations, the SCD oxyhemoglobin dissociation curve is often shifted to the right such that the P50 (the oxygen tension at which hemoglobin is 50% saturated) is increased from the normal value of 27 mm Hg ± 2 to 33 mm Hg ± 5.
- It is advisable to obtain oxygen saturation levels via pulse oximetry at routine clinic visits to establish the individual patient's baseline saturation level, which can then be referred to during times of acute illness.
- Low baseline oxygen saturation (<95% on room air) is an established risk factor for nocturnal hypoxemia and sleep-disordered breathing and should prompt consideration of referral for a sleep study.

Pulmonary Hypertension and SCD

- Hemolysis-associated pulmonary hypertension is well described in SCD and β-thalassemia.
- Pulmonary hypertension is characterized by lower pulmonary artery pressures than those with idiopathic pulmonary hypertension but is associated with a high risk of mortality.
- While echocardiography findings, such as an increased TRV ≥2.5 m/s, can be used to establish a presumptive diagnosis of pulmonary hypertension, this is not as valid as a diagnosis established via cardiac catheterization.
- Mortality risks of SCD pulmonary hypertension diagnosed via catheterization, as well as having an increased TRV, are well established in adults, but the prevalence and clinical significance of pulmonary hypertension are unclear among the pediatric population, partly because
  - Cardiac catheterization of pediatric patients with SCD is rarely performed.
  - Several observational studies have shown that increased TRV may be reversible in children with SCD, even in the absence of any intervention.

Pulmonary Surveillance of the Pediatric Patient with SCD

- In an ideal scenario, pulmonary care should be colocated in a multidisciplinary SCD clinic that includes providers from hematology, respiratory therapy, and social work to optimize convenience, communication, and coordination of care.
- Pulmonary consultation is recommended for all patients with SCD who have or are at risk for developing respiratory abnormalities. This includes but is not limited to
  - Recurrent ACS episodes or history of a severe ACS episode
  - History of asthma or wheezing
  - Exercise limitation and/or dyspnea on exertion
  - Resting steady-state daytime oxygen saturation <95%
  - Snoring, excessive daytime fatigue, and/or nocturnal enuresis
  - Any abnormal lung function test result

- In addition to evaluating explicit respiratory symptoms, all patients should be evaluated for the possibility of sleep-disordered breathing, even in the absence of overt snoring.
- Lung function testing in otherwise asymptomatic patients is not currently recommended in the National Heart, Lung, and Blood Institute Guidelines for the management of SCD as part of routine care for patients with SCD but should be considered for patients with respiratory symptoms.
  - Despite the guidelines, spirometry (pre- and postbronchodilator) is a noninvasive, low-cost, widely available test that can be used to identify patients at risk for pulmonary abnormalities.
- Patients with abnormal spirometry results should be referred for plethysmography, 6MWT, and lung diffusion measurements (diffusing capacity of the lung for CO, divided by the alveolar volume) (adjusted for the patient's measured hemoglobin level).

Chapter 88

Respiratory Considerations in Children With Congenital Heart Disease

Saumini Srinivasan, MD, MS, and Jean A. Ballweg, MD

Introduction

- Severe lung disease can cause cardiac alterations; conversely, changes in blood flow and pressures in the great vessels and pulmonary vascular bed can cause serious airway and lung changes.
- Symptoms referable to the pulmonary system may be the initial or only manifestation of cardiac disease, especially in the infant.
- A common early symptom of congestive heart failure is tachypnea, which is initially comfortable but, if untreated, progresses to dyspnea with intercostal and subcostal retractions. Tachypnea is initially caused by increased pulmonary venous pressure or volume.
- Later in the clinical course, bronchial compression, caused by either enlarged pulmonary arteries or an enlarged left atrium, leads to hyperinflation and atelectasis.
- In some patients, the clinical picture is dominated by pulmonary symptoms such as chest discomfort, dyspnea, wheezing, and cough, leading to the term "cardiac asthma."
- Vascular anomalies that affect the major thoracic vessels can cause symptoms of airway compression, including stridor, dysphagia, and wheezing, which can result in respiratory distress.

Alterations in Respiratory Physiology in Congenital Heart Disease

Congenital Heart Disease With Increased Pulmonary Blood Flow

An example of this is given in Figure 88-1.

- Increased pulmonary blood volume results in ventilation-perfusion inequality owing to perfusion in excess of ventilation.
- Partial pressure of oxygen (Pa_{O_2}) decreases and hypoxia occurs when alveolar ventilation is inadequate for pulmonary blood flow.

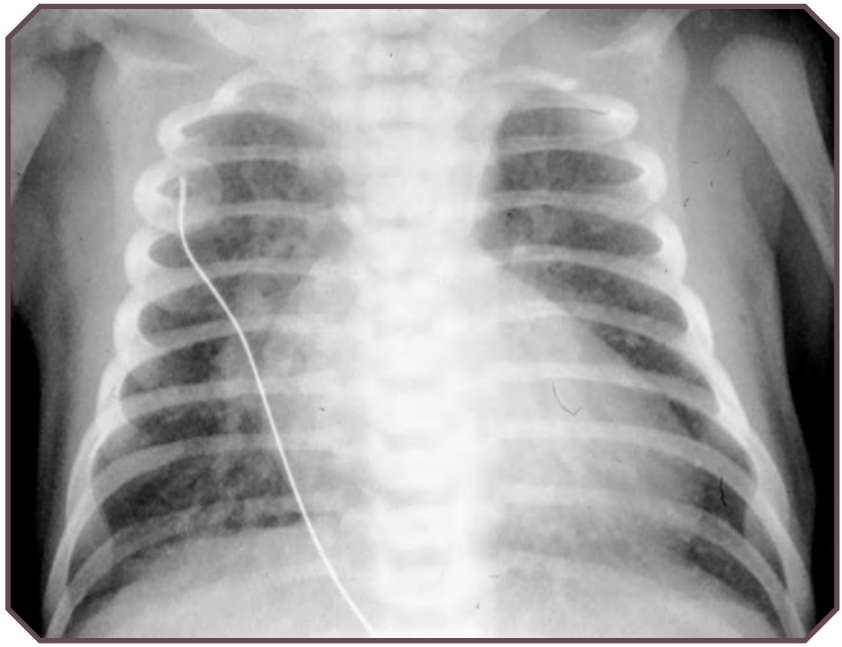

Figure 88-1. Transposition of the great vessels in a newborn with dyspnea. Frontal chest radiograph shows cardiomegaly and increased perihilar pulmonary vascularity (blood flow) typical for a right-to-left shunt.

- Increased pulmonary blood volume results in increased lung weight, and the higher flow leads to increased pressures in pulmonary arterioles, capillaries, and venules.
- The increased pulmonary vascular pressures favor the accumulation of increased extravascular fluid.
- Along with atelectasis, this fluid accumulation results in loss of lung volume. Hence, with lower tidal volumes, a higher respiratory rate (and resultant tachypnea) becomes the only means to maintain minute 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 almost diametrically opposite effects on respiratory mechanics when compared with lesions with increased pulmonary blood flow.
- Decreased pulmonary flow results in a decreased lung weight, improved lung compliance, and alterations in ventilation-perfusion matching.
- Wasted ventilation (physiological dead space) increases because of ventilation of underperfused lung.

- The increase in wasted ventilation 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 Pa_{O_2}. Thus, the acutely hypoxic newborn with decreased pulmonary blood flow typically has effortless tachypnea and cyanosis due to both increased wasted ventilation and stimulation of hypoxic pulmonary drive.
- Chest radiographs demonstrate reduced pulmonary vascularity and hyperlucent, oligemic lungs.

Airway Involvement With Congenital Heart Disease

- Vascular compression of the airway in children may be caused by congenital anomalies of the great vessels (vascular rings, vascular slings) or enlargement of otherwise normal structures (see Chapter 14, Tracheomalacia, Vascular Rings and Slings, and Bronchomalacia).
- Large- and small-airway obstruction can occur in patients with increased pulmonary blood flow.
- Small-airway obstruction results from 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.
- Left atrial enlargement predisposes the patient to large-airway compression and, consequently, air trapping or atelectasis.
- Large-airway obstruction results in restriction to airflow, primarily during exhalation. When obstruction is severe, inspiration may also be compromised.
- Airway compression may be diagnosed bronchoscopically, and the specific cause of the airway compression may be delineated at upper gastrointestinal examination, computed tomography, or magnetic resonance imaging (Figure 88-2).
- These modalities can be used to *(a)* demonstrate not only vascular anomalies but also the relationship of vascular structures to the airway and *(b)* assess airway caliber.
- Longstanding 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 stent placement in the airways, offer temporary relief or are often unsuccessful.

Pulmonary Arterial Hypertension

- Pulmonary arterial hypertension (PAH) in children and adults is defined as an increased mean pulmonary arterial pressure of ≥25 mm Hg, with a normal pulmonary artery wedge pressure (≤15 mm Hg) and increased pulmonary vascular resistance (PVR) in children >3 months old at sea level.

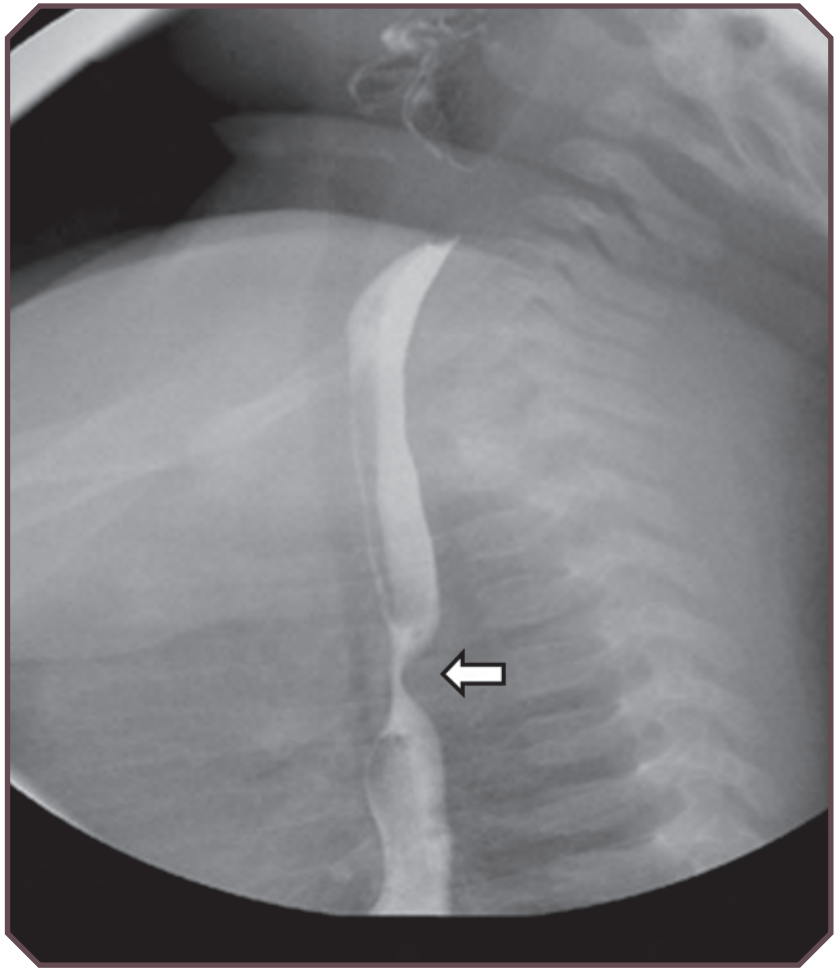

Figure 88-2. Vascular ring. Lateral fluoroscopic image from an upper gastrointestinal examination shows focal mass effect on the posterior esophagus (arrow).

Causes of PAH

Persistent PAH in the Newborn

- Persistent PAH in the newborn (PPHN) is frequently associated with conditions like meconium aspiration, pneumonia, and sepsis.
- PPHN is characterized by increased PVR, right-to-left shunting at the atrial or the ductal level, and severe hypoxemia.
- It is a transient condition that resolves with appropriate therapy. However, it can be fatal in a small percentage of affected children.

PAH Beyond the Neonatal Period

- PAH secondary to congenital heart disease (CHD) results from increased pulmonary blood flow, usually due to left-to-right shunting through a ventricular septal defect or across a patent ductus arteriosus. Usually, the pulmonary artery wedge pressure is normal.
- Idiopathic PAH is PAH secondary to lung disease.
  - Secondary PAH can be seen in association with pulmonary disease, such as bronchopulmonary dysplasia, the interstitial lung diseases, and severe advanced cystic fibrosis.
  - The pathophysiology varies, but the common factors include chronic hypoxia with resulting vasoconstriction and muscular arteriolar hypertrophy.
  - PAH can also result from other conditions with unrecognized long-term hypoxia, like untreated obstructive sleep apnea.

Diagnosis

- Symptoms
  - The symptoms are nonspecific and include lethargy, poor appetite, poor growth, nausea, and vomiting.
  - Children with PAH without shunting across a patent foramen ovale or caused by CHD may present with syncope.
  - Older children and adolescents tend to present with exertional dyspnea, chest pain, and presyncope or syncope.
- Signs
  - At physical examination, patients tend to have poor weight gain and are usually tachypneic and tachycardic.
  - The pulmonic component of the second heart sound is accentuated.
  - Right ventricular (RV) hypertrophy and/or dysfunction results in an RV heave.
  - A cardiac murmur from tricuspid regurgitation may be present.
  - 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.
  - Clinical signs of right-sided heart failure, such as hepatomegaly, peripheral edema, and acrocyanosis, are rare in infants but can be observed in older children and adults.
- Laboratory testing
  - Initially, the chest radiographs of patients with large ventricular septal defects and congestive heart failure demonstrate a large heart with increased pulmonary vascular markings. A decrease in vascular engorgement and decrease in cardiomegaly occur as pulmonary vascular disease worsens. Severe PAH is characterized by an enlarged main pulmonary artery segment and diminished pulmonary vascularity (Figure 88-3).
  - Echocardiography can be used to confirm a clinical suspicion of PAH and evaluate RV function.

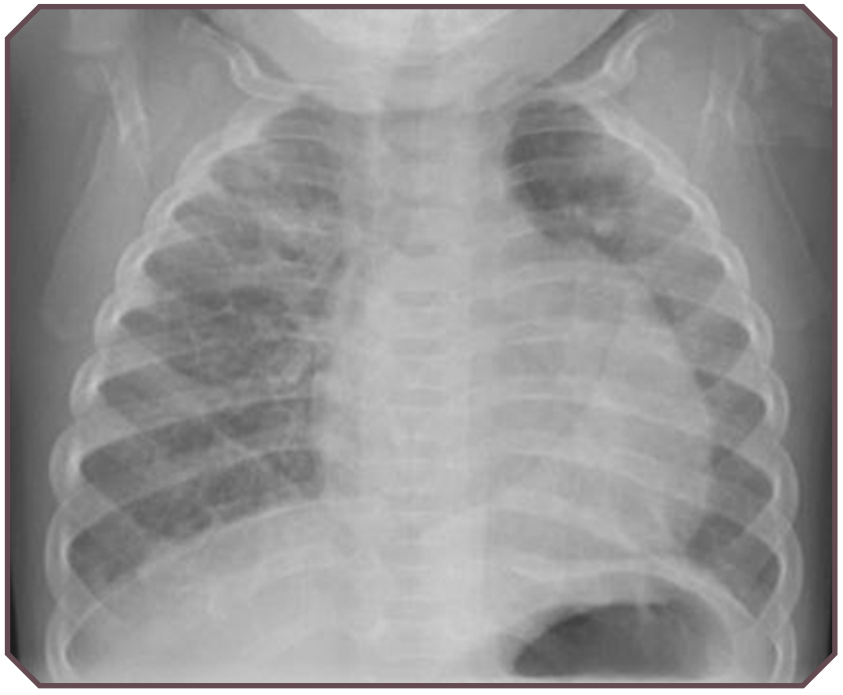

Figure 88-3. Pulmonary hypertension in a 1.5-year-old. Frontal chest radiograph shows bilateral, diffuse, coarse, increased pulmonary markings.

  - The most direct estimate of pulmonary artery pressure is obtained via the velocity of the tricuspid regurgitation jet. The peak velocity of the tricuspid regurgitation jet is proportional to the RV and right atrial pressure.
  - Other indirect observations can suggest the presence of PAH, such as flattening of the interventricular septum, RV hypertrophy, and pulmonary insufficiency with a high estimated pulmonary artery end-diastolic pressure.
- The definitive test for the evaluation of a patient with advanced PAH is cardiac catheterization with testing of the reactivity of the pulmonary vascular bed.

Management of PAH

Chapter 77, Pulmonary Hypertension, provides details on management of PAH.

Viral Respiratory Infections in Children With CHD

- Children with CHD represent a high-risk group for viral respiratory infections.
  - Risk factors for hospitalization due to respiratory illness (in order of decreasing odds ratio) include presence of 22q11 deletion, weight below the 10th percentile for age, previous respiratory infections,

incomplete prophylaxis against respiratory syncytial virus (RSV), recent cardiopulmonary bypass, trisomy 21, and siblings <11 years of age.
  - Infection with RSV carries mortality rates of 2.5%–3.6%. Morbidity is 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 use of palivizumab for immunoprophylaxis.
  - Current guidelines from the American Academy of Pediatrics (AAP) recommend RSV prophylaxis for certain infants ≤12 months of age with hemodynamically significant CHD, including *(a)* for infants with acyanotic heart disease who are taking medication to control congestive heart failure and who will require cardiac surgical procedures, and *(b)* for infants with moderate to severe PAH.
  - Decisions regarding palivizumab prophylaxis for infants with cyanotic heart defects in the first year of life should be made in consultation with a pediatric cardiologist.
  - Currently, prophylaxis is not recommended by the AAP for children with hemodynamically insignificant CHD, those with cardiomyopathy who are not taking medical therapy, those with surgically repaired CHD who are not taking therapy for heart failure, or children with hemodynamically significant CHD in their second year of life.
- In this patient population, symptoms of other respiratory infections, even if trivial, should be treated with close follow-up and early hospitalization if indicated.

Resources for Families

- The Children's Heart Foundation. www.childrensheartfoundation.org
- Little Hearts, Inc. www.littlehearts.org
- Cove Point Foundation: Congenital Heart Disease (Johns Hopkins University). www.pted.org

Clinical Pearls

- The cardiac and respiratory systems function as 1 unit, and pulmonary manifestations occur in most patients with CHD.
- Pulmonary blood flow is dependent on both cardiac output and pulmonary vascular resistance.
- Increased pulmonary blood flow and PAH are seen in many forms of CHD with left-to-right shunts and are a cause of impairment of lung mechanics.
- Pulmonary vascular disease is the end result of severe PAH and carries a high risk of mortality and morbidity.
- Newer treatment strategies for PAH, 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 CHD; appropriate prophylaxis with palivizumab is important in this patient population to reduce morbidity and mortality.

Acknowledgment

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Chapter 89

Respiratory Disorders Associated With Collagen Vascular Disease

Paul C. Stillwell, MD, FAAP, and Robin R. Deterding, MD

Introduction/Etiology/Epidemiology

- Collagen vascular diseases (CVDs), also known as *connective tissue diseases* or *rheumatic diseases,* are a diverse group of multisystem diseases caused by autoimmune antibodies.
- Table 89-1 shows the relative frequency of the individual CVDs in children. Table 89-2 shows the type of lung disease and the relative frequency for each CVD. This group includes
  - Juvenile idiopathic arthritis (JIA)
    - Of the 8 subtypes of JIA, pulmonary involvement most often occurs with systemic-onset JIA and rheumatoid factor–positive polyarticular arthritis.
  - Systemic lupus erythematosis
  - Juvenile systemic sclerosis

Table 89-1. Epidemiological Characteristics of Collagen Vascular Diseases

	JIA	SLE	JSS	JDM
Incidence (per 100,000 people)	16–150	6–18	0.45–1.9	0.2–0.4
Age of onset (y)	1–3	12	8	6–7
Common antibodies	Rheumatoid factor	ANA, anti-dsDNA	ANA, anti-Scl-70	Jo-1
Pulmonary involvement	Possible	Frequent	Frequent	Frequent or significant
Female-to-male ratio	2:1	4:1 (after puberty)	4:1	2:1
Ethnic predisposition	None	AA, Hispanic, Native American, Asian	AA, Native American	None

AA, African American; ANA, antinuclear antibody; anti-dsDNA, anti–double-stranded DNA antibody; anti-Scl-70, anti-topoisomerase 1 antibody; JDM, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; JSS, juvenile systemic sclerosis; RF, rheumatoid factor; SLE, systemic lupus erythematosus.

Table 89-2. Clinical Characteristics of Collagen Vascular Diseases as They Relate to the Lungs

	JIA	SLE	JSS	JDM
Pleuritis and/or effusion	Occasional	Common	Rare	Rare
Interstitial lung disease	Possible	Common	Frequent	Often
Alveolar hemorrhage	Rare	Often	Rare	Rare
Abnormal PFT results	Possible	Common	Common	Common
Abnormal diffusing capacity	Possible	Common	Common or significant	Common
Pneumonia	Rare	Often	Common	Common
Weakness	Occasional	Rare	Common	Often
Dysphagia and/or aspiration	Rare	Rare	Often	Often
Pulmonary hypertension	Rare	Common	Often	Rare
Pulmonary alveolar proteinosis	Possible	Rare	Rare	Rare

JDM, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; JSS, juvenile systemic sclerosis; PFT, pulmonary function test; SLE, systemic lupus erythematosus.

  - Juvenile dermatomyositis
  - Mixed connective tissue disease
  - Juvenile ankylosing spondylitis
  - Sjogren syndrome
- The most commonly occurring CVDs have the lowest incidence of pulmonary involvement; the less commonly occurring CVDs have a higher risk of pulmonary involvement.
- There is considerable overlap between the lung involvement with CVD, pulmonary vasculitis, and granulomatous lung disease (see Chapter 90, Vasculitis-Related Respiratory Disorders, and Chapter 91, Granulomatous Respiratory Disorders).
  - Although not explicitly a rheumatologic disease, pulmonary capillaritis is a neutrophilic vasculitis in the lung that results in life-threatening pulmonary hemorrhage.
  - These patients may develop a CVD over time and are frequently treated with many of the same agents used for CVD.
- In addition to the pulmonary involvement by the primary CVD, treatment of the CVD often renders the patient immunocompromised; therefore, opportunistic infections may be a cause of the respiratory disease.
- Some of the therapies for the CVD can be responsible for direct lung injury, such as methotrexate, and some of the new biological treatments, such as rituximab or rapamycin (sirolimus), can cause clinically significant immunosuppression.

- As new biological therapies evolve and are used in treatment regimens, there will need to be vigilance to recognize both positive and potentially negative effects on the lung.

Clinical Features

- Pulmonary symptoms may be the initial manifestation of the CVD.
- The symptoms of pulmonary involvement can be subtle and insidious.
  - Dyspnea with activity
  - Dry cough
  - Fatigue
- With alveolar hemorrhage, the presentation can be dramatic.
  - Severe dyspnea
  - Hemoptysis
- Crackles may be heard with interstitial lung disease.
- Dullness on percussion may be noted if there is a pleural effusion.
- The pulmonic component of the second heart sound may be increased when pulmonary hypertension is present.
- Wheezing may be evident with bronchiolitis obliterans, which is a rare disease process that can co-travel with CVD.

Diagnostic Considerations

- The diagnosis of the CVD is usually established with the assistance of a rheumatologist.
- The type of pulmonary disease is discerned by knowing the CVD type and what pulmonary diseases might be associated with that particular CVD.
- Clarification of pulmonary involvement is aided by findings at chest radiography, chest computed tomography, and, often, flexible bronchoscopy.
- Lung biopsy is usually required for the specific diagnosis of interstitial lung disease or pulmonary capillaritis.
- Bronchoscopy with bronchoalveolar lavage helps determine whether the pulmonary issue is an opportunistic infection, alveolar hemorrhage, or pulmonary alveolar proteinosis.

Treatment

- Treatment of the underlying CVD is usually treatment of the pulmonary component, as well, and specific treatment varies considerably, depending on the specific CVD.
- Common therapies include glucocorticoids, cyclophosphamide, methotrexate, and, more recently, biological agents such as rituximab (monoclonal antibody against CD20 protein) and anakinra (interleukin-1 receptor antagonist).
- Infectious complications often require intravenous antibiotics or antivirals.

Prognosis

- The short-term prognosis depends on the response of the primary CVD to initial therapy but is commonly favorable.
- Alveolar hemorrhage can be fatal, despite appropriate therapy.
- Recurrence of the pulmonary process is common with flares of the CVD.
- Progression to end-stage fibrosis may occur when ILD or pulmonary alveolar proteinosis with systemic JIA is present.
- If pulmonary hypertension is present, the prognosis is guarded.

When to Refer

- Pulmonary involvement with the CVDs requires multidisciplinary team involvement from pulmonology, rheumatology, infectious diseases, immunology, and, often, critical care medicine. Referral for evaluation and establishment of a follow-up plan should happen at the earliest sign of pulmonary disease.

Resource for Families

- Collagen Vascular Lung Disease (American Thoracic Society). www.thoracic.org/patients/patient-resources/breathing-in-america/resources/chapter-6-collagen-vascular-lung-disease.pdf

Clinical Pearl

- Symptoms of pulmonary disease may be the first indication of the presence of a CVD or may develop gradually over time, long after the diagnosis is established. All patients with CVD should be screened and followed up for pulmonary involvement, with a minimum of oxygen saturation evaluations and pulmonary function testing for anyone with pulmonary symptoms.

Chapter 90

Vasculitis-Related Respiratory Disorders

Paul C. Stillwell, MD, FAAP, and Robin R. Deterding, MD

Introduction/Etiology/Epidemiology

- Pulmonary vasculitides include a variety of systemic diseases with vessel involvement in many organ systems, including the lung (Table 90-1).
- These can be classified according to the size of the vessels primarily involved or by the association with antineutrophil cytoplasmic antibodies (ANCA) (cytoplasmic ANCA [c-ANCA] and perinuclear ANCA [p-ANCA]) (Box 90-1).
- Some of the more common causes of vasculitis in childhood, such as Henoch-Schönlein purpura and Kawasaki disease, do not often involve the pulmonary vessels.
- The most common pulmonary-renal syndromes are compared in Table 90-2.

Table 90-1. Common Childhood Vasculitides and the Relative Frequency of Organ System Involvement

Organ System	HSP	MPA	GPA	EGPA
Skin	Frequently present	Sometimes present	Sometimes present	Sometimes present
Renal	Sometimes present	Frequently present	Often present	Sometimes present
Otolaryngological	Typically not present	Sometimes present	Frequently present	Sometimes present
Musculoskeletal	Often present	Often present	Often present	Sometimes present
Neurological	Typically not present	Sometimes present	Sometimes present	Often present
Pulmonary	Typically not present	Sometimes present	Frequently present	Often present
Gastrointestinal	Often present	Sometimes present	Sometimes present	Sometimes present

EGPA, eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome); GPA, granulomatous polyangiitis (formerly Wegener granulomatosis); HSP, Henoch-Schönlein purpura; MPA, microscopic polyangiitis.

Box 90-1. Vasculitides Classified According to the Size of Vessels Commonly Involved

Small Vessels (Arterioles and Capillaries)	Medium Vessels (Arteries and Arterioles)	Large Vessels (Aorta and Major Branches)
MPA		
GPA	Polyarteritis nodosa	Giant cell arteritis
EGPA	Kawasaki disease	Takayasu arteritis
Goodpasture syndrome		

EGPA, eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome); GPA, granulomatous polyangiitis (formerly Wegener granulomatosis); MPA, microscopic polyangiitis. c-ANCA–positive vasculitis is most commonly GPA, whereas MPA and EGPA are more commonly p-ANCA positive.

Table 90-2. Comparison of the Most Common Pulmonary-Renal Syndromes in Children

Finding	Goodpasture Syndrome	SLE	GPA	MPA	EGPA
Alveolar hemorrhage	Frequently present	Sometimes present	Often present	Often present	Not often present
Renal disease	Frequently present	Often present	Often present	Often present	Not often present
Otolaryngological involvement	None	Not often present	Frequently present	Not often present	Sometimes present
Skin involvement	None	Frequently present	Often present	Often present	Not often present
Musculoskeletal involvement	None	Frequently present	Often present	Sometimes present	None
Increased erythrocyte sedimentation rate	None	Frequently present	Frequently present	Frequently present	None
Serologic or blood markers	Anti-GBM	ANA Anti-dsDNA	Antiprotease (c-ANCA)	Antimyeloperoxidase (p-ANCA)	Eosinophilia

ANA, antinuclear antibody; anti-dsDNA= anti–double-stranded DNA antibody; anti-GBM, anti-glomerulobasement membrane antibody; c-ANCA, cytoplasmic antineutrophil cytoplasmic antibodies; EGPA, eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome); GPA, granulomatous polyangiitis (formerly Wegener granulomatosis); MPA, microscopic polyangiitis; p-ANCA, perinuclear antineutrophil cytoplasmic antibodies; SLE, systemic lupus erythematosis.

Clinical Features

- The initial presentation may be hemoptysis caused by alveolar hemorrhage with respiratory failure.
- Presentation may be more insidious with involvement of other systems, such as
  - — Arthralgia
  - — Fatigue
  - — Skin manifestations
  - — Renal dysfunction
  - — Otolaryngological problems
- Pulmonary symptoms may be minimal, despite considerable radiographic abnormality.
- Abnormalities found in the physical examination may be minor and include
  - — Inspiratory crackles
  - — Decreased-intensity breath sounds
  - — Unexplained fever

Diagnostic Considerations

- Serologic testing facilitates establishing a specific diagnosis in many cases (Table 90-2).
- Chest radiographic and chest computed tomographic findings are often highly suggestive of a vascular pulmonary disease (Figure 90-1).
- Pathologic diagnosis with lung biopsy or biopsy of other involved tissue may be required to document the vasculitis.
  - — Pulmonary capillaritis, which is often associated with these diseases, can be difficult to identify *(a)* without expert and experienced pathology assistance or *(b)* if corticosteroid therapy has already been initiated.
  - — Bronchoscopy can help establish the presence of alveolar hemorrhage with increased bloody or pink-colored return on sequential lavage samples.
  - — Bronchoalveolar lavage can also help with exclusion of infectious causes for infiltrates.

Treatment

- Treatment regimens are determined by the specific type of vasculitis, as well as the severity of the illness at presentation.
- Intravenous corticosteroids are often the initial treatment.
- Additional therapy may include cyclophosphamide, methotrexate, or similar medications.
- Rituximab has proven to be effective in patients with granulomatous polyangiitis.
- Courses of therapy can be prolonged, and relapses can occur.

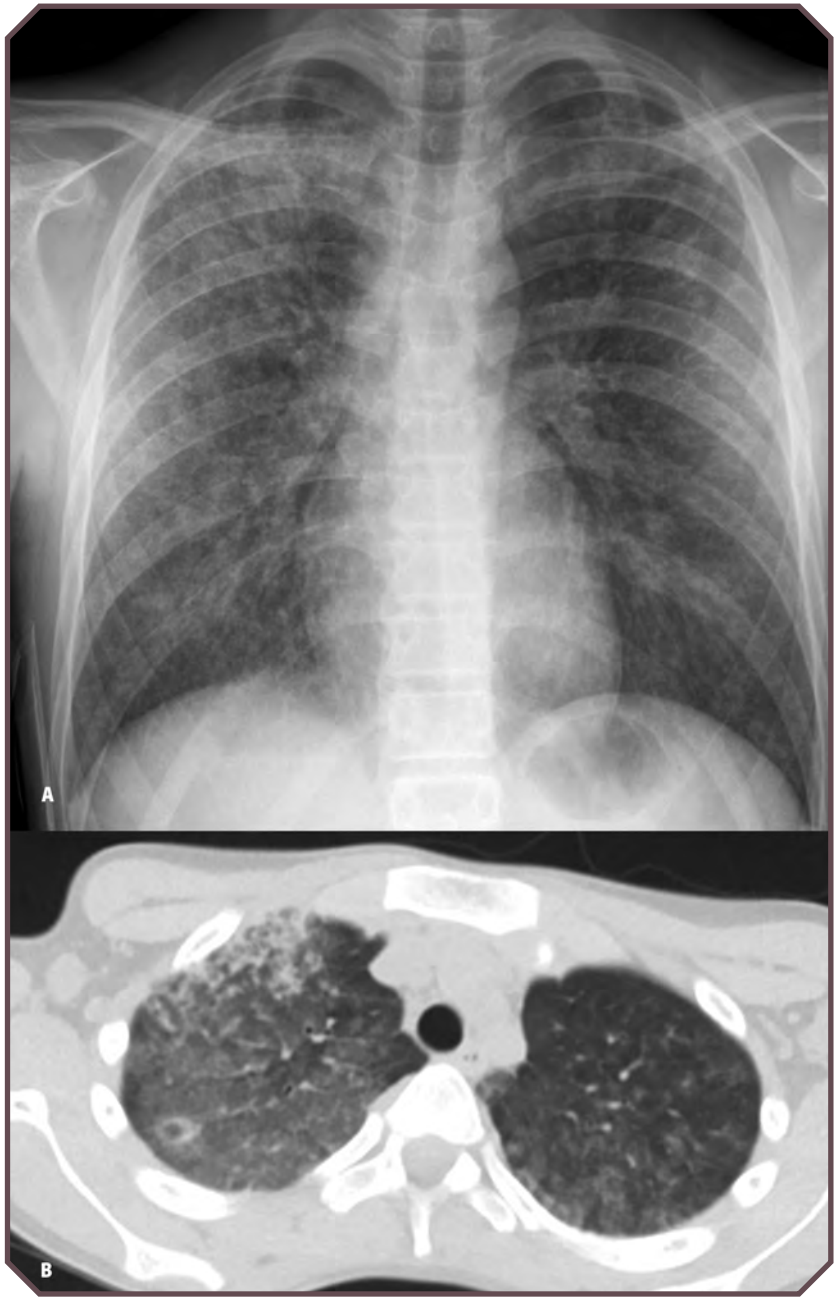

Figure 90-1. Granulomatosis with polyangiitis in a 15-year-old old boy with malaise, fatigue, dry cough, and anemia. A. Frontal chest radiograph shows bilateral, diffuse, coarse markings and scattered small nodules, especially in the upper lobes. B. Axial chest computed tomographic image with lung windows demonstrates ground-glass opacities, thickened interstitial markings, and upper-lobe predominant cavitary foci.

Prognosis

- The prognosis is generally favorable with specific and intense therapy and careful follow-up.
- Relapses and exacerbations can occur and require intensification of therapy.
- Alveolar hemorrhage with respiratory failure can be fatal.
- End-stage renal disease may challenge the quality of life for some patients.

When to Refer

- Because this group of systemic vasculitic diseases can be challenging to diagnose, treatment often requires a multispecialty team, including rheumatologists, pulmonologists, infectious diseases specialists, and intensive care specialists.
- Early referral offers the opportunity for effective treatment prior to extensive tissue damage.

Resource for Families

- Vasculitis Foundation. www.vasculitisfoundation.org

Clinical Pearl

- Pulmonary vasculitis is often the cause of diffuse alveolar hemorrhage that can be life-threatening.

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Chapter 91

Granulomatous Respiratory Disorders

Paul C. Stillwell, MD, FAAP, and Robin R. Deterding, MD

Introduction/Etiology/Epidemiology

- Granulomatous lung disease is categorized on the basis of several features of the granulomas, such as caseating and noncaseating and infectious or noninfectious etiologic origin (Boxes 91-1 and 91-2).
- The common feature is the pathologic appearance of an aggregate of histiocytes that are elongated and have indistinct borders.
  - — Multinucleated giant cells, lymphocytes, and plasma cells may also be present.
  - — If central necrosis is present, the granuloma will appear to have caseation and is most commonly caused by an infection (Figure 91-1).
- Granulomatous lung diseases are often associated with granulomas in several other organ systems, including the skin, subcutaneous tissues, and lymph nodes.
- Notable causes of granulomatous lung disease include
  - — Sarcoidosis
    - A multisystem disease of unknown etiologic origins
    - Noncaseating granulomas are the hallmark pathologic finding.

Box 91-1. Common Infectious Causes of Granulomatous Lung Disease in Children

Mycobacteria
Mycobacterium tuberculosis
Nontuberculous mycobacteria

Fungus
Histoplasma capsulatum
Blastomyces dermatitidis
Coccidioides immitis
Cryptococcus

Parasites
Dirofilaria (rare)
Toxoplasma gondii

Box 91-2. Common Noninfectious Causes of Granulomatous Diseases in Children

Sarcoidosis

Hypersensitivity pneumonitis
- **Bird fancier disease**
- **Farmer lung**
- **Hot tub lung**

Vasculitis
- **Granulomatosis with polyangiitis (formerly Wegener granulomatosis)**
- **Eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome)**

Aspiration (chronic)

Immunodeficiency
- **Chronic granulomatous disease**
- **Common variable immunodeficiency (granulomatous lymphocytic interstitial lung disease)**
- **Hypogammaglobulinemia**

Lymphoid interstitial pneumonitis

Crohn disease

Bronchocentric granulomatosis (often associated with *Aspergillus*)

  - Pulmonary involvement occurs in approximately 85% of adult patients; it may be slightly less common in children, particularly those <5 years of age.
  - Other organ systems commonly affected include the eyes, reticuloendothelial system (liver, lymph nodes, and spleen), skin, heart, and central nervous system.
  - In the United States, sarcoidosis is more prevalent and more severe in the African American population.
- Granulomatous lymphocytic interstitial lung disease (GLILD) associated with common variable immunodeficiency has been recognized with increasing frequency and, in some areas, is more common than sarcoidosis.
- Other causes include mycobacterial tuberculosis (see Chapter 58, Tuberculosis), nontuberculous mycobacterial lung disease (see Chapter 59, Nontuberculous Mycobacterial Pulmonary Disease), vasculitis (granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis; see Chapter 90, Vasculitis-Related Respiratory Disorders), hypersensitivity pneumonitis (see Chapter 75, Hypersensitivity Pneumonitis), and chronic granulomatous disease.

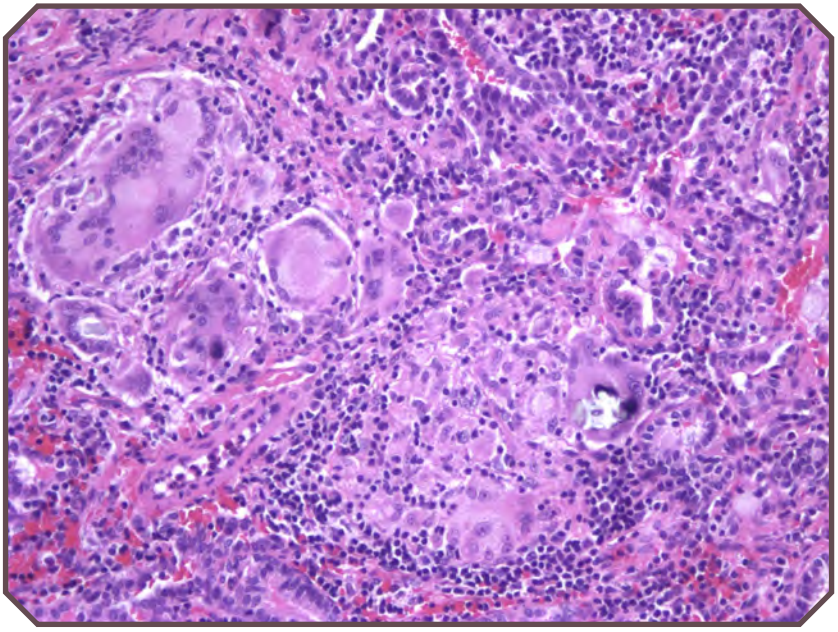

Figure 91-1. Photomicrograph (hematoxylin-eosin stain) of a lung biopsy specimen from a child with sarcoidosis demonstrates multiple noncaseating granulomas with large epithelioid cells, surrounded by lymphocytes (image courtesy of David Carpentieri, MD, Phoenix Children's Hospital).

Signs and Symptoms

- Signs and symptoms vary from being completely asymptomatic to demonstrating severe dyspnea and hypoxemia.
- Most children will have a chronic cough.
- Crackles are often present on auscultation.
- Cutaneous findings and lymphadenopathy may also be present.
- Malaise, fatigue, and low-grade temperature increases may be present, reflecting the systemic nature of the inflammation.

Diagnostic Considerations

- General comments on radiologic findings
  - — Asymptomatic granulomatous disease may be identified incidentally with a chest radiograph obtained for other reasons.
  - — The chest radiographic findings of more extensive disease may show increased interstitial opacities that may be reticular or reticulonodular.
- Hilar adenopathy is often present with sarcoidosis and mycobacterial infections.
  - — Sarcoidosis is a diagnosis of exclusion; alternative explanations, such as fungal infection, mycobacterial infection, and lymphoma, should be ruled out (Boxes 91-1 and 91-2).

— Radiographically, sarcoidosis often shows bilateral hilar adenopathy, interstitial infiltrates, pulmonary nodules, effusions, cystic change, and, in the most severe cases, extensive cysts (honeycomb lung) (Figure 91-2).
— Chest computed tomography (CT) is often performed to more completely assess granulomatous diseases (Figure 91-3). Images often show increased interstitial thickening and lymphadenopathy, but CT findings are generally not diagnostic, and lung tissue examination is required (Figures 91-4 and 91-5).
— Diagnosis of sarcoidosis requires histologic documentation of granulomatous involvement of at least 2 organ systems.
  - Tissue biopsy should be conducted from the most easily accessible site, often an enlarged peripheral lymph node.
  - Transbronchial biopsy is a useful source of tissue to establish a diagnosis.
  - Noncaseating granulomas are found in >90% of biopsy samples, even with mild or no changes on chest radiographs.

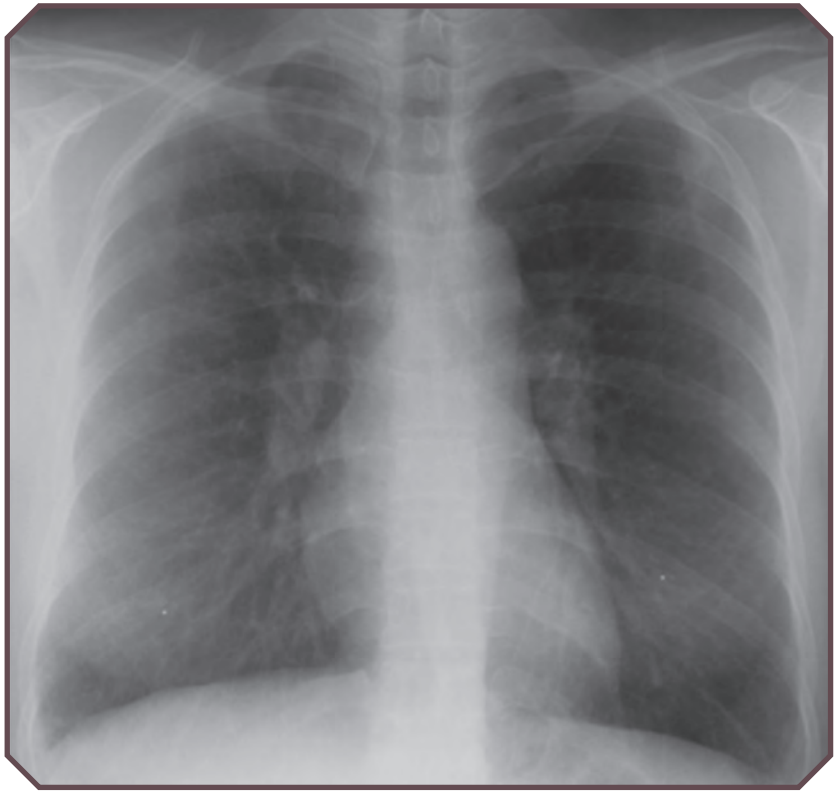

Figure 91-2. Sarcoidosis in a child. Frontal radiograph shows prominent reticulonodular interstitial opacities and subtle bilateral hilar adenopathy. Courtesy of Amy Filbrun, MD.

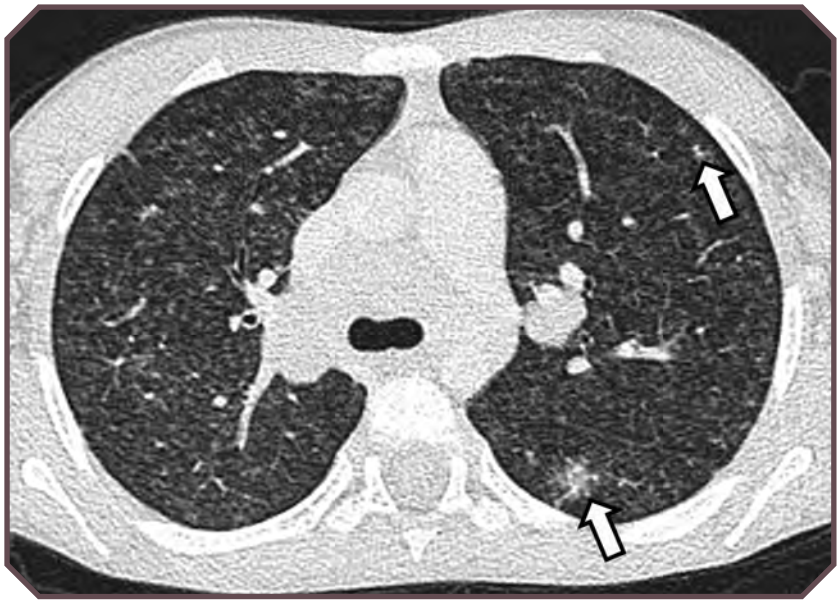

Figure 91-3. Granulomatous lymphocytic interstitial pneumonitis in a 17-year-old boy with pneumonia complicating common variable immunodeficiency. Axial chest computed tomographic image demonstrates increased interstitial lung markings with superimposed pulmonary nodules (arrows). The diagnosis was confirmed via lung biopsy.

- Supportive laboratory findings include hypercalcemia, hypercalciuria, increased serum angiotensin-converting enzyme (ACE) level, increased erythrocyte sedimentation rate, and eosinophilia.
  - An increased ACE level is not sensitive but is fairly specific and is not pathognomonic of sarcoidosis; the positive predictive value is high, but the negative predictive value is not.
- Pulmonary function testing may show a restrictive pattern with impaired diffusion capacity, but an obstructive pattern may also be present, as well as evidence for bronchial reactivity.
- Bronchoalveolar lavage (BAL) is not a helpful tool to establish the diagnosis of sarcoidosis, although it is commonly performed at the time of bronchoscopy for assessment of other granulomatous diseases. The primary utility of BAL in sarcoidosis is to help exclude fungal, mycobacterial, or atypical mycobacterial infection or other infectious processes.

Treatment

- Treatment should be directed at the underlying infection, if one has been clearly established as the etiologic origin of the granulomatous lung disease.

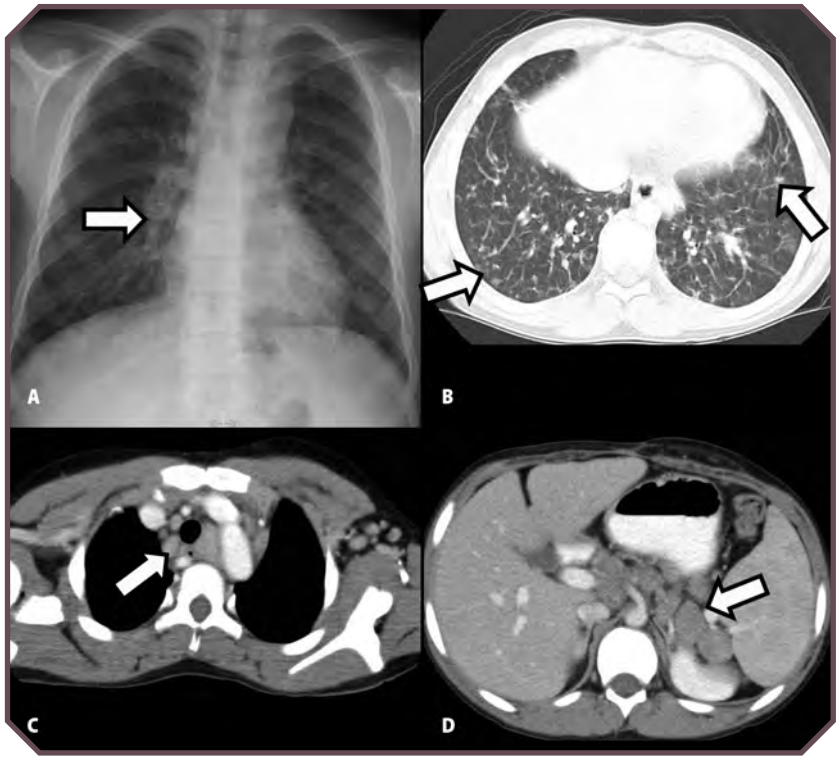

Figure 91-4. Sarcoidosis in a 6-year-old girl with chronic cough. A. Frontal chest radiograph demonstrates bilateral, coarse reticulonodular markings; right hilar adenopathy (arrow); and mediastinal widening, which suggests additional nodes. B. Axial chest computed tomographic (CT) lung window shows bilateral reticulonodular interstitial markings and demonstrates interstitial markings with multiple superimposed, ill-defined focal nodules (arrows). C. Axial contrast-enhanced CT image of the upper chest confirms mediastinal lymphadenopathy (arrow). D. Axial CT image of the abdomen shows extensive retroperitoneal nodes (arrow).

- If hypersensitivity pneumonitis is the cause, the offending antigen should be sought and eliminated from the patient's environment; corticosteroids are often needed to reverse the acute lung dysfunction.
- Treatment of sarcoid lung disease may not be indicated if the patient is not ill and if chest radiographs show only mild abnormalities.
  - More extensive pulmonary disease usually responds well to corticosteroids.
- For patients with granulomatous lymphocytic interstitial lung disease (GLILD), further genetic testing to guide treatment of the immunodeficiency is indicated, as well as pulse corticosteroids and intravenous immunoglobulin for the pulmonary disease. Rituximab has also been shown to have benefit.

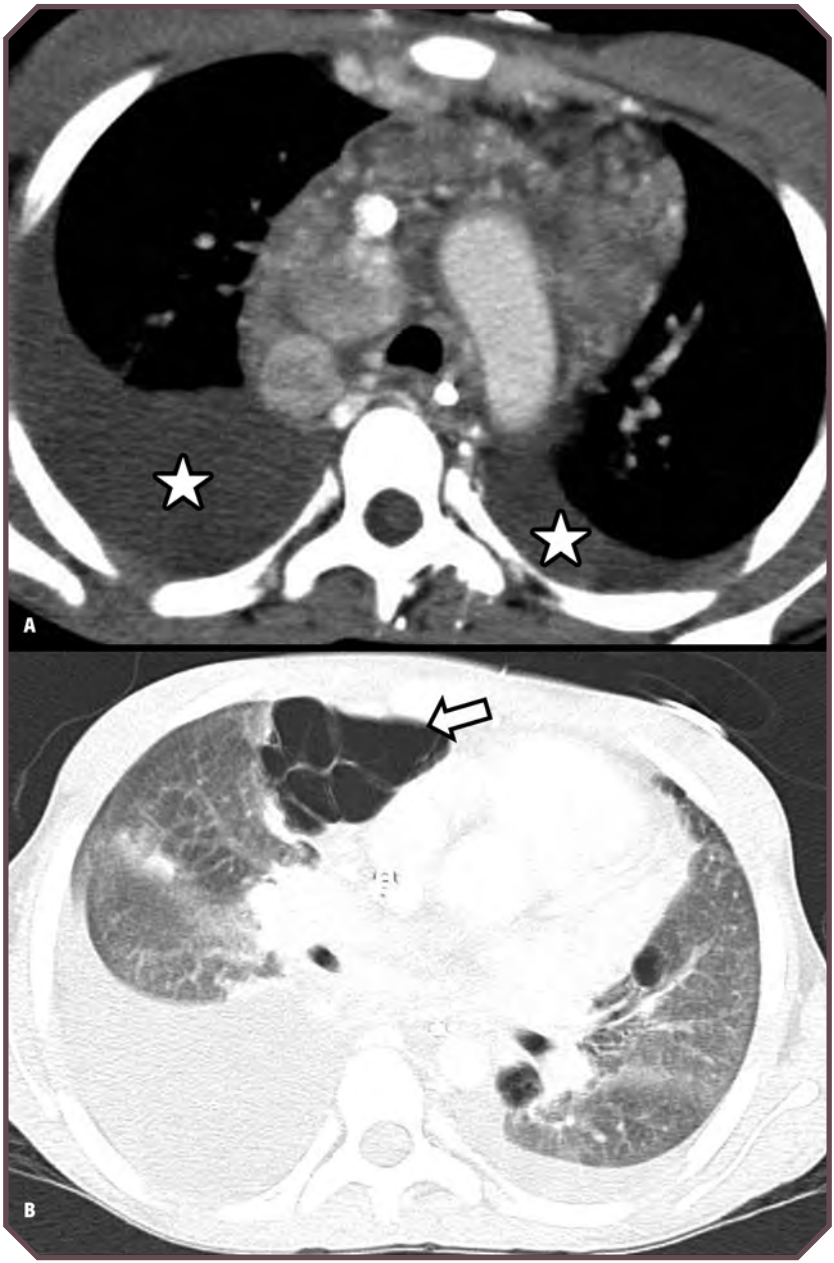

Figure 91-5. Chronic severe sarcoidosis in a 17-year-old girl. Axial contrast-enhanced computed tomographic images of the chest in A. soft-tissue and B. lung windows demonstrate mediastinal lymphadenopathy, bilateral pleural effusions (stars on A), diffuse reticulonodular interstitial markings, and extensive cystic changes (arrow on B).

Prognosis

- The outcome for immunocompetent patients is usually good.
- Some cases of sarcoidosis resolve without therapy.
  - Rarely, sarcoid lung disease can progress to fibrotic end-stage lung disease.
- The infectious causes of granulomatous lung disease generally respond well to appropriate antimicrobial therapy.
- Patients with GLILD may have a more guarded prognosis.

When to Refer

- Progressive respiratory symptoms, worsening radiographic findings, worsening difficulty in associated organ systems, or difficulty establishing the diagnosis

Resources for Families

- Sarcoidosis (Mayo Clinic). www.mayoclinic.org/diseases-conditions/sarcoidosis/home/ovc-20177969
- Sarcoidosis (WebMD). www.webmd.com/lung/arthritis-sarcoidosis

Clinical Pearl

- Pulmonary granulomatous disease has a wide differential diagnosis, and determining a cause can be challenging. Biopsy of affected tissues may be necessary to establish the correct diagnosis.

Chapter 92

Respiratory Disorders Associated With Gastrointestinal and Hepatic Disease

Edward W. Fong, MD

Introduction/Etiology/Epidemiology

- Many different respiratory disease processes are associated with gastrointestinal (GI) and liver disease (Tables 92-1 and 92-2, Box 92-1).
- Respiratory disease is typically a complication or sequela of GI or hepatic disease. It may be variable in course and prognosis:
  - — It may be transient and mild if GI or hepatic disease is self-limiting and/or amenable to a treatment regimen, such as gastroesophageal reflux (GER).
  - — It may be debilitating and severe if GI or hepatic disease is chronic, as in the case of progressive disease with limited response to treatment regimen, such as α_1-antitrypsin deficiency with liver disease, severe sarcoidosis, or Langerhans cell histiocytosis.

Table 92-1. Pulmonary Disorders Associated with GI Disorders

Gastrointestinal Disease	Pulmonary Disorder
Gastroesophageal reflux disease	Recurrent or persistent cough and/or wheeze, apnea, nocturnal cough, recurrent pneumonia, hemoptysis, stridor, hypertrophied adenoids, snoring
Aspiration	Recurrent or chronic infection, hyperreactive airway disease, airway inflammation, apnea, bronchiectasis, recurrent or chronic cough and/or wheeze, vocal hoarseness
Inflammatory bowel disease	Airway inflammation, bronchiolitis obliterans, interstitial lung disease, granulomas
Cystic fibrosis	Tracheobronchitis, pneumonia, atelectasis, bronchiectasis, hyperreactive airway disease, cysts, bullae, pneumothorax, pulmonary hemorrhage, pulmonary hypertension

Table 92-2. Pulmonary Disorders Associated with Hepatic Disorders

Hepatic Disease	Pulmonary Disorder
Infections	Hilar adenopathy, pneumonia tracheobronchitis, pleural effusions
α_1-antitrypsin deficiency	Wheezing, chronic obstructive pulmonary disease, emphysema, recurrent lung infections in adults
Wilson disease	Hepatopulmonary syndrome, clubbing, cyanosis
Primary sclerosing cholangitis	Bronchitis, bronchiectasis
Chronic granulomatous disease of childhood	Hilar adenopathy, pneumonia, atelectasis, pleural effusion, abscess, honeycomb lung, pulmonary hypertension
Cystic fibrosis	Tracheobronchitis, pneumonia, atelectasis, bronchiectasis, hyperreactive airway disease, cysts, bullae, pneumothorax, pulmonary hemorrhage, pulmonary hypertension
Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease)	Pulmonary angiodysplasia
Langerhans cell histiocytosis	Hilar adenopathy, pneumonitis, interstitial fibrosis, pleural effusion, pneumothorax, honeycomb lung, pulmonary hypertension
Sarcoidosis	Hilar adenopathy, reticulonodular infiltrates, atelectasis, hyperreactive airway disease, granulomata, bronchial stenosis, interstitial pneumonitis, interstitial fibrosis, pleural effusion, pneumothorax, nodules, cysts, pulmonary hemorrhage, pulmonary hypertension
Chronic active hepatitis	Pneumonia, atelectasis, interstitial pneumonitis, interstitial fibrosis, fibrosing alveolitis, pleural effusion, pulmonary hypertension, pulmonary hemorrhage
Liver transplant	Pleural effusion, pneumonia, atelectasis, pulmonary edema, acute respiratory distress syndrome
Cirrhosis (alcoholic, postnecrotic, cryptogenic)	Pneumonia, pleural effusion, pulmonary angiodysplasia, pleural vasodilatations, pulmonary hypertension
Primary biliary cirrhosis	Hyperreactive airway disease, interstitial pneumonitis, interstitial fibrosis, fibrosing alveolitis, pulmonary hypertension
Portal hypertension	Dyspnea, pulmonary hypertension, hepatopulmonary syndrome, hemoptysis

Adapted from Ozdogan S, Fong E. Pulmonary complications of gastrointestinal diseases. In: Light MJ, Blaisdell CJ, Homnick DN, Schechter MS, Weinberger MM, eds. *Pediatric Pulmonology.* Elk Grove Village, IL: American Academy of Pediatrics;2011:799–814.

Box 92-1. Pulmonary Disorders Associated with Pancreatitis

Acute Pancreatitis

- Pleural effusion
- Empyema
- Hemidiaphragm elevation
- Atelectasis: left lower lobe
- Pneumonia: left lower lobe
- Pulmonary embolism
- Pulmonary infarction
- Acute respiratory distress syndrome
- Pulmonary edema

Chronic Pancreatitis

- Pancreaticopleural fistula
- Pancreaticobronchial fistula
- Pancreaticobronchopleural fistula
- Recurrent pleural effusion
- Recurrent lobar pneumonia

Adapted from Ozdogan S, Fong E. Pulmonary complications of gastrointestinal diseases. In: Light MJ, Blaisdell CJ, Homnick DN, Schechter MS, Weinberger MM, eds. *Pediatric Pulmonology.* Elk Grove Village, IL: American Academy of Pediatrics;2011:799–814.

- Early consideration that leads to early evaluation and management of GI or hepatic disease is the best way of avoiding pulmonary complications.
  - The diagnosis and management of respiratory disease are typically indicated for symptom management to mitigate the severity or progression of disease.
- The etiologic origins of pulmonary disease are varied and dependent on specific disease processes. In general, the common pathway is through an inflammatory process that leads to irritation, inflammation, impaired innate defense, infection, obstruction, and fibrosis.
- The epidemiology of pulmonary disease depends on the frequency and often the severity of GI or hepatic disease.

Pathophysiology

- Aspiration: Central nervous system immaturity or disease, swallowing dysfunction, or anatomic defects lead to foreign material being deposited in the airways and alveoli, which can impair innate defenses and/or cause direct injury of the parenchyma.
- GER: In spite of a strong association, the mechanism is not clearly understood; direct injury caused by acidic or nonacidic stomach contents has been proposed.

- Inflammatory bowel disease (IBD): The mechanism is not understood; direct inflammation of the airways and parenchyma caused by underlying inflammatory process is the most likely.
- α_1-antitrypsin deficiency: Loss of inhibition of neutrophil elastase leads to protease-mediated tissue destruction of the lungs; it is possibly expedited in cigarette smokers because cigarette smoke increases protease activity.
- Liver disease or cirrhosis: Different mechanisms are dependent on the underlying disease process, which could cause
  - Direct lung injury from infections, increases in toxins or medications (directly or through immunosuppression), or hepatic infiltration
  - Indirect lung injury via cirrhosis that could also lead to hepatopulmonary syndrome and/or portopulmonary hypertension
    - Hepatopulmonary syndrome is characterized by hypoxemia and dyspnea secondary to formation of intrapulmonary arteriovenous dilations. Portal hypertension is thought to lead to this because of either increased hepatic production or decreased hepatic clearance of vasodilators.
- Pancreatitis: The mechanism is typically an indirect consequence of the injury and/or inflammatory response to the pancreatitis.

Clinical Features

- Aspiration: Stridor, wheeze, cough, hoarseness, apnea, pneumonia
- GER: Stridor (in infants), brief resolved unexplained events (BRUE) (possibly), wheeze, cough, hoarseness, apnea, throat clearing, pneumonia, chest pain
- IBD: Cough, dyspnea, chest pain, wheeze
- α_1-antitrypsin deficiency: Wheeze, dyspnea, cough, exercise intolerance, chronic sputum production, and digital clubbing may develop in young adults, especially smokers. Lung disease does not develop during childhood.
- Liver disease or cirrhosis:
  - Dyspnea, exercise intolerance, hypoxemia, digital clubbing, orthopnea, fatigue, and syncope
  - Characteristic (but not pathognomonic) features include dyspnea ("platypnea") and hypoxemia ("orthodeoxia"), which are worse in the upright position and are improved by lying supine because of a gravitational increase in blood flow through dilated vessels in the lung bases.
- Pancreatitis: Hypoxemia, painful deep inspiration, cough, and chest pain

Diagnostic Considerations

- Aspiration
  - — Clinical evaluation by a feeding, speech, or occupational therapist
  - — Imaging studies
    - ▪ Direct evidence: Videofluoroscopic swallow study (also known as a modified barium swallow) and fiber-optic endoscopic evaluation of swallowing
    - ▪ Indirect evidence: Radionuclide salivagram, gastric-emptying scintigraphy with delayed imaging, chest radiography
  - — The lipid-laden macrophage index from bronchoalveolar lavage (BAL) may be helpful, but results need to interpreted in context, because this index is increased in a number of other inflammatory airway conditions (Figure 92-1).
- GER
  - — Clinical evaluation
  - — Esophageal pH level and impedance monitoring
  - — Imaging studies: Upper GI study is limited in both sensitivity and specificity but is frequently used.
  - — Gastric-emptying scintigraphy may be used if delayed emptying is the suspected cause of symptoms.
  - — Endoscopy with or without biopsy
  - — Lipid-laden macrophage index from BAL (also see Figure 92-1)

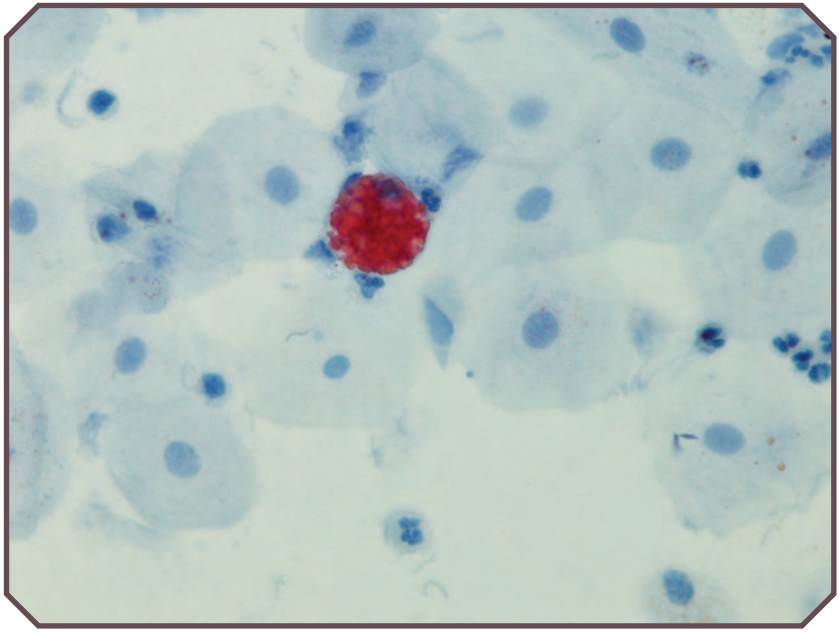

Figure 92-1. Photomicrograph (red oil O stain; original magnification, ×1,000) shows a lipid-laden macrophage. Image used with the permission of Elaine Cham, MD, Department of pathology, UCSF Benioff Children's Hospital, Oakland.

- IBD
  - Direct: Lung biopsy
  - Indirect: Computed tomography (CT) or magnetic resonance (MR) imaging, barium contrast studies, pulmonary function testing
- α_1-antitrypsin deficiency
  - Direct: Genetic testing for alleles, serum testing for α_1-antitrypsin protein
  - Indirect: CT, pulmonary function testing
- Liver disease or cirrhosis
  - General testing: Liver function testing, γ-glutamyltransferase test; ultrasonography (US) and CT may show features of cirrhosis, such as hepatosplenomegaly and varices
  - Specific testing
    - Hepatitides: Serum testing
    - Wilson disease: Ophthalmologic evaluation for Kayser-Fleischer rings; serum ceruloplasmin; urinary, serum, or hepatic copper levels
    - Portal hypertension: Ultrasonography, endoscopy, transient elastography
    - Hepatopulmonary syndrome: Bubble echocardiography, blood gas, cardiac catheterization
- Pancreatitis
  - Amylase and lipase are useful for screening. US, endoscopy, CT, or MR imaging can be used to demonstrate anatomic causes and complications of pancreatitis.

Treatment/Management

- Aspiration
  - Alternative method of feeding: Nasogastric tube, gastrostromy tube, gastrojejunostomy tube, jejunal tube
  - Feeding therapy: Adjustment of thickness of food, avoidance of straws in older children, and use of special nipples in infants, as guided via video fluoroscopic swallow study
  - Medical: Anticholinergic medication, glycopyrrolate may decrease aspiration of saliva
  - Surgical: Partial ablation of salivary glands, Lindeman tracheoesophageal diversion
- GER
  - Medical: H_2 antihistamine, proton pump inhibitor, reflux precautions, prokinetic agents, feedings that bypass the stomach (short term, nasojejunal; long term, gastrojejunal)
  - Surgical: Nissen fundoplication
- IBD
  - Dependent on type; immunosuppression, chemotherapy

- α_1-antitrypsin deficiency
  - — Augmentation therapy via infusion of α_1-antitrypsin
  - — Management of pulmonary complications: airway clearance therapies, bronchodilators, antibiotics as indicated
- Liver disease or cirrhosis
  - — Dependent on underlying disease
  - — Consider ursodiol and liver transplantation
  - — Specific management
    - ▪ Hepatitides
      - ~ B: Lamivudine, adefovir dipivoxil
      - ~ C: Peginterferon, ribavarin
    - ▪ Wilson disease: Chelating agents
    - ▪ Portal hypertension: Transjugular intrahepatic shunting
    - ▪ Hepatopulmonary syndrome: Transjugular intrahepatic shunting, inhaled nitric oxide, liver transplant
- Pancreatitis
  - — Partial or complete bowel rest

Prognosis of Pulmonary Disease

- Aspiration: Good if aspiration is well controlled
- GER: Good if GER is well controlled or resolved
- IBD: Dependent on control of IBD
- α_1-antitrypsin deficiency: Ranges from good to poor; dependent on mutation type, whether liver is involved, and progression of disease
- Liver disease or cirrhosis: Poor, especially if associated with portal hypertension and worse if associated with hepatopulmonary syndrome
- Pancreatitis

When to Refer

- Aspiration
  - — Pulmonary: If the patient has a pneumonia or pneumonitis episode, stridor, or BRUE (formerly known as *apparent life-threatening events*)
  - — GI: Immediately, especially if an alternative method of feeding is required
- GER
  - — Pulmonary: If the patient has recurrent wheezing and/or coughing episodes, BRUE, or recurrent pneumonia
  - — GI: If the disease is severe or refractive to medical therapy
- IBD
  - — Pulmonary: Typically not necessary after a diagnosis of IBD is established because management of IBD alleviates pulmonary involvement; only needed if IBD is refractory to treatment and there is progression of pulmonary disease
  - — GI: Immediately

- α_1-antitrypsin deficiency
  - Pulmonary: Not routinely necessary because lung involvement starts in adulthood, but plausible if the family requires education
  - GI: Immediately for evaluation and surveillance of liver involvement
  - A pulmonary or GI specialist may start augmentation therapy
- Liver disease or cirrhosis
  - Pulmonary: Dependent on the degree of pulmonary involvement
  - Cardiology: If evaluation and management of pulmonary hypertension are required
  - GI: Immediate for evaluation and management
- Pancreatitis
  - Pulmonary: Not typical unless cystic fibrosis is diagnosed or is a comorbidity or management of pancreatic complication is required (eg, acute respiratory distress syndrome leads to chronic respiratory failure, bronchofistula, empyema)
  - GI: Immediate for evaluation and management

Resources for Families

- Crohn's and Colitis Foundation of America. www.ccfa.org
- IBD Support Foundation. www.ibdsf.org
- Alpha-1 Foundation. www.alpha1.org

Chapter 93

Respiratory Disorders Associated With Cerebral Palsy and Neurodegenerative Diseases

Laura Beth Mann Dosier, MD, and Richard M. Kravitz, MD, FAAP

Introduction/Etiology/Epidemiology

- Cerebral palsy (CP) is not a disease per se but is the consequence of perinatal insults, such as hypoxia, infection, prematurity, and intrauterine growth retardation.
- There can be many manifestations of CP, depending on the severity of damage present; these may include
  - Central nervous system (CNS) complications (seizures, developmental delay)
  - Musculoskeletal complications (spasticity, hypotonia, contractures, scoliosis)
  - Respiratory complications
- Neurodegenerative diseases represent a separate and distinct group of illnesses that have multiple different etiologic origins.
- CP and neurodegenerative diseases have a common final pathway that can lead to respiratory complications.
- The most common respiratory problems in children with CP and neurodegenerative diseases include
  - Airway clearance abnormalities (weakened or ineffective cough)
  - Aspiration (with or without gastroesophageal reflux [GER])
    - Recurrent aspiration may lead to bronchiectasis.
  - Recurrent pneumonia
  - Asthma (independent of aspiration)
  - Restrictive lung disease
  - Sialorrhea
  - Sleep disturbances
    - Snoring
    - Obstructive and central apnea
  - Upper-airway obstruction

Pathophysiology

- Muscle tone abnormalities can lead to
  - Ineffective or diminished cough
  - Altered swallowing function
    - Inability to handle oral secretions
    - Higher risk for aspiration of secretions and food
  - Altered upper-airway tone with subsequent collapse and obstruction
    - Obstructive sleep apnea
    - Hypoventilation
    - Fragmented sleep
- CNS-related dysfunction
  - Altered sleep patterns (reversed day-night cycles)
  - Insomnia
  - Excessive tiredness
- Orthopedic complications
  - Scoliosis
    - Development of restrictive lung disease
    - Altered airway clearance
    - Abnormal insertion of the esophagus through the diaphragm and loss of lower esophageal sphincter tone, which leads to GER.
- Gastrointestinal complications
  - Increased GER
  - Secondary aspiration

Clinical Features of Pulmonary Comorbidities

- Symptoms
  - Coughing or wheezing
    - May be related to aspiration, exacerbation of bronchiectasis, or comorbid asthma
  - Feeding-related symptoms
    - Choking with subsequent coughing and/or wheezing and aspiration
  - Upper-airway symptoms
    - Noisy breathing
  - Sleep-related symptoms
    - Snoring
    - Apneas
    - Gasping respirations while asleep
- Signs
  - Scoliosis
  - Wet voice (especially with feeding)
  - Altered cough (usually weak in quality)
  - Chest congestion (rattling sound)
  - Stridor
  - Stertor
  - Snoring

Establishing the Etiologic Origin of Pulmonary Disease

- Chest imaging (chest radiography and computed tomography) may show
  - Atelectasis (Figure 93-1)
  - Recurrent pneumonia
  - Bronchiectasis
  - Scoliosis (Figure 93-2)
- Swallowing studies are used to assess the presence of aspiration
  - Radiologic examination (videofluoroscopic swallow study [modified barium swallow]; radionuclide salivagram)
  - Speech consultation (observe feeding)
  - Videofluoroscopic swallow study or fiber-optic endoscopic evaluation of swallowing
- Evaluation for GER
  - Upper-gastrointestinal study is limited in both sensitivity and specificity but is frequently used.
  - Gastric-emptying scintigraphy may be used if delayed emptying is the suspected cause of symptoms.
  - Esophageal pH level or impedance monitoring
  - Endoscopy with biopsy to assess the presence of esophagitis
- Pulmonary function testing (when available)
  - Spirometry
    - Assess the extent of restrictive lung disease
    - Assess the response to bronchodilators
  - Monitoring of oxygenation and ventilation
    - Noninvasive (pulse oximetry; capnography)
    - Invasive (capillary, arterial, or venous blood gas)
  - Respiratory muscle strength testing
    - Maximal expiratory pressure
    - Maximal inspiratory pressure
    - Cough peak flow

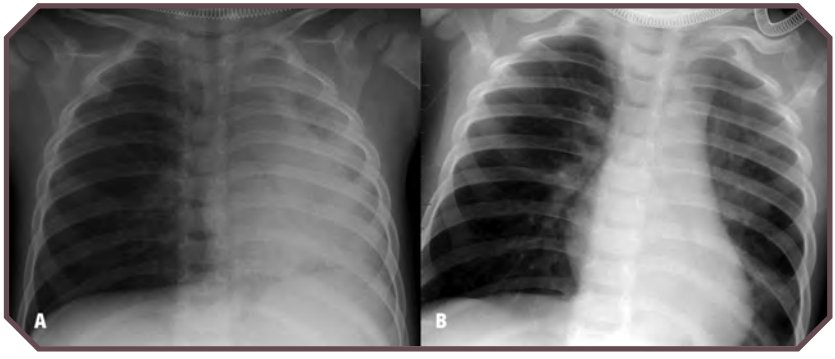

Figure 93-1. Atelectasis in a 2-year-old girl with shortness of breath. A. Frontal chest radiograph shows loss of left lung volume and shift of mediastinum from left to right. B. Frontal chest radiograph obtained 4 hours later demonstrates near-complete resolution of findings, consistent with resolved atelectasis.

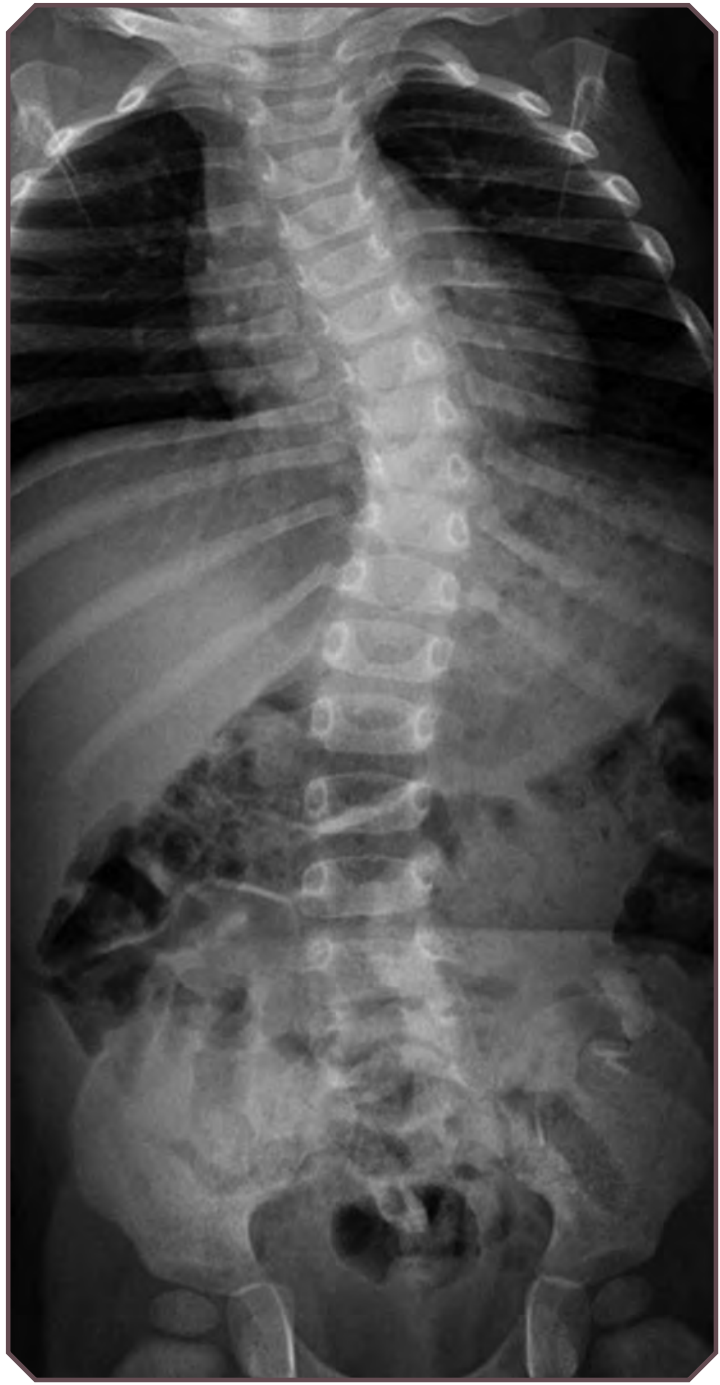

Figure 93-2. Scoliosis in a 5-year-old girl. A. Frontal spine radiograph shows levoconvex scoliosis and decreased lung volumes bilaterally.

- Polysomnography may be used in patients with clinical symptoms suggestive of
  - Sleep-disordered breathing (obstructive and/or central apnea)
  - Hypoventilation (hypoxia and/or hypercarbia)
  - Sleep fragmentation
- Bronchoscopy
  - To evaluate sources of airway obstruction
  - To obtain cultures for pneumonia
  - Cytologic study to assess the presence of (possible) aspiration

Management

- Airway clearance augmentation in patients with diminished cough
  - Manual chest physiotherapy (with postural drainage)
  - High-frequency chest wall oscillation (ie, "the vest")
  - Cough augmentation (mechanical insufflation-exsufflation with the "cough assist" machine)
  - Consider trial mucolytic agents on a case-by-case basis because there is no evidence to support their benefits.
    - Acetylcysteine
    - Dornase alfa (Use with caution: One study in adults with idiopathic bronchiectasis demonstrated an increased rate of exacerbations and hospitalizations associated with this medication.)
    - Hypertonic saline (0.9% vs 3% vs 7% concentration)
- Prevention of aspiration
  - Modified feeding plan (with assistance from a speech therapist)
  - Giving the patient nothing by mouth and using tube feedings (nasogastric, nasoduodenal, gastrostomy, gastrojejeunal)
- Treatment of GER
  - Pharmacological interventions
    - Acid blockers (ie, ranitidine, omeprazole)
    - Motility agents (ie, metoclopramide, erythromycin)
  - Surgical options
    - Gastrostomy tube with Nissen fundoplication
    - Gastrojejeunal feeding
  - (Comorbid) Asthma rescue bronchodilators (inhaled albuterol)
    - Parasympathetic agents (inhaled ipratropium) in select cases
    - Levalbuterol in the few select patients who do not tolerate albuterol
  - Inhaled steroids (for chronic, recurrent symptoms suggestive of asthma)
  - Oral steroids for acute exacerbations
- Infections
  - Use antibiotics judiciously when the patient is ill.
  - Treat the patient for community-acquired organisms.
    - Consider coverage for aspiration when indicated.
  - Consider chronic antibiotic therapy if bronchiectasis is present.

- Restrictive lung disease
  - Orthopedic consultation for treatment of scoliosis
  - Ventilatory support may be needed if chronic respiratory failure is present
- Sialorrhea
  - Anticholinergics for salivary control (glycopyrrolate, scopolamine)
    - Judicious use is warranted because these agents can dry lower-airway secretions, making them thicker and harder to expectorate.
  - Botox injections of salivary glands
  - Surgical ligation of salivary ducts (in more extreme cases)
- Sleep-disordered breathing
  - Supplemental oxygen for nocturnal hypoxia
  - Airway surgery (adenotonsillectomy, airway reconstruction, tracheostomy tube placement) or continuous positive airway pressure for obstructive sleep apnea
  - Bilevel pressure or noninvasive positive pressure ventilation for obstructive sleep apnea, central sleep apnea, mixed sleep apnea, or hypoventilation
  - Tracheostomy with mechanical ventilation when bilevel pressure or noninvasive positive pressure ventilation is not tolerated or indicated
- Insomnia
  - Behavioral modification
  - Sleep-inducing agents (ie, melatonin, clonidine, gabapentin)

Prognosis

- Highly variable; dependent on the severity of the underlying disease
- In 1 study, pneumonia (including aspiration pneumonia) was the cause of death in 40% of children with severe CP.

When to Refer

- Refer the patient to a pulmonologist for
  - Recurrent respiratory symptoms
  - Recurrent respiratory infections
  - Recurrent hospitalization for respiratory complications
  - Sleep-related issues
  - Persistent oxygen requirement
- Refer the patient to a speech therapist for
  - Swallowing dysfunction
  - Recurrent aspiration
- Refer the patient to an otolaryngologist for
  - Upper-airway obstruction
  - Sialorrhea
- Refer the patient to an orthopedist for
  - Scoliosis monitoring and correction

Prevention

- Have a low threshold for modifying feedings or giving the patient nothing by mouth if the risk for aspiration is high.
  - In these cases, optimize nutritional management to prevent malnourishment or obesity.
- Use aggressive airway clearance in patients with decreased cough reflex.
- Ensure that patients receive routine immunizations.
  - Yearly influenza vaccination
  - Pneumococcal vaccination in older patients
- Always temper treatment burden with quality-of-life issues.

Resources for Families

- American Academy of Cerebral Palsy and Developmental Medicine. www.aacpdm.org
- United Cerebral Palsy. ucp.org
- Cerebral Palsy Foundation. yourcpf.org
- Breathing Problems in Children With Neuromuscular Diseases (American Thoracic Society). www.thoracic.org/patients/patient-resources/resources/neuromuscular-breathing-proof-a5.pdf

Clinical Pearls

- While CP and neurodegenerative diseases have different etiologic origins, they share a common final pathway that can lead to respiratory complications.
- Commonly seen respiratory complications that warrant monitoring and potential interventions include aspiration and recurrent pneumonia, sialorrhea, restrictive lung disease, and progressive respiratory failure.
- Secretion management is a mainstay of therapy and includes both medical and surgical options.
- Airway clearance therapy may prove useful in maintaining pulmonary health.
- Nutritional support needs to be optimized in a safe manner to prevent aspiration.
- In more severe cases, close monitoring for sleep-disordered breathing and potential progressive respiratory failure is needed.

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Chapter 94

Respiratory Disorders Associated With Neuromuscular Disease

Laura Beth Mann Dosier, MD, and Richard M. Kravitz, MD, FAAP

Introduction/Etiology/Epidemiology

- Neuromuscular disease is not 1 specific entity but represents a variety of diseases where an abnormality develops anywhere between the peripheral nervous system and the muscle, resulting in muscle weakness.
- The point of origin of this defect can be
  - Lower motor neuron
  - Peripheral nerves
  - Neuromuscular junction
  - Muscle
- Various etiologic origins of this class of diseases include
  - Inherited
  - Autoimmune
  - Infectious
- Examples of the more commonly seen diseases include
  - Spinal muscular atrophy (types 1, 2, 3)
  - Charcot-Marie-Tooth disease
  - Guillain-Barré syndrome
  - Becker muscular dystrophy
  - Duchenne muscular dystrophy
  - Facioscapulohumeral muscular dystrophy
  - Limb girdle muscular dystrophy
  - Emery-Dreifuss muscular dystrophy

Pathophysiology

- Muscle tone abnormalities can lead to
  - Ineffective or diminished cough
    - Impaired airway clearance
  - Altered upper-airway tone with subsequent collapse and obstruction
    - Obstructive sleep apnea

  - Decreased muscle strength, resulting in hypoventilation (initially during sleep; eventually during wakefulness, as well)
    - Respiratory failure
  - Altered swallowing function (especially if bulbar dysfunction is present)
    - Inability to handle oral secretions
    - Higher risk for aspiration of secretions and food
    - Weight loss exacerbating further muscle weakness
- Scoliosis is the chief orthopedic complication and can lead to
  - Development of restrictive lung disease
  - Altered airway clearance
  - Abnormal insertion of the esophagus through the diaphragm and loss of lower esophageal sphincter tone, leading to gastroesophageal reflux (GER)
- Gastrointestinal complications include
  - Increased GER
  - Secondary aspiration
  - Constipation

Clinical Features

- Different neuromuscular diseases have various modes of presentation.
  - Duchenne muscular dystrophy
    - Symptoms are often evident by 4 years of age.
    - Duchenne muscular dystrophy usually manifests with tripping, falling, or difficulty standing up without assistance (pushing up on the legs to reach a standing position [Gower maneuver]).
  - Spinal muscular atrophy (SMA)
    - Type 1: Early hypotonia (<6 months old) and patient cannot sit independently
    - Type 2: Patient never able to walk but can sit independently (6–24 months old)
    - Type 3: Patient able to walk but may have gradually increasing weakness (>18 months old)
    - Type 4: Onset in adulthood
- Respiratory symptoms of neuromuscular disease include
  - Decreased exercise tolerance
  - Cough that is weak, chronic, or recurrent in quality
  - Chronic throat clearing
  - Recurrent lower respiratory tract infections
  - Progressive dyspnea
  - Sleep-related issues
    - Snoring
    - Apneas
    - Morning headaches
    - Daytime sleepiness
  - Feeding issues
    - Choking, gagging, and/or coughing with eating

- Respiratory signs of neuromuscular disease include
  - Weak cough
  - Snoring
  - Scoliosis
  - Gower maneuver (pushing up on the legs to reach a standing position)
  - Pseudohypertrophy of the calf muscles (in Duchenne muscular dystrophy)
  - Tongue fasciculations (in SMA)

Differential Diagnosis

- The differential diagnosis for respiratory distress (shortness of breath, tachypnea, retractions, hypoxia) in children with neuromuscular disease includes
  - Atelectasis secondary to
    - Weak cough and suboptimal secretion clearance
    - Recurrent infections
    - Hypoventilation with low lung volumes
    - Chronic microaspiration
  - Pneumonia
  - Aspiration
  - Restrictive lung disease secondary to
    - Muscle weakness
    - Scoliosis
  - Progressive respiratory failure
  - Heart failure (cardiomyopathy is seen in several muscular dystrophies)

Diagnostic Considerations

- Muscular dystrophy is diagnosed by means of
  - Creatine kinase level
  - Genetic testing
  - Electromyography
  - Muscle biopsy
  - Magnetic resonance imaging
- Chest imaging (chest radiography is usually sufficient) may be used to assess
  - Atelectasis
  - Pneumonia
  - Scoliosis
- Pulmonary function testing may include
  - Spirometry (upright and supine)
    - The weaker the patient, the greater the decline in forced vital capacity when in the supine versus the upright position
  - Lung volumes
  - Maximal inspiratory and expiratory pressures
    - Maximal expiratory pressure <60 cm H_2O is associated with an inadequate cough.

  - Cough peak flows
    - Cough peak flow <270 L/min is associated with an inadequate cough.
  - Pulse oximetry
  - End-tidal CO_2
    - Blood gas analysis may be needed (capillary analysis is preferable to venous analysis).
- Polysomnography
  - Should be periodically assessed if the patient is symptomatic or wheelchair bound
  - Used to assess the presence of
    - Obstructive sleep apnea
    - Sleep-related hypoventilation
  - Overnight oximetry may complement polysomnography data.
    - Oxygen desaturations suggest obstructions.
    - Hypoxia suggests hypoventilation.
- Swallowing studies are used to assess the presence of aspiration.
  - Radiologic examination (videofluoroscopic swallow study [modified barium swallow], radionuclide salivagram)
  - Speech consultation (observe feeding)
  - Videofluoroscopic swallow study or fiber-optic endoscopic evaluation of swallowing
- Evaluation for GER
  - Upper-gastrointestinal study is limited in both sensitivity and specificity but is frequently used.
  - Gastric-emptying scintigraphy may be used if delayed emptying is the suspected cause of symptoms.
  - Esophageal pH level and impedance monitoring
  - Endoscopy with biopsy to assess the presence of esophagitis

Management

- Optimization of airway clearance in patients with a diminished cough
  - Ineffective cough is seen when maximal expiratory pressure is <60 cm H_2O or when cough peak flow is <270 L/min.
  - The addition of assisted coughing maneuvers will be helpful.
    - Mechanical insufflation-exsufflation (the "cough assist" machine)
    - Manual cough maneuvers
  - The addition of manual chest physiotherapy or high-frequency chest wall oscillation ("the vest") may also prove useful.
  - Lung volume recruitment and assisted cough techniques should precede the initiation of noninvasive ventilation.
  - Cough augmentation and airway clearance maneuvers are especially important during upper respiratory tract infections and are key in preventing complications such as pneumonia, atelectasis, and respiratory failure.

- Assisted ventilation
  - Risk factors for sleep-disordered breathing (obstructive sleep apnea and/or hypoventilation) include
    - Apnea-hypopnea index >5 events per hour at polysomnography
    - Vital capacity <30%–50% at spirometry
    - Pulse oximetry <95%
    - Awake end-tidal CO_2 >45 mm Hg
  - Patients will often require the addition of nighttime ventilation before continuous ventilation is required.
  - Many patients may be asymptomatic despite having abnormal laboratory values.
  - The treatment of sleep-disordered breathing can include
    - Bilevel positive airway pressure (BPAP)
    - Noninvasive positive pressure ventilation (NIPPV)
    - Tracheostomy tube placement with mechanical ventilator
  - Treatment of daytime hypoventilation can include
    - BPAP
    - NIPPV
    - Sip-and-puff ventilation
    - Tracheostomy tube placement with mechanical ventilator
  - For BPAP and NIPPV, the mask interface should be either a nasal mask or nasal pillows. Full face-mask interfaces should be avoided unless the patient is being continuously monitored.
  - Tracheostomy tube placement with mechanical ventilation should be considered when
    - NIPPV is not tolerated by the patient
    - NIPPV does not adequately treat the underlying hypoventilation
    - Recurrent aspiration persists despite appropriate precautions in place
    - There is repeated failure of extubation from a ventilator to NIPPV
    - The family prefers this method of support
  - Hypoventilation needs to be ruled out in the presence of hypoxia. Supplemental oxygen will correct the desaturations and hypoxia while not addressing the etiologic origin. If oxygen is administered in the presence of unrecognized hypoventilation, this could lead to progressive and unexpected deterioration.
- Optimization of nutrition
  - Consult a nutritionist.
  - The patient should take enteral supplements when needed.
    - Supplementation may be provided orally or via gastrostomy tube or gastrojejunal tube.
    - Medical or surgical treatment of comorbid GER may be necessary.
  - Gastrointestinal issues, such as heartburn due to GER or constipation, may cause anorexia.

- Prevention of aspiration
  - The patient's feeding plan should be modified under the guidance of a speech therapist.
  - Tube feeding should be considered when the risk of oral aspiration is great and not amenable to medical management. GER should be considered as a cause of occult aspiration.
- Treatment of scoliosis
  - Orthopedic consultation should be sought early in life and when the patient is no longer ambulatory.
    - Spinal rod placement will often be needed at some point to prevent worsening of scoliosis and further pulmonary deterioration.
- Treatment of infections
  - Administer antibiotics judiciously when the patient is ill.
  - Treat the patient for community-acquired organisms.
    - Consider coverage for aspiration when indicated.
    - Broad-spectrum antibiotics are not always needed.
  - *Antibiotic treatment must be accompanied by cough augmentation maneuvers and airway clearance therapies to be effective.*
- Palliative care should be introduced early in life to optimize quality-of-life issues.
  - Consultation should take place before end-of-life issues arise.

Treating Associated Conditions

Patients should ideally be treated in a multidisciplinary setting or a medical home, with active consultation with

- A neurologist, for access to new medical therapies under investigation
- A pulmonologist, as discussed previously, to diagnose and treat sleep-disordered breathing, reduce risk of recurrent pneumonias, and diagnose and treat progressive hypoventilation
- A cardiologist, for management of cardiomyopathy and arrhythmias
- A gastroenterologist or nutritionist, for management of GER, constipation, obesity, and malnutrition
- An endocrinologist, for management of hyperglycemia or diabetes and osteopenia
- An orthopedist, for management of scoliosis and fractures
- Occupational, physical, and speech therapists, to help maintain function and prevent contractures or aspiration
- A social worker, for psychosocial and financial assistance

Expected Outcomes/Prognosis

- The prognosis is variable, depending on the underlying diagnosis.
- The most common causes of death include
  - Chronic respiratory failure
  - Pneumonia
  - Cardiac failure
  - Arrhythmia

When to Refer

- Pulmonary referral should occur at the time of diagnosis (prior to any respiratory manifestations).
- Frequency of follow-up will be individualized on the basis of the patient's underlying pulmonary dysfunction.
  - Follow-up should be yearly when the patient is ambulatory.
  - Follow-up should occur at least twice per year when the patient is in a wheelchair.
  - Follow-up should occur 2–4 times per year when the patient needs assisted ventilation.
- Assessment before and after elective surgery is warranted to minimize postoperative respiratory complications.

Prevention

- Have a low threshold for modifying feedings or giving the patient nothing by mouth if risk for aspiration is high.
  - In such cases, optimize nutritional management to prevent malnourishment or obesity.
- Use aggressive airway clearance for patients with a decreased cough.
- Use ventilatory support for muscle rest and to treat hypoventilation (initially seen when the patient is asleep, but it may progress to occurring while the patient is awake).
- Ensure that patients receive routine immunizations.
  - Yearly influenza vaccination
  - Pneumococcal vaccination in older patients
- Always temper the treatment burden with quality-of-life issues.

Resources for Families

- Breathing Problems in Children With Neuromuscular Diseases (American Thoracic Society). www.thoracic.org/patients/patient-resources/resources/neuromuscular-breathing-proof-a5.pdf
- Treating Breathing Problems in Children With Neuromuscular Disorders (American Thoracic Society). www.thoracic.org/patients/patient-resources/resources/neuromuscular-breathing-proof-b5.pdf
- Breathing Problems in Adults With Neuromuscular Diseases (American Thoracic Society). www.thoracic.org/patients/patient-resources/resources/neuromuscular-weakness-adult.pdf
- Neuromuscular Disease (American Thoracic Society). www.thoracic.org/patients/patient-resources/neuromuscular-disease.php
- Parent Project Muscular Dystrophy. www.parentprojectmd.org
- Cure SMA. www.curesma.org
- Cure CMD. www.curecmd.org

Clinical Pearls

- There are many different types of neuromuscular weakness with different prognoses; however, they all share a common final pathway that can lead to respiratory complications.
- Commonly seen respiratory complications that warrant monitoring and potential interventions include potential for aspiration, inadequate cough that may result in poor airway clearance and lower-airway complications, and progressive respiratory failure.
- Airway clearance therapy is vital in maintaining optimal pulmonary health.
- Nutritional optimization is indicated to prevent malnutrition and obesity. Nutrition must be delivered in a way in which the risk of aspiration is minimized.
- Progressive respiratory failure is a common complication, and close monitoring is needed to prevent its development. There are many options available, both invasive and noninvasive, to treat this progressive respiratory failure.

Chapter 95

Respiratory Disorders in Cancer Survivors

Matthew Schefft, DO, MSHA, FAAP, and H. Joel Schmidt, MD, FAAP, FCCP

Introduction/Etiology/Epidemiology

- With longer survival after pediatric cancer comes a greater likelihood of long-term complications, some of which may be respiratory in nature.
- The most common cancers associated with respiratory disease in cancer survivors (RDCS) are
  - Any condition that requires bone marrow transplantation
  - Acute myeloid leukemia
  - Astrocytoma and other brain tumors
  - Neuroblastoma
  - Hodgkin disease
- Many patients remain asymptomatic for years.
- Incidence measures vary; the prevalence of RDCS may be as high as 30%.
- Possible causes of RDCS include
  - Infections
  - Drug-induced origins
  - Radiation therapy
  - Surgery
  - Metastatic disease
  - Idiopathic causes
- Identifying the specific cause of RDCS is complicated.
  - Multiple drugs and possible drug-drug interactions can make identifying the exact cause of toxicity difficult.
  - Multiple drugs, radiation therapy, surgery, metastatic disease, and infection can all be involved.

Pathophysiology

Infectious Causes of RDCS

- Susceptibility to infections due to chemotherapy-related immunosuppression contributes to RDCS through sequelae such as fibrosis and airway remodeling.
- Notable organisms include
  - *Pneumocystis jirovecii* (formerly *Pneumocystis carinii*)
  - Fungal (*Aspergillus, Mucor, Fusarium,* and *Candida* species)

  - Viral (adenovirus, especially in patients with stem cell transplants, respiratory syncytial virus, and cytomegalovirus)

Drug-Induced RDCS

- May be dose related or dose independent (Table 95-1).
  - Bleomycin toxicity is dose related: Pulmonary function impairment can occur at any dose but is more likely at higher doses.
  - Methotrexate toxicity is thought to be dose independent: The likelihood of pulmonary function impairment does not vary according to the dose administered.
- Mechanisms of chemotherapeutic agent–induced toxicity include
  - Reactive oxygen metabolites
  - Interference with collagen metabolism (dose independent)

Radiation-Induced RDCS

- Dose dependent (Table 95-1)
  - The incidence of RDCS increases with higher radiation doses.
  - The effects of the cumulative dose include
    - Increased risk when the total dose is >15 Gy
    - Universal changes noted when the total dose is >40 Gy
  - Effects of the daily dose: For a given cumulative dose, RDCS is more likely to occur when the dose is administered over fewer fractions.
  - Coadministration of chemotherapeutic agents increases the risk of RDCS.
  - Coadministration of oxygen increases the risk of RDCS.
- Patient susceptibility is variable.
  - Host factors, such as innate inflammatory response to treatment, affect the natural course of RDCS.
- Mechanisms
  - Cytotoxicity
  - Cytokine-induced fibrosis

Hematopoietic Stem Cell Transplantation

- A unique subset of patients with pulmonary complications
- Hematopoietic stem cell transplantation (HSCT) is usually performed after failed courses of chemotherapy and radiation therapy.
- Pulmonary complications are the most common cause of morbidity and mortality after HSCT.
- Types of injury (Figure 95-1)
  - Acute
    - Pulmonary edema: 2–3 weeks after transplantation
    - Diffuse alveolar hemorrhage: 1–6 weeks after transplantation

Table 95-1. Description of Pulmonary Toxicity Associated With Various Pediatric Cancer Treatment Modalities

Treatment	Mechanism of Lung Injury	Sequelae	Likelihood of toxicity	Timing	Notes	Exacerbating Factors
Radiation Therapy						
	Chest wall hypoplasia, inflammation and impaired repair, diminished parenchymal growth	Decreased lung volume Decreased forced vital capacity Decreased diffusion capacity Obliterative bronchilitis Interstitial pneumonitis	50%	1–5 y		Younger age Higher dose (>15 Gy) Total lung vs focal Chemotherapy
Chemotherapy						
Bleomycin	Inflammation and fibroblast deposition due to lack of bleomycin hydrolase in the lung tissue	Bronchiolitis obliterans Eosinophilic hypersensitivity Interstitial pneumonia Pulmonary fibrosis Acute respiratory distress syndrome (rare)	3%–10%, depending on dose	Months	1%–2% mortality from pulmonary toxicity	Radiation therapy Oxygen therapy High cumulative dose (≥400 units)
Brentuximab	Cell death and cytokine-mediated inflammation	Pneumonitis Acute respiratory distress syndrome Noncardiogenic pulmonary edema Interstitial lung disease	5%	During treatment or in the months after treatment	Symptoms may improve if brentuximab is stopped	≤40% incidence of pulmonary toxicity when combined with standard Hodgkin treatment, including bleomycin

Continued

Table 95-1. Description of Pulmonary Toxicity Associated With Various Pediatric Cancer Treatment Modalities, *continued*

Treatment	Mechanism of Lung Injury	Sequelae	Likelihood of toxicity	Timing	Notes	Exacerbating Factors
Chemotherapy						
Busulfan	Lymphocyte and plasma cell infiltration into alveoli and interstitium	Interstitial fibrosis (can be severe)	Rare	1–10 y (mean onset, 3.5 y)	Insidious onset	Additional chemotherapeutic agents toxic to the lung Radiation therapy
Cyclophosphamide Lomustine Carmustine	Poorly understood	Early onset: <6 months from onset of treatment, resolves with steroids and cessation of drug treatment Late onset: >6 months, progressive and not responsive to treatment Leads to fibrosis	Late onset: <1% of cases	Months to years	No relationship between dose and toxicity	Additional chemotherapeutic agents toxic to the lung Radiation therapy
Gemcitabine	Cytokine-mediated inflammation within the alveolar capillary walls	Interstitial pneumonitis Diffuse alveolar damage Pleural effusion Noncardiogenic pulmonary edema Alveolar hemorrhage	10%	Acute (during treatment) or delayed (years after)	Recently introduced into pediatric cancer protocols	Additional chemotherapeutic agents toxic to the lung Radiation therapy

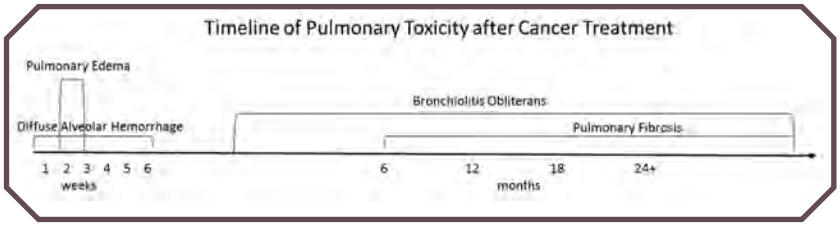

Figure 95-1. Timeline of pulmonary toxicity after cancer treatment.

- — Chronic
  - Bronchiolitis obliterans (also known as *constrictive bronchiolitis* and *obliterative bronchiolitis* and sometimes *bronchiolitis obliterans syndrome* if there is no biopsy confirmation) is a severe expression of graft versus host disease occurring months after transplantation.
  - Pulmonary fibrosis occurring months to years after transplantation

Clinical Features

- Infectious
  - — Acute onset
  - — Fever
  - — Productive cough
  - — Hypoxia
- Drug induced
  - — Chronic nonproductive cough
  - — Progressive exercise intolerance
- Radiation induced
  - — Pneumonitis—early
    - Insidious onset
    - Low-grade fever
    - Pleuritic chest pain
    - Pleural rub
    - Overlying skin erythema
  - — Fibrosis
    - Develops over 6–24 months
    - Can be associated with pulmonary hypertension if severe
    - Generally confined to the target area
    - Stable by 18–24 months
- HSCT
  - — Pulmonary edema
    - Rapid onset of dyspnea
    - Recent weight gain
    - Bibasilar crackles
    - Hypoxemia

  - Diffuse alveolar hemorrhage
    - Sudden onset of progressive dyspnea
    - Fever
    - Hypoxemia
    - Nonproductive cough
  - Bronchiolitis obliterans
    - Gradual-onset dyspnea
    - Wheezing
    - Obstructive defect at spirometry
- Features that may be present with all causes
  - Malaise
  - Dyspnea
  - Tachypnea
  - Cough
  - Supplemental oxygen requirement
  - Recurrent pneumonia

Differential Diagnosis

Cancer survivors may be affected by respiratory problems common among the general pediatric population.

- Allergies (asthma)
- Infection
- Autoimmune issues
- Secondary cancer

Diagnostic Considerations

- Chest radiographs may demonstrate
  - Diffuse alveolar or interstitial involvement (drug induced, edema, or posthemorrhagic) (Figure 95-2)
  - Focal involvement (targeted radiation)
  - Atelectasis
  - Normal findings (common with early bronchiolitis obliterans)
- Lung computed tomographic (CT) images may demonstrate
  - Early evidence of parenchymal disease
  - Findings in bronchiolitis obliterans
    - Decreased lung attenuation, mostly in the lower lobes (the most common CT finding in bronchiolitis obliterans)
    - Segmental or subsegmental bronchial dilation
    - Decreased peripheral vascularity
    - Centrilobular nodules
    - Nonhomogeneous air trapping on exhalation images
- Pulmonary function testing (PFT) may include
  - Spirometry results that show obstructive disease
  - Lung volume testing results that show restrictive disease
  - Diminished diffusion capacity
  - Exercise-induced hypoxia and intolerance

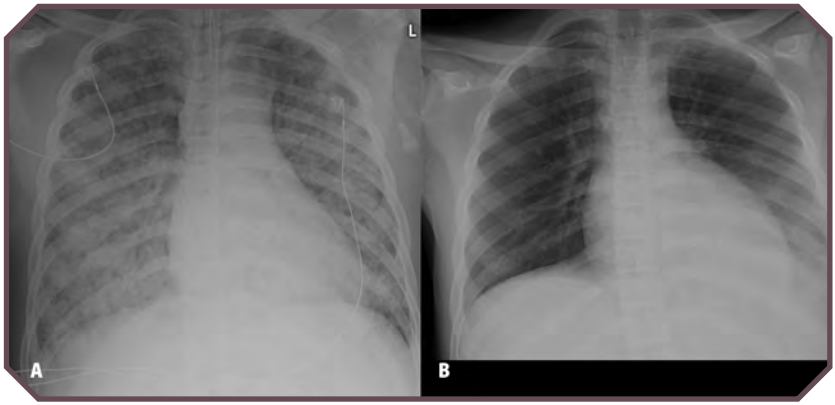

Figure 95-2. Acute bleomycin toxicity in a 14-year-old girl with persistent cough who had undergone treatment for Hodgkin lymphoma. A. Frontal chest radiograph demonstrates diffuse, ill-defined parenchymal markings. B. Follow-up radiograph obtained 2 years later shows resolution of toxic changes.

- Lung biopsy findings may include
  - Drug-induced disease
    - Increased numbers of fibroblasts
    - Type II cell hyperplasia
    - Interstitial thickening
  - Blood in >30% of alveolar surfaces in diffuse alveolar hemorrhage
  - Fibrosis, found in radiation-induced injury
  - Inflammatory-cell small-airway infiltrate, typically sparing the interstitium, found in bronchiolitis obliterans

Management

- Withdraw the offending agent if symptoms are acute.
- As-yet unproven efforts to cease inflammatory progression have included
  - Systemic corticosteroids
  - Inhaled steroids
  - Etanercept
  - Azithromycin
  - Fluticasone-azithromycin-montelukast combination
- Supportive care

Expected Outcomes/Prognosis

- Most cancer survivors will not experience pulmonary toxicity.
- Many survivors with pulmonary manifestations have subclinical disease that does not limit daily activity.
- The most common chronic manifestations include chronic cough, lung fibrosis, recurrent pneumonia, and oxygen requirement (Figure 95-3).
- Cumulative incidence of pulmonary mortality is 1.2% at 35 years after cancer diagnosis.

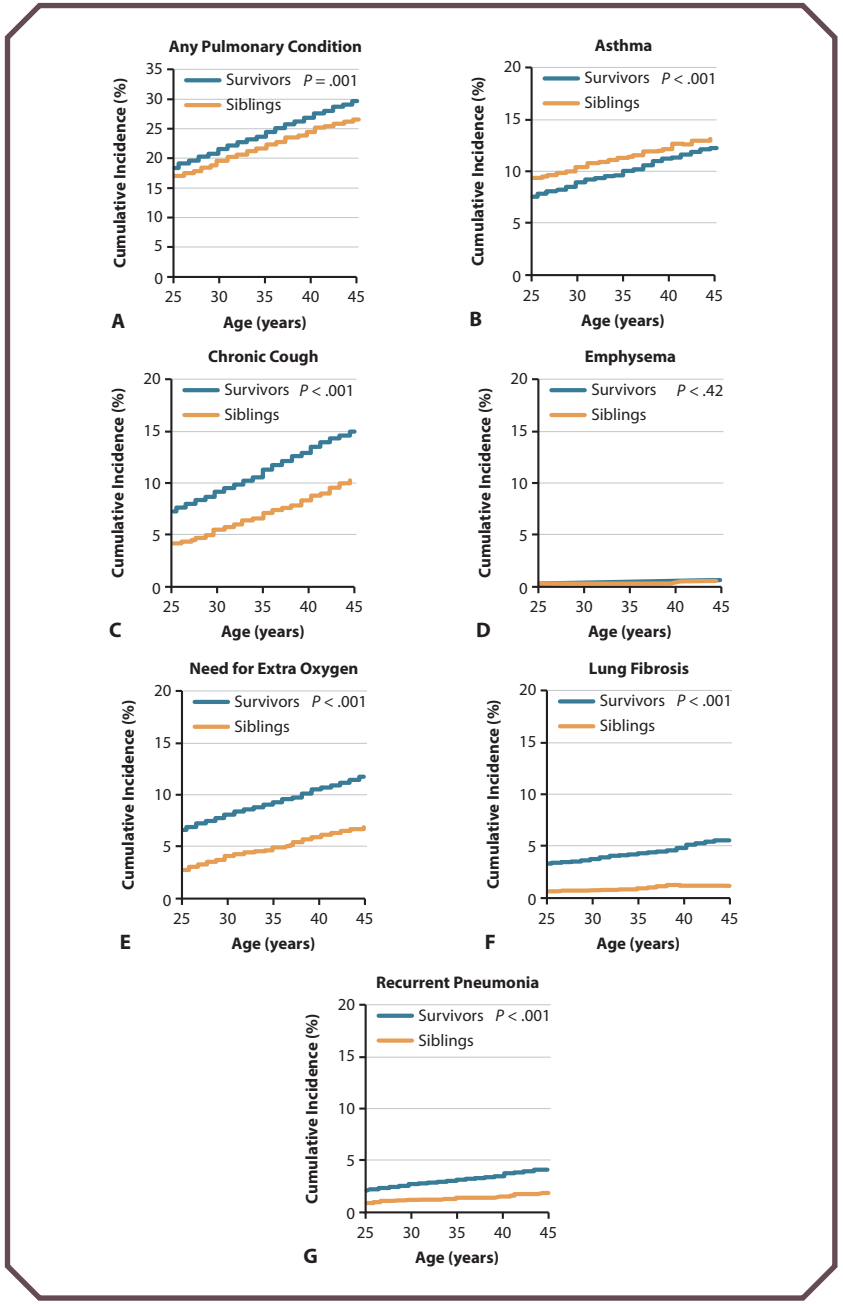

Figure 95-3. Incidence of pulmonary complications over time for pediatric cancer survivors, including A. any pulmonary condition, B. asthma, C. chronic cough, D. emphysema, E. need for extra oxygen, F. lung fibrosis, and G. recurrent pneumonia. From Dietz AC, Chen Y, Yasui Y, et al. Risk and impact of pulmonary complications in survivors of childhood cancer: a report from the childhood cancer survivor study. *Cancer.* 2016;122(23):3687–3696. Copyright 2016 American Cancer Society.

When to Refer

- Early referral to a pulmonologist is indicated if a childhood cancer survivor has any of the symptoms consistent with toxicity. It is important to ensure accurate diagnosis, treatment of reversible causes, and potential abatement of progression.

Monitoring and Prevention

- Routine PFT
- Preoperative evaluation

Resources for Families

- Childhood Cancer Survivor Study: An Overview (National Cancer Institute). www.cancer.gov/types/childhood-cancers/ccss
- Late Effects of Treatment for Children's Cancer (CureSearch). curesearch.org/Late-Effects-of-Treatment-for-Childhood-Cancer

Clinical Pearls

- RDCS is a common complication of childhood cancer treatment.
- The cumulative incidence of RDCS increases over time.
- RDCS can result from infection, chemotherapy, radiation therapy, or consequences of the cancer itself.
- Symptoms of RDCS are often slow and insidious in onset.
- Early referral to a pulmonologist is recommended at the earliest signs that are concerning for RDCS.

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Part VIII. Pediatric Sleep Medicine

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Chapter 96

Sleep Disorders: Evaluation and Prevention

Emma L. Peterson, PhD, and Jocelyn H. Thomas, PhD

Introduction: Typical Sleep in Pediatric Populations

- Children ≥6 months of age experience 4 stages of sleep in a typical night (Figure 96-1).
- All individuals (infants, toddlers, children, teenagers, adults) wake several times throughout the night.
- Self-soothers can return to sleep independently, without their parents.
- Recommended quantity of sleep in a 24-hour cycle is found in Figure 96-2.

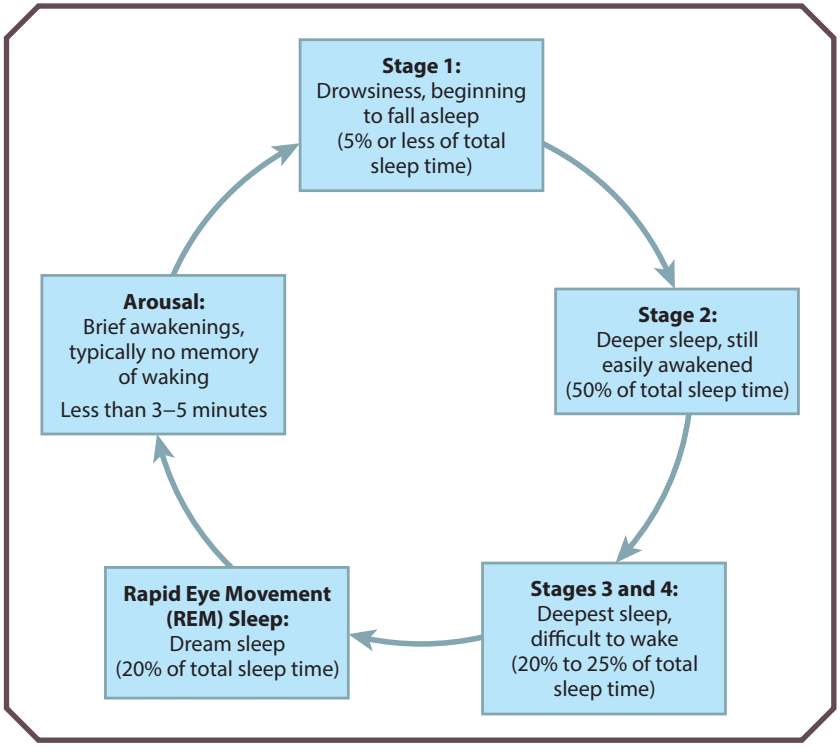

Figure 96-1. Stages of sleep.

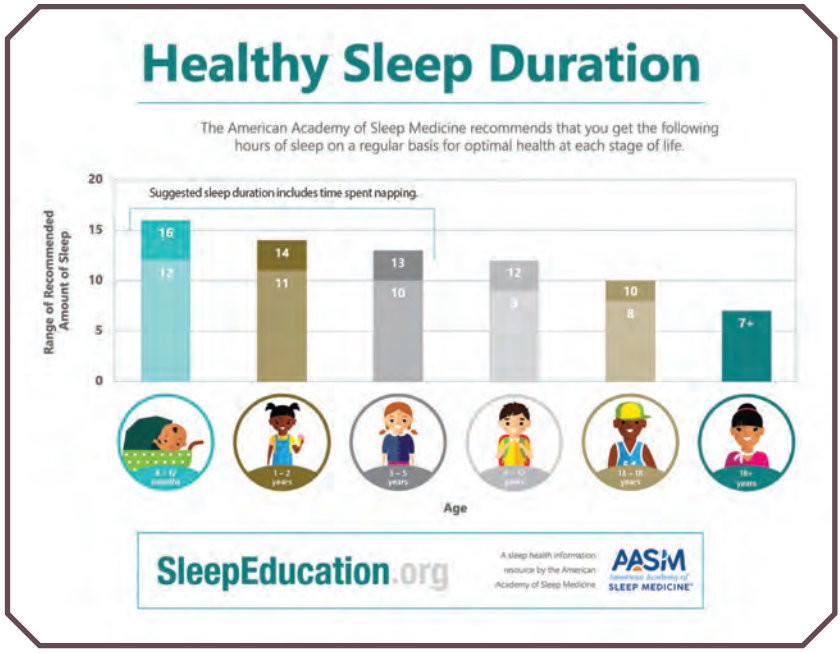

Figure 96-2. Recommended quantity of sleep in a 24-hour cycle. From Paruthi S, Brooks LJ, D'Ambrosio C, et al. Recommended amount of sleep for pediatric populations: a consensus statement of the American Academy of Sleep Medicine. *J Clin Sleep Med*. 2016;12:785.

Consequences of Insufficient Sleep

- Poor cognitive development
- Poor mood regulation
- Reduced attention
- Increased physical aggression, hyperactivity, and impulse control
- Reduced metabolic and immune functioning
- Accidental injuries

Clinical Features of Sleep Disorders

- Excessive daytime sleepiness (EDS) (ie, dozing, falling asleep)
  - — This is different than general fatigue (ie, feeling tired)
  - — Several factors contribute to EDS
    - ▪ Insufficient sleep (sleep restriction)
    - ▪ Fragmented sleep (sleep interruption) may be
      - ~ Extrinsic (noise, light, etc)
      - ~ Intrinsic (obstructive sleep apnea, periodic limb movement syndrome, etc)

  - Primary sleep disorders of EDS
    - ~ Narcolepsy, idiopathic hypersomnolence, etc
  - Circadian rhythm disorders
- Additional behavioral or medical symptoms
  - — Heightened irritability
  - — Poor concentration in school
  - — Hyperactivity
  - — Snoring
  - — Nocturnal enuresis
  - — Restless sleep

Evaluation: Conducting a Sleep Interview

- Caregivers may not recognize some behavioral or medical symptoms as indicators of sleep disorders. However, sleep difficulties may be identified in primary care settings through routine screening questions (see Table 96-1).
- Routine screenings can help to identify the need for a more comprehensive sleep interview.
- A sleep interview is used to obtain additional information and assess the presence of sleep disorders (both behaviorally and biologically based).
- A sleep interview is critical for differential diagnosis.
  - — Different sleep disorders often manifest with similar symptoms (eg, excessive daytime sleepiness). Yet, the treatment varies, depending on the diagnosis.
  - — Multiple sleep disturbances may coexist, and the presence of one sleep disorder may exacerbate another.
- Sleep disorders can be secondary to, or exacerbated by, physical and mental conditions; thus, a sleep interview that includes a comprehensive history allows for the evaluation of possible contributing factors to the sleep disturbance.
- Components of a sleep interview are described in Table 96-2.

Prevention and Intervention

- "Sleep hygiene" is a variety of different habits and practices that are intended to promote better-quality sleep.
- Components of sleep hygiene are described in Box 96-1.

Prognosis

- Sleep problems in children are persistent and are unlikely to spontaneously resolve without appropriate intervention.
- Sleep problems in children are likely to affect other areas of functioning (eg, behavioral, academic, psychological).

Table 96-1. "BEARS" Screening Questions

"BEARS" Parameter	Preschool Age (2–5 y)	School Age (6–12 y)	Adolescent (13–18 y)
Bedtime problems	Does your child have any problems going to bed or falling asleep?	Does your child have any problems at bedtime? (Parent) Do you have problems going to bed? (Child)	Do you have any problems falling asleep at bedtime? (Child)
Excessive daytime sleepiness	Does your child seem overtired or sleepy a lot during the day? Does he/she still take naps?	Does your child have difficulty waking in the morning, seem sleepy during the day, or take naps? (Parent) Do you feel tired a lot? (Child)	Do you feel sleepy a lot during the day in school or while driving? (Child)
Awakenings during the night	Does your child wake up a lot at night?	Does your child seem to wake up a lot at night? Does he/she have any sleepwalking or nightmares? (Parent) Do you wake up a lot at night or have trouble getting back to sleep? (Child)	Do you wake up a lot at night? Do you have trouble getting back to sleep? (Child)
Regularity and duration of sleep	Does your child have a regular bedtime and wake time? What are they?	When does your child go to bed and get up on school days and weekends? Do you think he/she is getting enough sleep? (Parent)	What time do you usually go to bed on school nights and weekends? How much sleep do you usually get? (Child)
Sleep-disordered breathing	Does your child snore a lot or have difficulty breathing at night?	Does your child have loud or nightly snoring or any breathing difficulties at night? (Parent)	Does your teenager snore loudly or nightly? (Parent)

The "BEARS" sleep screening tool includes bedtime problems, excessive daytime sleepiness, awakenings during the night, regularity and duration of sleep, and sleep-disordered breathing. From Owens JA, Dalzell V. Use of the "BEARS" sleep screening tool in a pediatric residents' community clinic: a pilot study. *Sleep Med.* 2005;6:63–69.

Table 96-2. Components of a Sleep Interview	
Component	**Details**
Presenting complaint	Patient and/or parent's primary concern Family's ultimate goal (eg, sleeping independently, sleeping through the night, falling asleep independently)
Bedtime	Presence of set bedtime Typical sleep schedule during a 24-hour period
Bedtime routine	Activities, timing, location, and length
Sleep-onset associations	Events occurring and people present at the time the child falls asleep (eg, feeding, rocking, parent in bed, television on, music playing) Sleep associations will generally need to be repeated during nighttime awakenings, as well
Bedtime behaviors	Types, intensity, duration, frequency, what typically terminates them
Sleep onset	Time and location
Sleep environment	Characteristics of the bedroom (eg, location, temperature, light, sound, type of bed, people present)
Daytime sleeping	Timing, frequency, duration
Nocturnal behaviors	Night awakenings (frequency, number, timing, duration, identifiable triggers) Behaviors that occur upon waking (eg, calling out for parents, parental response to awakenings) Presence and nature of episodic nocturnal events (eg, disorders of arousal and nightmares) Symptoms suggestive of sleep-disordered breathing and periodic limb movement disorder
Daytime behaviors	Time of morning awakening Daytime fatigue and sleepiness Daytime functioning Caffeine intake
Review of medical history	Current and past medical diagnoses, previous surgeries, hospitalizations, and injuries
Daytime functioning	Timing of developmental milestones Functioning at school
Family medical history	Particularly related to obstructive sleep apnea, narcolepsy, and parasomnias
Psychosocial history	Psychological and mental health Social history
Physical examination	Often normal

Box 96-1. Sleep Hygiene Considerations

Sleep Schedule

- Presence of set bedtime and morning wake time
  - Bedtime before 9:00 pm for infants and toddlers
- Allows for sufficient quantity of sleep (refer to Figure 96-2)
- Consistent sleep schedule every day (within 1–2 hours if variation exists on the weekends)

Bedtime Routine

- Presence of bedtime routine
- Caregiver supervision of bedtime routine for infants, toddlers, and children
- Consistent order of 3–4 activities each night, slowly moving in the direction of the bedroom
  - Feeding should occur early in the routine for infants and toddlers to avoid falling asleep while nursing or drinking from a bottle.
  - Save new stories and books for daytime to avoid excitement and overstimulation.
  - Some children may enjoy visual schedules to indicate the order of the bedtime routine.
  - Some children may benefit from positive reinforcement (eg, stickers, verbal praise) for completing each step of the routine.
  - Make the child's favorite activity in the routine occur last (eg, cuddling with a caregiver, story time).
  - Avoid the use of electronics during the bedtime routine.
- Routine lasting 20–30 minutes (45 minutes if including a bath or shower)

Positive Sleep-Onset Associations

- Sleep-onset associations must be independent of adults (ie, adults are not present at the moment the infant is falling asleep).
  - Avoid feeding the child at the end of the routine to prevent the development of an association between sleep and feeding.
  - Put the infant in the crib while drowsy but still awake.
  - Avoid having the caregiver remain in bed or in the bedroom as the child is falling asleep.
- The presence of a transitional object (eg, a special blanket or stuffed animal) can be soothing at bedtime.
- Avoid any activities other than sleep (eg, homework, talking on the phone) in bed.
- Avoid sleeping in other locations (eg, in front of the TV, on a couch).

Box 96-1. Sleep Hygiene Considerations, *continued*

Sleep Location

- Consider the type of bed.
  - It is best to transition infants to a crib at about 3 months of age.
  - Crib safety considerations
    - Use a firm, tight-fitting mattress.
    - There should be no missing, loose, broken, or improperly installed screws, brackets, or hardware.
    - The crib slats should be no more than 2⅜ inches apart.
    - No corner posts should be over 1/16 inch high.
    - The headboard and footboard should have no cutouts.
    - Use a crib that was manufactured since 1990 and has been certified to meet national safety standards.
  - No pillows should be used for children <2 years of age.
- When possible, individuals should sleep in a room alone—sharing a room with other family members can disrupt sleep.
- Reduce light and noise in the bedroom.
- Make the sleep area an appropriate temperature.

Electronics

- No electronic devices should be used in the bedroom.
- Avoid use of electronic devices within 1 hour of bedtime.
- Avoid using electronic devices as a sleep aid.
- Limit screen time to <2 hours per day.

Daytime Behavior and Naps

- Increase the exposure to light in the morning upon waking.
- The napping schedule should be predictable.
- Specified times each day (eg, 12:30 pm) or at a fixed interval (eg, every 2 hours)
- Avoid napping past 4:30 pm.
- Naps should occur in same location as nighttime sleeping.
- Consider the length of naps.
  - <30 minutes
    - Reduced sleep inertia (grogginess that lasts 15–30 minutes after a nap)
    - Short-term boost in cognitive functioning (1–3 hours)
  - >30 minutes
    - Increased immediate sleep inertia
    - Longer-term boost in cognitive function

Continued

Box 96-1. Sleep Hygiene Considerations, *continued*

Caffeine Intake

- Avoid caffeine consumption for infants, toddlers, and children.
- If caffeine consumption does occur, avoid caffeine consumption 6–8 hours before bedtime.

Additional Considerations According to Age Group

Infants and toddlers (0–3 y)	• By 6 months of age, most babies are physically capable of sleeping through the night without feeding.
Young and school-aged children (4–12 y)	• Avoid using staying up as a reward or going to bed early as a punishment—this gives the subtle message that "sleep is bad." • Avoid using the bed as a place for time-out. • Avoid cognitive and emotional stimulation before bedtime. • For individuals experiencing anxiety or stress around bedtime, a variety of relaxation strategies may be useful, including diaphragmatic breathing, progressive muscle relaxation, and visualizations.
Adolescents (≥13 y)	• Avoid using a cell phone as an alarm clock.

Resources for Families

- Moon R, ed. *Sleep: What Every Parent Needs to Know* (American Academy of Pediatrics). shop.aap.org
- Owens JA, Mindell JA. *Take Charge of Your Child's Sleep: The All-in-One Resource for Solving Sleep Problems in Kids and Teens.*
- Pediatric Sleep Council. www.babysleep.com

Chapter 97

Brief, Resolved, Unexplained Events and Sudden Infant Death Syndrome

Lourdes M. DelRosso, MD, and Lee J. Brooks, MD, FAAP

Brief, Resolved, Unexplained Events (Formerly *Apparent Life-Threatening Events*)

Introduction

- A brief, resolved, unexplained event (BRUE) is defined as an episode that occurs in an infant <1 year of age and is reported by the observer as a sudden, brief, and now-resolved episode that included ≥1 of the following:
  - Color change (cyanosis or pallor)
  - Change in breathing (absent, irregular, or decreased)
  - Change in muscle tone (hypertonia or hypotonia)
  - Altered level of responsiveness
- Previously, an apparent life-threatening event (ALTE) was defined as an episode that was frightening to the observer and was characterized by some combination of apnea, color change, marked change in muscle tone, choking, or gagging. In some cases, the observer believed the infant had died.
- In 2016, the American Academy of Pediatrics (AAP) proposed the use of *BRUE* instead of *ALTE* in infants when there was no explanation for the event after obtaining a history and performing a physical examination.
- To date, there has been little specific research on the new BRUE terminology; most of the following guidelines apply to studies of ALTE.

Etiology

- In contrast to BRUE, ALTE is a manifestation of another condition, and as such, it has many potential etiologic origins (Figure 97-1).
- The most common diagnoses identified include
  - Gastroesophageal reflux disease (GERD) (found in 30% of patients)
  - Seizures (10%)
  - Respiratory infections (8%)

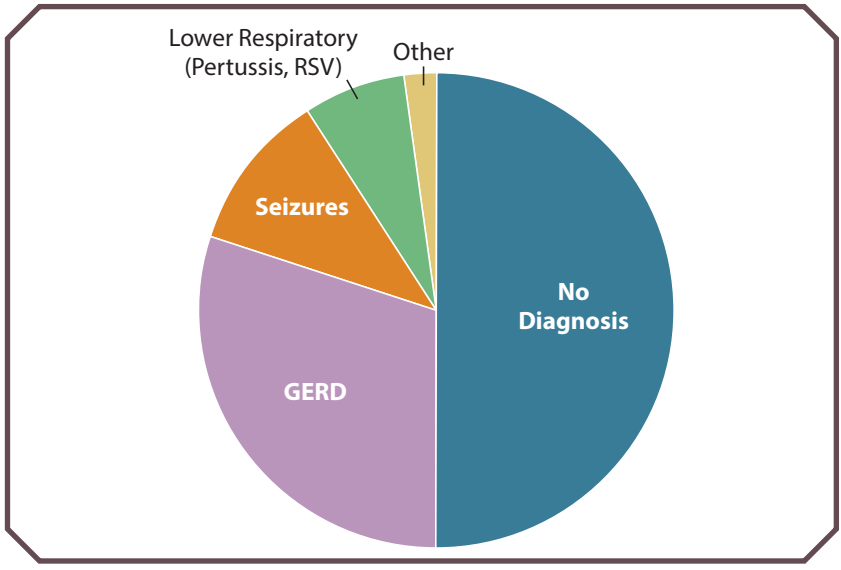

Figure 97-1. Etiologic origins of apparent life-threatening events. GERD = gastroesophageal reflux disease, RSV = respiratory syncytial virus.

- Less common causes are hypoxemia, sepsis, anemia, long QT syndrome, and child abuse.
- The respiratory infections found are often bronchiolitis, pertussis, or lower respiratory infections.
- Child abuse has been detected in 2.3% of infants who present to the emergency department with ALTE.
- The cause of ALTE is not found in 50% of cases.

Epidemiology

- The incidence of BRUE has not yet been clearly established.
- Previously, the incidence of ALTE was estimated at 0.6 per 1,000 live births, with a peak incidence during the first 2 months of life.
- Risk factors include the following.
  - — Premature infants have twice the risk of the general population for ALTE. This may be secondary to immature central control of breathing and airway reflexes.
  - — Upper respiratory infection
  - — Exposure to smoking
  - — History of recent anesthesia

Pathophysiology

- There are diverse pathophysiological contributors to ALTE.
- Apneic causes can be secondary to immature breathing centers. Apneic episodes could be central, obstructive, and periodic breathing.

- Autonomic causes include abnormalities in heart rate variability and blood pressure changes.
- GERD is the most common diagnosis identified in infants with ALTE, but gastroesophageal reflux is also common in all infants. Causality is therefore difficult to prove.
- ALTE has been reported while the infant is in the car seat, likely because of airway obstruction that occurs during cervical flexion.

Clinical Features

- The infant usually presents with a sudden change in behavior that alarms the caregiver.
- The most common presentations include loss of muscle tone, color change (usually pallor or cyanosis), arrest of breathing, choking, and gagging.
- The event may end spontaneously or may require parental intervention.
- Parental intervention ranges from position change (picking up the infant) and vigorous stimulation to cardiopulmonary resuscitation (CPR).
- The infant may or may not present with signs of acute illness.

Diagnostic Considerations

- A detailed clinical history must include
  - The description and duration of the event: Did the event occur while the infant was asleep or awake? Was there a skin color change? Was the infant limp or rigid? Descriptions from all witnesses are helpful.
  - Description of the postevent recovery: Did the infant recover spontaneously? Did the infant require gentle or vigorous resuscitation? Was CPR performed?
  - Was the child completely healthy before the symptoms occurred, or were there symptoms of other illness?
  - Account of previous similar events
  - Birth history and gestational age
  - Feeding history: Vomiting, weight gain, choking
  - Comorbidities: Seizures, metabolic disorders, cardiorespiratory status
  - Medications
  - Recent injury or trauma
  - Social history: Parental smoking or drug use or history of report of possible child abuse in the past
  - Family history: Similar episode in a sibling or a sudden unexpected death in a relative
- Physical examination
  - Height, weight, and head circumference
  - Vital signs, including pulse oximetry
  - Complete and detailed physical examination
  - Funduscopic examination may aid in the detection of trauma.

- Laboratory investigations
  - Routine laboratory testing is not indicated if the event was mild or if a diagnosis is identified via the history and physical examination.
  - Further laboratory evaluation should be directed by the history and physical findings.
  - For severe reported cases or when the physical examination findings do not indicate a diagnosis, evaluation may include
    - Cardiorespiratory monitoring in the emergency department
    - Blood tests (complete blood count, glucose and electrolyte levels, toxicology assessment, blood culture, lactate level, *Bordetella pertussis* and respiratory syncytial virus testing)
    - Lumbar puncture
    - Esophageal pH level and manometry monitoring
- Imaging
  - Chest radiography
  - Brain computed tomography or magnetic resonance imaging
- Polysomnography is indicated if obstructive apnea is suspected.
- No single study has a high predictive value for diagnosis of an underlying condition.

Management

- Care of the infant with a BRUE or ALTE should start during the event. This should include stimulation of the infant and CPR if needed.
- Management should be individualized, because the clinical presentation can be secondary to various underlying conditions.
- Infants with history of multiple BRUEs or ALTEs, with clinically significant symptoms at the time of evaluation (fever, respiratory distress, evidence of trauma, etc) or with clinically significant compromise during the event (sustained cyanosis, requiring resuscitation), may require hospitalization.
- When an underlying condition is evident (ie, infection), the condition should be treated promptly.
- Home cardiorespiratory monitoring may be indicated. Cardiorespiratory monitors do not prevent apnea or bradycardia, but they alert the family to the presence of an event so they can intervene. If home monitoring is chosen, all caregivers must be trained on how to respond to alarms, up to and including CPR.
- Stable, low-risk infants may be discharged from the emergency department if
  - The patient experienced only 1 event
  - The event was brief
  - The infant recovered spontaneously
  - The history and physical examination findings are normal

- Guidelines for low-risk BRUE have been published. Low-risk infants include
  - Those >60 days old
  - Gestational age ≥32 weeks and postconceptional age ≥45 weeks
  - No history of prior BRUE
  - BRUE duration of <1 minute
  - CPR not required
  - No concerning history or physical examination findings
- Management strategies for these infants include
  - Parental education
  - Follow-up arrangement and shared decision about future evaluation
  - CPR training
  - Potential pertussis testing and 12-lead electrocardiography
  - Possible brief monitoring of continuous oximetry and serial observations

When to Admit

- Admit infants who have recurrent episodes without an explanation.
- Admit infants with a clear diagnosis who are unstable—that is, infants who require ventilation or intravenous antibiotics.
- Admit infants without a clear diagnosis but with an abnormal history or physical examination findings that require further inpatient evaluation.
- Admit infants with clinically significant compromise (a prolonged event that requires CPR).

Expected Outcomes/Prognosis

- Most infants with BRUE or ALTE will proceed to have a benign course without any long-term sequelae.
- Only 12% of infants will require admission for further evaluation.
- Up to 24% of infants will have a recurrent episode.
- A history of prematurity and recurrent events is associated with a higher probability of finding an occult condition.
- In about 50% of infants, a careful history and physical examination findings will indicate a diagnosis.
- There is insufficient evidence to estimate the risk of a subsequent event or the presence of an underlying diagnosis in infants who are asymptomatic.

Prevention

- If there is a pulmonary concern in a premature newborn, establish whether travel in a car is safe before hospital discharge. The newborn may be observed in his or her own car safety seat for 90–120 minutes or the anticipated length of the trip to be monitored for desaturation, apnea, or bradycardia. Parents should be educated about proper positioning.
- Avoid exposure to smoking. Recommend smoking cessation to parents and caregivers.

- Early identification and management of underlying illnesses are key for the prevention of BRUE.
- Promote safe sleep practices, including supine positioning, the use of a firm sleep surface, and the avoidance of soft bedding and overheating.
- Parents should be educated about CPR.
- Consider home cardiorespiratory monitoring for
  - Severe ALTE
  - Infants with vulnerable airway (tracheostomy)
  - Technology-dependent infants, such as those requiring mechanical ventilation
  - Infants with symptomatic chronic lung disease, especially those requiring oxygen or those who have experienced an ALTE
  - Home monitoring can relieve anxiety for some parents and heighten anxiety in others, so monitors should only be prescribed after careful consideration of risks and benefits.

Sudden Infant Death Syndrome

Introduction

- Sudden infant death syndrome (SIDS) is defined as the sudden death of any infant <1 year of age, which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history.
- SIDS and accidental sleep-related suffocation are the most commonly reported types of sudden unexpected infant death (SUID).

Etiology

- The etiologic origins are unknown but are postulated to be related to a combination of factors.
  - Apnea of prematurity is not necessarily a precursor of SIDS.
  - BRUE or ALTE is not necessarily a precursor of SIDS.

Epidemiology

- SIDS is the leading cause of death in infants <1 year of age. Ninety percent of deaths occur before 6 months of age.
- The incidence is 0.54 per 1,000 live births in the United States.
- SIDS is more prevalent among African American infants.
- There has been a major reduction in SIDS since the launch of the Safe to Sleep (formerly Back to Sleep) Campaign in 1994.
- In spite of the reduction of SIDS, the incidence of SUID remains stable because of an increase in other causes of SUID (accidental sleep-related suffocation).

Pathophysiology

- The pathophysiology of SIDS is not completely understood. With the triple-risk hypothesis, a combination of 3 factors is postulated: a vulnerable infant (an abnormality in control of breathing), a critical developmental stage, and an outside stressor (sleeping in the prone position, parental smoking).
- The basis of a higher risk of SIDS when sleeping in the prone position may be secondary to upper-airway occlusion, rebreathing CO_2, or having an increased arousal threshold.
- Hyperthermia may produce peripheral vasodilation with a fatal drop in blood pressure.
- Autonomic nervous system dysregulation has been postulated because of sweating, hyperthermia, and tachycardia, followed by bradycardia preceding the death of the infant.
- Box 97-1 shows risk factors and protective factors.

Box 97-1. Risk Factors and Protective Factors for SIDS

Maternal Risk Factors	Infant Risk Factors	Environmental Risk Factors	Protective Factors
Low socioeconomic status	Sibling of an infant who died of SIDS	Car seats	Room sharing
Young maternal age	Male sex (60%)	Winter months	Pacifier
Higher parity	Premature	Soft bedding	Breastfeeding
Smoking	Small for gestational age	Bed sharing	Immunizations
	Sleeping position (prone or side)	Overheating	Use of a fan

SIDS, sudden infant death syndrome.

Prevention

- The AAP updated the recommendations for a safe infant sleeping environment in November 2016.
  - — Place infants to sleep on their backs.
  - — Use a firm sleep surface.
  - — Breastfeed.
  - — Share a room, but not a bed, with the infant.
  - — Remove pillows and loose bedding.
  - — Do not smoke during pregnancy or after birth.

— Do not drink alcohol or use illicit drugs during pregnancy or after birth.
— Offer the infant a pacifier at naptime and bedtime.
— Avoid overheating the infant.
— Seek prenatal care.
— Immunize the infant according to AAP recommendations.

Resource for Families

- Safe to Sleep: What Is SIDS? (National Institutes of Health). www.nichd.nih.gov/sts/about/SIDS/Pages/default.aspx

Clinical Pearls

- The AAP recommends use of the term *BRUE* for brief, sudden, and now-resolved episodes of color change, altered responsiveness, irregular or absent breathing, and change in muscle tone that occurred in an infant <1 year of age.
- Low-risk infants with BRUE include those >60 days old, those with gestational age ≥32 weeks, those with postconceptional age ≥45 weeks, those with BRUE lasting <1 minute who did not require CPR, and those with no concerning history of physical examination findings.
- SIDS risk factors include exposure to smoking, male sex, prematurity, small size for gestational age, and sleeping in the prone position or on the side.
- Protective SIDS factors include breastfeeding, use of a pacifier, and sharing a room.

Chapter 98

Obstructive Sleep Apnea

Karen Kay Thompson, MD, and John Norman Schuen, MD, FAAP

Introduction/Etiology/Epidemiology

- Obstructive sleep apnea (OSA) is characterized by episodes of complete or partial upper-airway obstruction during sleep. When this is accompanied by clinical sequelae, such as daytime sleepiness or hypertension, it can be called *OSA syndrome (OSAS)*.
- OSA may cause gas exchange abnormalities, impaired sleep, and long-term sequelae.
- The overall incidence of OSAS in the pediatric population is 2%–5%.
- OSAS is most common in patients 2–15 years of age, with a peak between 3 and 6 years of age.
- Risk factors include a family history, African American race, sinus disease, obesity, asthma, and prematurity, as well as congenital syndromes—particularly those that affect the craniofacial structures or neurological development.
- Infant OSAS is distinctly different from childhood and adult OSAS. OSAS in infancy is less common and is often related to specific clinical conditions: gastroesophageal reflux, craniofacial abnormalities, lower-airway structural abnormalities, congenital syndromes, and abnormal neuromotor tone.

Pathophysiology

- OSAS is caused by conditions that result in upper-airway narrowing, increased upper-airway collapsibility, or both.
- Enlarged tonsils and adenoids represent the most common etiologic origin for OSAS in childhood.
- Increased risk occurs in children with congenital syndromes, craniofacial abnormalities, and neuromuscular disorders, including but not limited to
  - Down syndrome
  - Achondroplasia
  - Pierre Robin syndrome
  - Beckwith-Wiedemann syndrome
  - Muscular dystrophy and spinal muscular atrophy
  - Cerebral palsy
- Several factors can coexist in a child and lead to a complex interaction of various upper-airway (and rarely lower-airway) influences (see Figure 98-1).

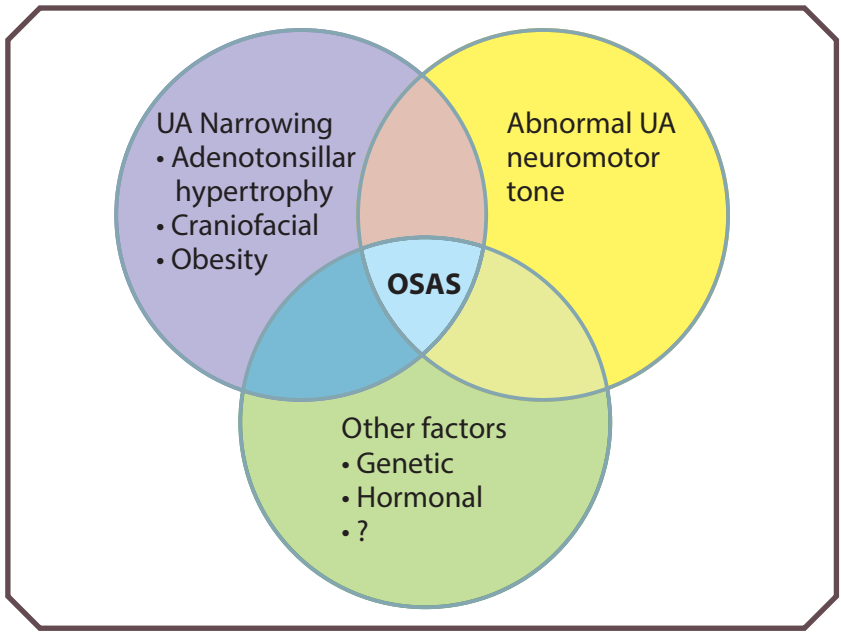

Figure 98-1. Multifactorial model of childhood obstructive sleep apnea syndrome (OSAS). UA = upper airway. Modified from Brooks LJ. Obstructive sleep apnea syndrome in infants and children: clinical features and pathophysiology. In: Sheldon S, Feber R, Kryger M, eds. *Principles and Practice of Pediatric Sleep Medicine.* Philadelphia, PA: Elsevier Saunders; 2005:223–229. Copyright 2005, with permission from Elsevier.

Clinical Features

- Sleep symptoms can include
  - — Snoring that is persistent (not just during upper respiratory infections or secondary to allergic rhinitis)
  - — Labored breathing during sleep
  - — Disturbed sleep with frequent gasps, snorts, or pauses
  - — Nocturnal enuresis
- Other signs and symptoms may include
  - — Morning headaches
  - — Daytime sleepiness (less common in children than adults)
  - — Difficulty with attention, possibly including attention-deficit/hyperactivity disorder
  - — Learning impairments
  - — Behavioral concerns
  - — Cardiovascular problems
  - — Poor growth and developmental delay

Diagnostic Considerations

- During routine health supervision visits, children should be screened regularly for habitual snoring.
- Physical examination findings to consider include
  - Swollen nasal mucous membranes
  - Deviated septum
  - Mouth breathing
  - Intraorbital darkening (allergic shiners)
  - Tonsillar hypertrophy
  - High, arched palate
  - Overbite
  - Crowded oropharynx
  - Macroglossia
  - Micrognathia or retrognathia
  - Failure to thrive
  - Loud P_2 heart sound
- Consider OSAS if any of the clinical features or examination findings herein are present in both snoring and nonsnoring children.
- The preferred evaluation for children who exhibit signs of OSAS is an overnight, in-laboratory polysomnogram (PSG) (Figures 98-2, 98-3, and 98-4).

Management

- As a first step, all children with OSAS confirmed by means of polysomnography and large tonsils and/or adenoids should be referred to an otolaryngologist for consideration of adenotonsillectomy.
- Adenotonsillectomy has a high likelihood of resolving or markedly improving OSA and is considered first-line therapy for most otherwise healthy children with OSAS.
- If clinically indicated, preoperative evaluation of children with severe OSAS might include
  - 12-lead electrocardiography or echocardiography to evaluate the presence of right ventricular hypertrophy
  - Hemoglobin and/or hematocrit level to evaluate the presence of polycythemia
  - Bicarbonate level to evaluate the presence of hypercarbia
  - Venous or capillary blood gas analysis first thing in the morning to look for gas exchange abnormalities
- The PSG should be repeated 1–2 months postoperatively in children with severe OSA, as well as in children with less severe OSA who remain symptomatic after surgery. A “split night” study may be considered so that positive airway pressure (PAP) may be instituted. This should be discussed with the family, and the child should be introduced to PAP prior to the study.

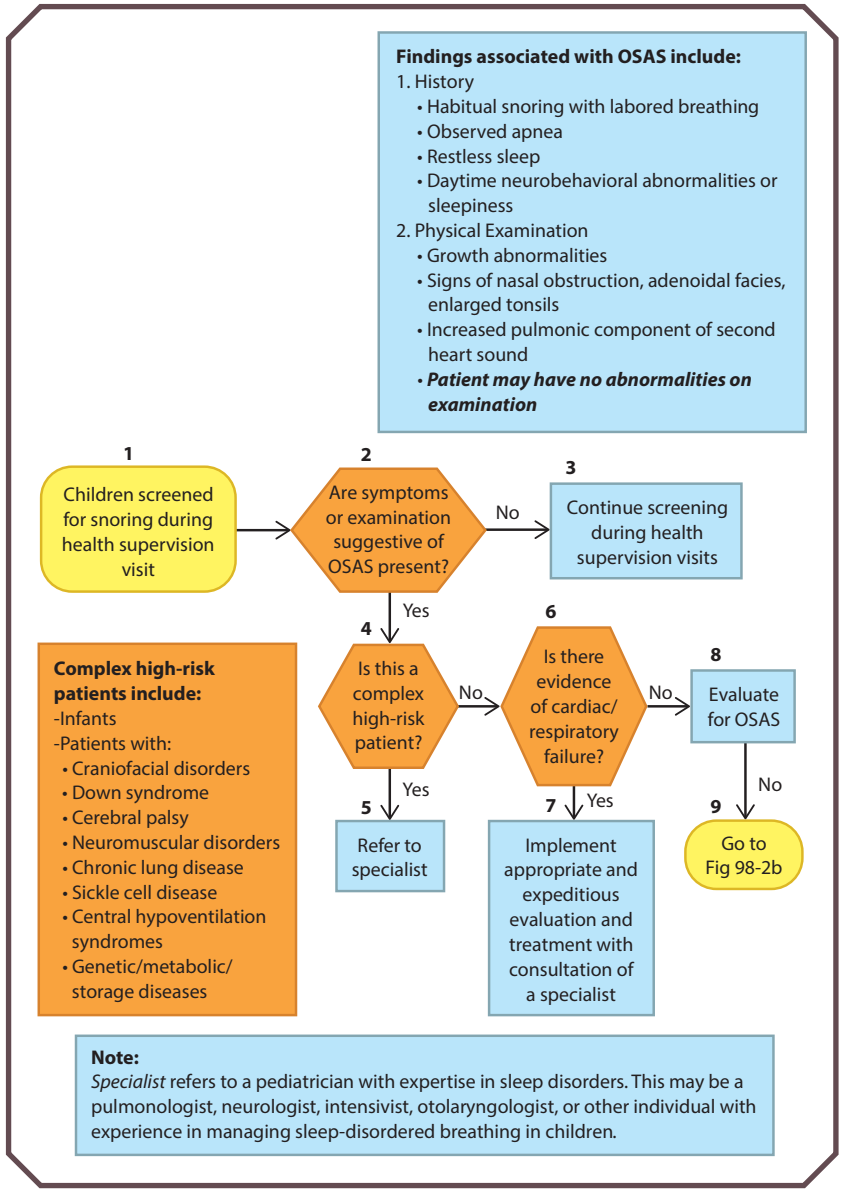

Figure 98-2a. American Academy of Pediatrics diagnostic algorithm for obstructive sleep apnea syndrome (OSAS). BiPAP = bilevel positive airway pressure, CPAP = continuous positive airway pressure, PSG = polysomnogram. Adapted from American Academy of Pediatrics Section of Pediatric Pulmonology, Subcommittee of Obstructive Sleep Apnea Syndrome. Clinical practice guideline: diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics.* 2002;109:704–712.

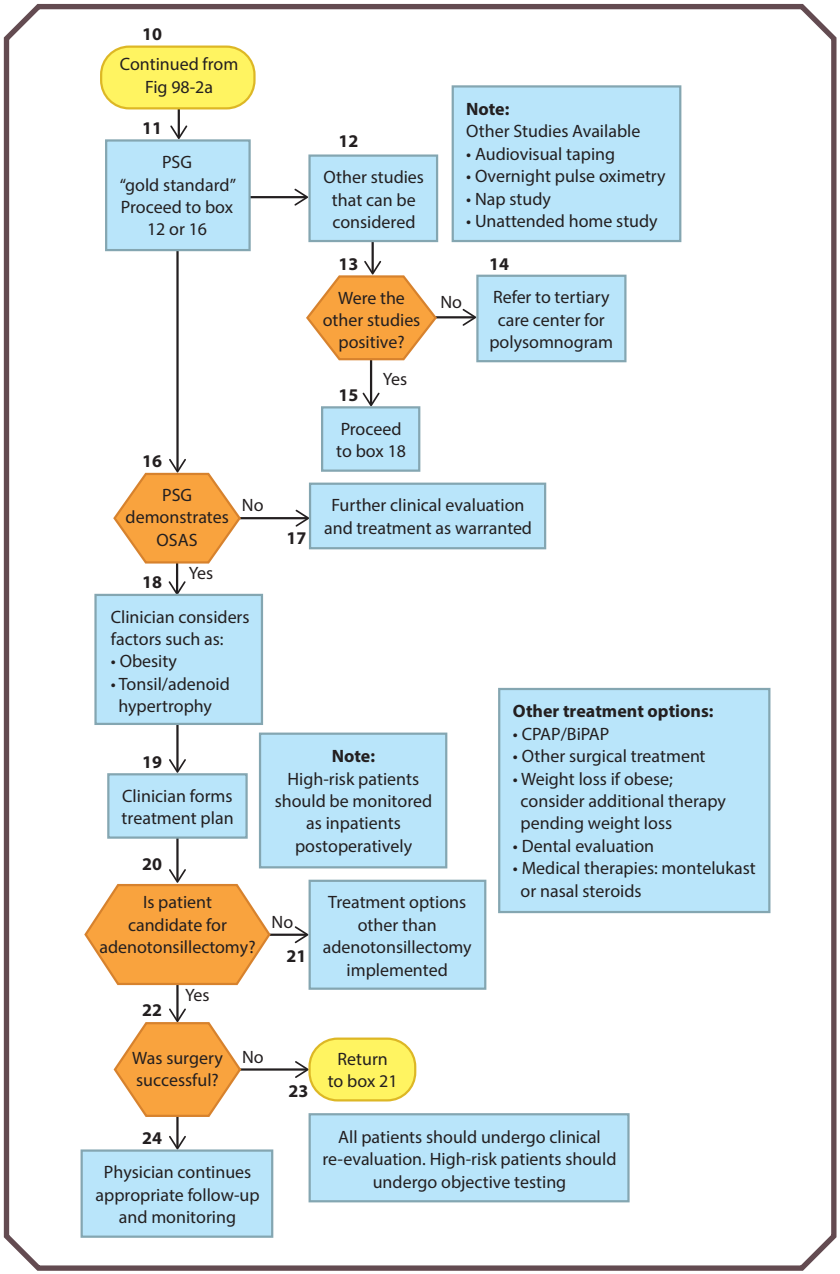

Figure 98-2b. American Academy of Pediatrics diagnostic algorithm for obstructive sleep apnea syndrome (OSAS). BiPAP = bilevel positive airway pressure, CPAP = continuous positive airway pressure, PSG = polysomnogram. Adapted from American Academy of Pediatrics Section of Pediatric Pulmonology, Subcommittee of Obstructive Sleep Apnea Syndrome. Clinical practice guideline: diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics.* 2002;109:704–712.

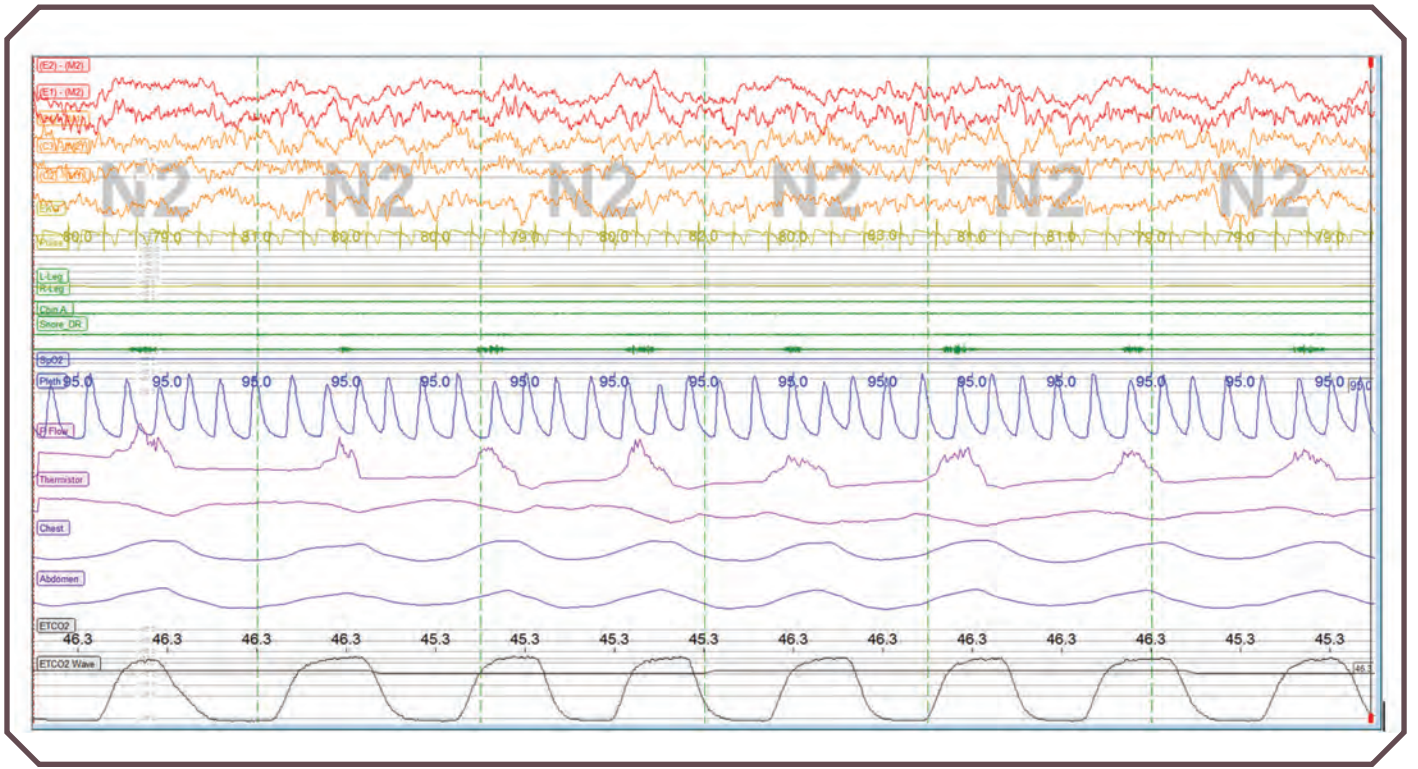

Figure 98-3. Normal polysomnographic tracing (30-second epoch). Note the regular breathing pattern, with the chest wall and abdomen moving synchronously.

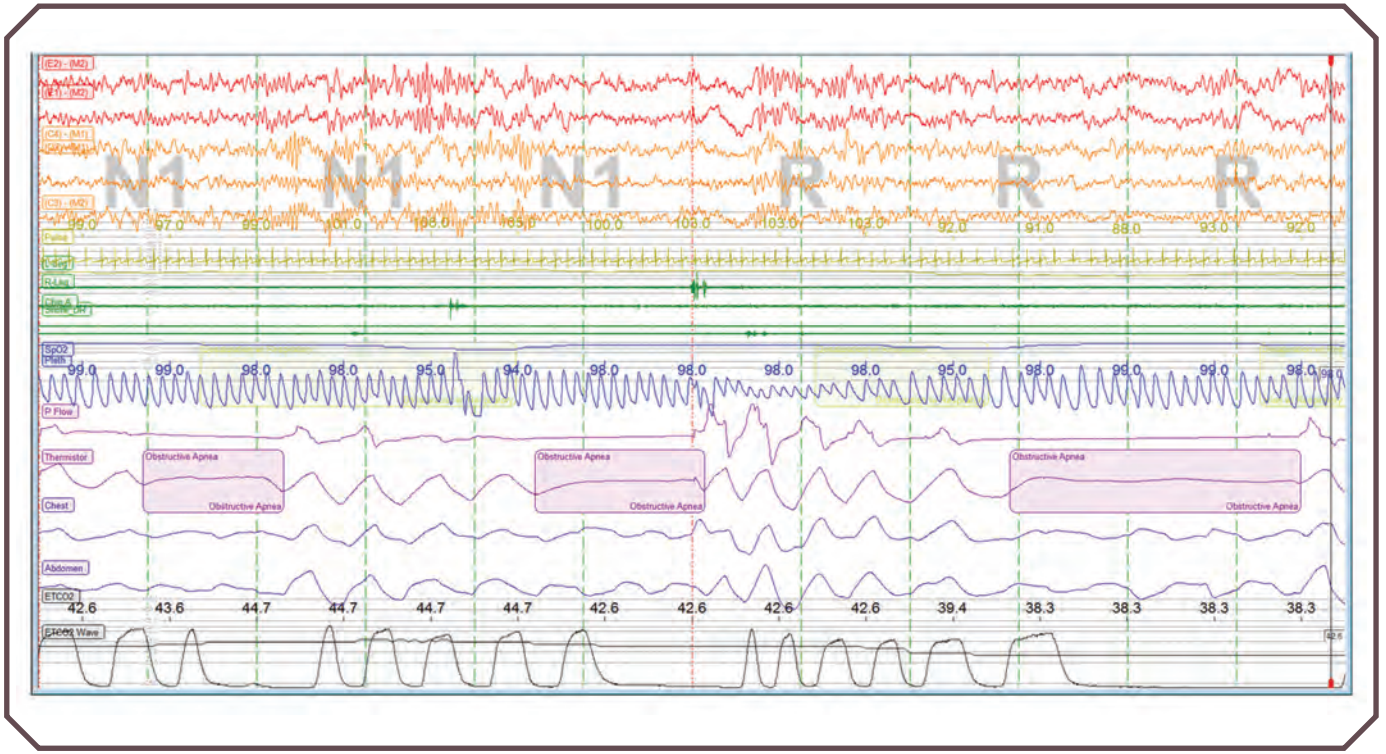

Figure 98-4. Polysomnographic tracing of a child with 3 obstructive episodes (60-second epoch). Note the absence of air flow with the asynchronous movement of the chest wall and abdomen ("paradoxical" breathing).

- In some cases, supraglottoplasty, craniofacial reconstruction, dental devices (palatal expansion), or tracheostomy may be the preferred treatment for OSAS.
- In cases of mild OSAS, treatment with nasal steroids and montelukast may be beneficial. Verification of improvement is important.
- Positional techniques (placing the child prone or lying on the side) may be helpful when OSAS occurs primarily in the supine position.

Treating Associated Conditions

- In overweight or obese children, weight loss should be encouraged and supported.
- Nasal steroids and montelukast can be used to treat children with coexisting allergic rhinitis.
- Treating gastroesophageal reflux may be helpful for some, particularly in infants with OSAS.

Expected Outcomes/Prognosis

- When childhood OSAS is treated appropriately, the outcomes can be excellent with regard to academic performance, behavior, prevention of multisystem disease, and growth.
- Regrowth of adenoids can occur and cause reappearance of OSAS.
- There is a higher prevalence of OSA in asthmatic children. Treatment of OSA in that group of poorly controlled asthmatics resulted in improved asthma control.
- Untreated OSAS, especially if severe, can lead to severe sequelae, including
  - Pulmonary hypertension
  - Somatic growth retardation
  - Poor school performance
  - Behavioral problems
  - Increased intracranial pressure
  - Hypoxic seizures

When to Refer

- All children with concerns for OSAS should be referred, when possible, to a pediatric sleep disorders center for overnight polysomnography. Patients with complicated conditions may be best served through evaluation by a pediatric sleep specialist.

When to Admit

Children with the following are at risk for surgical complications and should be closely monitored in an inpatient setting after adenotonsillectomy:

- Age <3 years
- More severe OSAS
  - Obstructive apnea index >10
  - Oxyhemoglobin saturation nadir ≤80%
  - Cardiac complications of OSAS (right ventricular hypertrophy)
- Neuromuscular or craniofacial syndromes
- Comorbid conditions
  - Prematurity with respiratory difficulties
  - Obesity
  - Failure to thrive

Resources for Families

- Sleep Apnea Detection (American Academy of Pediatrics). www.healthychildren.org/English/ages-stages/baby/sleep/Pages/Sleep-Apnea-Detection.aspx
- Positive Airway Pressure (PAP) for the Treatment of Obstructive Sleep Apnea in Children (American Thoracic Society). www.thoracic.org/patients/patient-resources/resources/pap-peds-2015.pdf

Clinical Pearls

- Persistent snoring represents one of the most common symptoms that is suggestive of OSA.
- Morbidity and mortality risk factors have been identified in relation to adenotonsillectomy (for treatment of OSA) that allow clinicians to take steps that may improve patient safety.
- After any treatment for OSA, clinician follow-up is important to make sure that the patient truly resolves their OSA.
- Multiple therapies have been shown to be beneficial in treating OSA that were not available until recently. Given the clinical scenario, medical, dental and/or surgical treatments may be considered to tailor a plan best suited for each patient.

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Chapter 99

Congenital Central Hypoventilation Syndrome

Iris A. Perez, MD, FAAP, Emily S. Gillett, MD, PhD, FAAP, and Thomas G. Keens, MD, FAAP

Introduction/Etiology/Epidemiology

- Congenital central hypoventilation syndrome (CCHS) is a rare genetic disorder characterized by failure of automatic control of breathing and autonomic nervous system dysfunction.
- The most severe manifestation is profound alveolar hypoventilation during sleep, particularly non–rapid eye movement sleep; hypoventilation may extend into times when the patient is awake.
- It is most often caused by a mutation in the *PHOX2B* gene that affects neural crest cell migration and autonomic nervous system dysfunction.
- Most patients with *PHOX2B* gene mutations have a polyalanine repeat expansion mutation (PARM); 10% of cases are due to non-PARM (NPARM).
- Autosomal dominant inheritance occurs with variable penetrance.
- In France, the estimated incidence is 1 in 200,000 live births. In Japan, the incidence is 1 in 148,000 live births.
- Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD syndrome) is a rare and poorly understood syndrome that is similar to CCHS (see later discussion).

Clinical Features

- CCHS typically presents in the newborn period.
  - — Recurrent apnea and cyanosis
  - — Hypoventilation and hypoxemia without increase in breathing frequency
  - — Intubation and assisted ventilation in the nursery and failure to extubate
- Some patients with CCHS present in later infancy, childhood, and adolescence
  - — Recurrent apneas and apparent life-threatening events
  - — Diaphoresis and cyanosis during sleep
  - — Pulmonary hypertension

  - Delay in waking or achieving adequate ventilation after general anesthesia or failure to wean the patient from mechanical ventilation after appropriate treatment of severe pneumonia
- Autonomic nervous system dysfunction is also a major manifestation; the presence and severity are dependent on *PHOX2B* gene mutation.
  - Ophthalmologic abnormalities include sluggish pupils, strabismus, convergence insufficiency; Marcus Gunn jaw-winking phenomenon
  - Cardiovascular: Sick sinus syndrome, reduced heart rate variability, decreased heart rate response to exercise, postural hypotension; decreased blood pressure response to head tilt and standing
  - Gastrointestinal: Esophageal dysmotility, Hirschsprung disease (20%)
  - Endocrine: Abnormal glucose metabolism that leads to hypoglycemia or hyperglycemia
  - Tumors of neural crest origin: Ganglioneuromas and ganglioneuroblastomas (6%)
  - Dysregulation of body temperature with decreased baseline body temperature; poor heat tolerance; sporadic profuse sweating (can be unilateral)

Diagnostic Considerations

- CCHS should be suspected in the presence of hypoventilation that is not explained by lung disease, ventilatory muscle weakness, or obvious neurological disorders.
- *PHOX2B* gene mutation is essential in establishing the diagnosis, predicting the severity of ventilatory and autonomic nervous system disorder, and associated complications.
- While waiting for gene mutation analysis results, perform tests to rule out other causes of hypoventilation.
  - Neurological evaluation, including magnetic resonance imaging and/or computed tomography of the brain, to rule out gross anatomic lesions
  - Metabolic screening
  - Polysomnography (PSG) to establish the presence of hypoventilation and sleep-related breathing disorder
  - Blood gas analysis performed while the patient is awake to document daytime hypoventilation
  - Chest radiography
  - Fluoroscopy of the diaphragm
  - Echocardiography
  - Muscle biopsy, as necessary

Management

- Patients with CCHS require ventilatory support throughout life; weaning from ventilatory support is not realistic.
- The goal of ventilatory support is to ensure optimal ventilation and oxygenation both during sleep and while awake.
- Oxygen supplementation alone is not adequate and should be minimized because it does not alleviate the hypoventilation, and it can disarm providers and caregivers that may not be aware of clinically significant hypercapnia.
- There is currently no pharmacological treatment for management of respiratory insufficiency in CCHS.
- Most patients with CCHS have little or no lung disease; thus, there are different options for evaluation, including positive pressure ventilation (PPV) via tracheostomy, noninvasive PPV (NPPV), and diaphragm pacing.
  - PPV via tracheostomy
    - PPV is most often prescribed in the first years of life because infants may be unstable, and minor respiratory infections may cause severe apneas and worsen respiratory failure.
    - Ventilatory support by using pressure control or assist control mode is provided to maintain end-tidal CO_2 pressure between 30 and 45 mm Hg and oxygen saturation at pulse oximetry (Spo_2) ≥95%.
    - Use of smaller tracheostomy tubes may decrease the risk for the development of tracheomalacia and allows a larger leak to assist with speech.
      - ~ Some CCHS centers prefer to treat patients with uncuffed tracheostomy tubes, and some centers suggest using cuffed tubes when the patient receives ventilation. There are advantages and disadvantages of the 2 approaches that are beyond the scope of this brief review.
  - NPPV
    - NPPV is an option for stable older children who require ventilatory support only during sleep.
    - NPPV can be provided via bilevel positive airway pressure (BiPAP). NPPV can be provided with a variety of equipment and ventilator modes. Two common modes are BiPAP and average volume-assured pressure support ventilation, administered via nasal or full-face mask.
    - Patients with CCHS do not increase their respiratory rate with hypercapnia or hypoxemia; hence, an appropriate rate provided by spontaneous/timed or timed mode is necessary. Midface hypoplasia and dental malocclusion have been reported.
  - Diaphragm pacing
    - Uses the patient's own diaphragm as the ventilator pump

  - May improve the quality of life for some patients for 2 reasons
    - ~ Permits tracheostomy decannulation for those who are ventilator dependent only during sleep
    - ~ Permits freedom from the ventilator during the day in patients who are dependent on a ventilator full time; details of diaphragm pacing via phrenic nerve stimulation are discussed in Chapter 117.
- Patients with CCHS are biologically incapable of developing respiratory distress and are notorious for fooling families and health care providers because they always "look fine." The only way to know if a patient with CCHS is being ventilated adequately is to monitor both pulse oximetry and partial pressure of carbon dioxide (P_{CO_2}) by using capnography. Alarms are usually set at 85% for Sp_{O_2} and 55 mm Hg for end-tidal CO_2 pressure. This minimizes nuisance alarms but still allows the caregiver to respond to emergencies.

Follow-up and Treatment of Associated Conditions

- Patients with CCHS should undergo yearly echocardiography to assess the presence of pulmonary hypertension or cor pulmonale.
- In patients with CCHS, pulmonary hypertension and cor pulmonale are likely caused by inadequate ventilation. Thus, patients with CCHS require yearly PSG (sleep study) to assess oxygenation and ventilation during sleep and adjust ventilator settings as necessary. Thus, pulse oximetry and P_{CO_2} monitoring (end tidal or transcutaneous) are necessary elements of PSG.
- Patients with CCHS should undergo a comprehensive eye examination to determine the nature of ophthalmologic involvement and allow for early intervention to avoid developing problems with learning.
- Patients with CCHS should undergo yearly monitoring to assess the presence of life-threatening cardiac sinus pauses—preferably at least 72 hours of recording time via Holter monitor or other portable electrocardiographic device. More prolonged cardiac monitoring is becoming increasingly available, including 2-week monitoring systems and even subcutaneous cardiac monitoring that functions for years.
- Other monitoring and follow-up studies depend on the *PHOX2B* gene mutation (Table 99-1).
- Patients with CCHS should undergo at least yearly tracheostomy tube assessment by an otolaryngologist and perhaps more often if patients have recurrent tracheitis, bloody tracheal secretions, or increased end-tidal P_{CO_2} levels.
- Patients with CCHS should be assessed for development of midface hypoplasia and dental malocclusion if they are receiving NPPV via mask.
- Some but not all patients with CCHS are unable to increase their own ventilation adequately with exercise. It is important that this potential risk be recognized and assessed for each patient.

Table 99-1. Recommended Testing to Characterize Congenital Central Hypoventilation Syndrome Phenotype					
***PHOX2B* Genotype**	**Annual In-Hospital Comprehensive Physiological Testing (Awake and Asleep), Exogenous and Endogenous Gas Challenges, Autonomic Testing[a]**	**Assessment for Hirschsprung Disease**	**Annual Neurocognitive Assessment[a]**	**Annual 72-h Holter Recording and Echocardiogram[a]**	**Annual Imaging to Assess the Presence of Tumors of Neural Crest Origin**
PARM					
20/24 and 20/25	X		X	X	
20/26	X	X	X	X	
20/27	X	X	X	X	
20/28–20/33	X	X	X	X	X[b]
NPARM	X	X	X	X	X[c]

NPARM, non-PARM (missense, nonsense, frameshift); PARM, polyalanine repeat expansion mutation. From Weese-Mayer DE, Berry-Kravis EM, Ceccherini I, et al. An official ATS clinical policy statement: congenital central hypoventilation syndrome: genetic basis, diagnosis, and management. *Am J Respir Crit Care Med.* 2010;181(6):626–644.

[a] Children <3 years of age should undergo comprehensive evaluations every 6 months.

[b] Annual chest and abdominal imaging should be performed to identify ganglioneuromas and ganglioneuroblastomas.

[c] Abdominal imaging and urine catecholamine testing should be performed every 3 months in the first 2 years, then every 6 months until 7 years of age, to identify neuroblastomas.

- Patients with CCHS have abnormal responses to hypoxia and hypercapnia; thus, when unexplained problems such as seizure or lethargy occur, they should be stabilized via hyperventilation with 100% oxygen until the source of the problem is identified. In children with CCHS, the etiologic origin of any such problem is likely to be hypoventilation until proven otherwise. A brief period of hyperventilation will not be harmful but may be lifesaving.

Expected Outcomes/Prognosis

- Patients with CCHS require ventilatory support for life.
- The overall mortality rate ranges between 8% and 38%. Most deaths occur before 2 years of age. The causes of death are varied but are mainly linked to tracheostomy and ventilator dependence.
- Fatal episodes of bradycardia are also seen in a fraction of patients with CCHS.
- With early identification and intervention, as well as advances in ventilatory support, most children mature to adulthood with only relatively moderate impairment of quality of life in some.
- Preschool- and school-aged children with CCHS can have neurocognitive impairment that necessitates close monitoring and early intervention.
- Patients with CCHS are vulnerable to the respiratory-depressant effects of alcohol and drugs. Patients who are usually able to maintain normal blood gas levels without ventilator support while awake may be unable to do so when drinking. Therefore, patients must be counseled against the consumption of alcohol and drugs prior to achieving adolescence.

ROHHAD Syndrome

- ROHHAD syndrome is a rare disorder characterized by severe alveolar hypoventilation.
- Patients are typically developing until onset of symptoms, generally before 10 years of age (median age of 3 years).
- There is rapid onset of excessive weight gain, followed by hypothalamic dysfunction (hyperprolactinemia, hypothyroidism, growth hormone deficiency, diabetes insipidus, fluid imbalance), autonomic dysregulation (bradycardia, hypotension, thermal dysregulation), and severe alveolar hypoventilation. Other features include ophthalmologic abnormalities and neural crest tumors.
- Hypoventilation may not occur right away. Some patients may initially present with a sleep-related breathing disorder only—mostly obstructive sleep apnea (OSA)—thus indicating the need for monitoring with serial PSG.
- Patients may have evidence of abnormal control of breathing while awake, with central apneas and oxygen desaturations.
- Unlike CCHS, *PHOX2B* gene mutation is absent.

- Affected patients require ventilatory support either full time or during sleep only.

When to Refer

- Patients with suspected CCHS should be referred to a pediatric pulmonologist with knowledge and expertise in this disorder.
- Patients with CCHS who have syncopal episodes should be referred to a cardiac electrophysiologist for evaluation and management.

When to Admit

- The presence of pulmonary hypertension indicates inadequate ventilatory support until proven otherwise. Consider inpatient admission to address possible causes that include inadequate ventilator settings or tracheostomy caliber, unrecognized hypoventilation while awake, and noncompliance with ventilatory support.

Resources for Families

- Congenital Central Hypoventilation Syndrome (American Thoracic Society). www.thoracic.org/patients/patient-resources/resources/congenital-central-hypoventilation-syndrome.pdf
- CCHS Network. www.cchsnetwork.org

Clinical Pearls

- CCHS and ROHHAD syndrome are disorders of respiratory control characterized by profound hypoventilation that require ventilatory support for life.
- CCHS and ROHHAD syndrome are associated with autonomic dysfunction.
- Suspect CCHS in patients with recurrent apneas, cyanosis, and failure to wean off of respiratory support.
- Patients with CCHS lack appropriate responses to hypercapnia and hypoxemia and lack perception of dyspnea; thus, their appearance can be misleading.
- Suspect ROHHAD syndrome in a young child with apneas; sudden, excessive weight gain; hypothalamic dysfunction; and autonomic nervous system dysfunction.

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Chapter 100

Insomnia

Priya Prashad, MD

Introduction/Etiology/Epidemiology

- By 3–6 months of age, an infant's circadian rhythms have matured to the point where the infant may begin to sleep through the night.
- During the first 6 months of infancy, parents should begin to establish healthy sleep habits to prevent later sleep problems.
- One of the main sleep problems to arise 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%–30% of infants, toddlers, and preschoolers.
- Chronic insomnia is defined as difficulty initiating and maintaining sleep, waking up earlier than desired, resisting going to bed on an appropriate schedule, or having difficulty sleeping without parent or caregiver intervention ≥3 times a week for ≥3 months.

Pathophysiology

Behavioral Insomnia of Childhood

The classic description of behavioral insomnia of childhood includes 3 types:

- Sleep-onset association type: Children become dependent on specific sleep-onset associations (eg, rocking, feeding, parental presence) to fall asleep at bedtime and to return to sleep. For older children, sleep onset may be associated with watching television or the use of other electronics.
- Limit-setting type: Children refuse to go to bed and/or make repeated requests or attempts to delay bedtime (eg, asking to use the bathroom or to read one more story). Parents demonstrate difficulties in adequately enforcing bedtime limits.
- Combined type: This occurs when a child has a negative association with sleep, coupled with resistance or refusal to go to bed, due to a lack of limit-setting by caretakers.

Psychophysiological Insomnia

- For older children and adolescents, problems with initiating and maintaining sleep are typically described by the term *psychophysiological insomnia* from the adult literature.

- This form of insomnia involves an excessive amount of anxiety and worry regarding sleep and sleeplessness.
- The individual's heightened anxiety makes falling asleep more challenging, which in turn makes sleep a more negative experience and may lead to a vicious cycle.

Delayed Sleep Phase Syndrome

- Adolescents typically undergo a delay in the timing of sleep onset (≥2 hours) that appears to be driven by both biological and social factors (see Figure 100-1).
- Estimated prevalence of 10%
- Characterized by changes in the underlying period of the circadian clock that regulates sleep-wake timing (delayed release of melatonin)
- Characterized by a stable sleep schedule that is substantially later than the conventional or desired time
- Patients have sleep-onset insomnia and extreme difficulty arising when they attempt to conform to a conventional work schedule or other social demands; this can be a factor in academic failure.

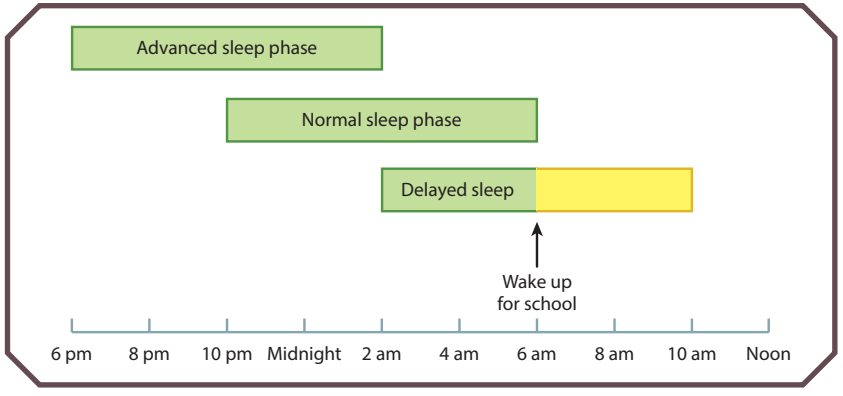

Figure 100-1. Normal sleep phase and variations.

Differential Diagnosis/Treating Associated Conditions

- A referral to a sleep laboratory for a polysomnography study is not necessary to diagnose behavioral insomnia but may be needed if primary sleep disorders, such as sleep-related breathing disorders, narcolepsy, and periodic limb movement disorder, are being considered.
- These disorders may manifest similarly to behavioral insomnia as night awakenings or daytime sleepiness.

Diagnostic Considerations

Health care providers should routinely ask parents and/or the child about sleep, including regularity and duration of sleep, bedtime resistance, sleep-onset delay, night awakenings, symptoms of sleep-disordered breathing, and signs of increased daytime sleepiness.

Management

- Behavioral treatments are the most appropriate first line of treatment for behavioral 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.
- These interventions also frequently rely on parent training to effect changes in the parent's behavior, which facilitate changes in the child's behavior.
  - Graduated extinction involves parents ignoring bedtime crying and tantrums for predetermined periods before briefly checking on the child to facilitate self-soothing.
  - Limit-setting with young children 2–6 years of age may involve limiting the number of times the child can make a request, whereas limit-setting for school-aged children 6–11 years of age often revolves around how late the child can watch television, do homework, or use the Internet.
  - Promoting sleep hygiene and addressing nighttime fears can help reduce negative associations with sleep.
  - Interventions for the adolescent with a delayed sleep phase typically include sleep hygiene education, relaxation strategies, and sleep restriction (ie, limiting the time in bed based on how long one actually sleeps), using the bed for sleep only, and removing oneself from bed if unable to sleep to create more positive associations with sleeping and a greater physiological pressure for sleep. Taking melatonin about 2 hours before bedtime and letting in bright light in the morning can help shift the circadian clock to an earlier schedule.
- Hypnotic medications may have rapid short-term effects on sleep problems, but medications typically do not have long-term positive effects on sleep.
- There are no Food and Drug Administration–approved medications for the treatment of insomnia in children, and there are concerns about the safety and side effects of these medications.

Expected Outcomes/Prognosis

- A growing body of literature suggests that behavioral interventions for childhood insomnia are effective, particularly during the first few years of life.

- Behavioral interventions lead not only to improvements in children's sleep, but also to improvements in child behavior and parental well-being.

When to Refer

- A referral to a sleep medicine specialist may be needed for any persistent and complex cases, especially those requiring pharmacotherapy.
- Behavioral insomnia in children with autism spectrum disorder, attention-deficit/hyperactivity disorder, and anxiety and mood disorders might warrant a referral to a developmental pediatrician or neurologist.
- Referral to a psychologist or psychiatrist may be needed if there is underlying anxiety and/or depression that contributes to the insomnia.

When to Admit

- Insomnia is most effectively treated on an outpatient basis with a customized treatment plan, including cognitive behavioral therapy and frequent follow-up.

Prevention

- The best strategy for reducing sleep problems in infants is educating parents to prevent sleep issues from starting.
- 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 on healthy sleep habits, particularly keeping regular schedules and not sleeping in excessively on weekends (>1 hour later than on weekdays), allows them an opportunity to consciously make informed choices about their sleep habits.

Resources for Families

- Sleep Problems in Children (American Academy of Pediatrics). patiented.solutions.aap.org/handout.aspx?resultClick=24&gbosid=156710
- Sleep Tips for Your Family's Mental Health (American Academy of Pediatrics). www.healthychildren.org/English/healthy-living/emotional-wellness/Pages/Sleep-and-Mental-Health.aspx

Clinical Pearls

- Medication should rarely be the first or only option for the treatment of insomnia in children.
- If used, medication should always be combined with behavioral interventions.
- Behavioral strategies that are customized to the individual family situation have a higher chance of success than a "one model fits all" approach.

Chapter 101

Excessive Somnolence

Nadav Traeger, MD, FAAP, FCCP, DABSM

Introduction

- Excessive somnolence 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 avoidance of accidental injuries and motor vehicle crashes.

Etiology

- The most common etiologic origins for excessive somnolence are
  - — Inadequate amount of sleep relative to the person's needs. This may be voluntary (to have more time for homework, sports, reading, socializing, watching TV, etc) or because of an inability to fall asleep and/or stay asleep (insomnia).
  - — Disruption of sleep. This may be due to extrinsic or 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 sync with conventional time).
    - Less common but often underdiagnosed are central disorders of hypersomnolence, which include narcolepsy, 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.

Epidemiology

- The epidemiology of excessive somnolence is unknown.

Clinical Features

- Increased tendency to fall asleep
- Low energy or motivation
- Crankiness, moodiness, irritability, crying
- Hyperactivity
- Inattention
- Memory impairment
- Decreased school performance

- Behavioral problems
- Increased tendency for errors and/or accidents
- Excessively long nights of sleep
- Persistence of naps past the age the child should have been outgrown them or recurrence of previously discontinued daytime napping

Diagnostic Considerations

- Obtain a thorough history by covering the following:
  - Sleep habits
    - Ask about the typical time the child gets into bed, falls asleep, and wakes up. From this, estimate the typical amount of sleep obtained by the patient and then compare that to what is typical for his or her age.
    - The American Academy of Sleep Medicine Consensus Statement regarding Recommended Amount of Sleep for Pediatric Populations (endorsed by the American Academy of Pediatrics) states that the following amount of sleep should be obtained per 24 hours on a regular basis to promote optimal health:
      ~ Infants 4–12 months: 12–16 hours (including naps)
      ~ Children 1–2 years: 11–14 hours (including naps)
      ~ Children 3–5 years: 10–13 hours (including naps)
      ~ Children 6–12 years: 9–12 hours
      ~ Teenagers 13–18 years: 8–10 hours
    - Review the bedtime routine for behaviors or activities (on the part of both the patient and the parents) that may be contributing to difficulty with initiation or maintenance of sleep.
    - It may be easiest to work backward—that is, determine what time the child needs to wake up for school, determine how many hours of sleep he or she should get, and then count in reverse to determine the desired bedtime. This may require some negotiation.
    - Ask about factors in the sleep environment that would make it more conducive to sleep. (Is the bedroom dark, quiet, cool?)
    - Inquire if there are activities other than sleep that are performed in bed (using electronics, reading, homework, eating, etc) during any part of the day.
  - Symptoms of sleep disorders (eg, snoring, difficulty falling asleep or staying asleep, narcolepsy symptoms)
    - If there are symptoms of sleep disorders, such as OSAS or narcolepsy, then direct further investigation toward those, performing an overnight polysomnogram (sleep study) or providing a referral to a pediatric sleep medicine specialist as clinically indicated.
  - Obtain a medical history, including conditions and medications that may cause excessive somnolence.
  - Screen for psychiatric disorders, as well as substance use, because many of these involve sleep disturbances.

- The severity of daytime sleepiness can be quantified subjectively by using tools such as the modified (pediatric) Epworth Sleepiness Scale (Figure 101-1). Have the patient or parent fill it out. When clinically appropriate, the severity of daytime sleepiness can be objectively measured by using the Multiple Sleep Latency Test (MSLT).
  - Note: These various measures of daytime sleepiness (history, questionnaires, MLST) do not always correlate with each other and must be used with appropriate clinical judgment.

Treatment

Treatment is directed at the underlying etiologic origins.

- For those who get insufficient sleep, increase the amount of sleep.
- Address underlying sleep-onset or sleep-maintenance insomnia.
- Address any habits or environmental factors that may be interfering with getting a good night's sleep.
- Treat OSAS, if present.
- If the excessive somnolence seems to be caused by a medication, and it is possible to stop it or switch to a nonsedating alternative, then do so.
- Address psychiatric disorders and substance use.

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 listening to a story):	_____
Watching TV:	_____
Sitting inactive in a public place (eg, a movie theater):	_____
Being 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):	_____
Being in a car, stopped for a few minutes in traffic:	_____
Total:	_____

Figure 101-1. The Epworth Sleepiness Scale (for ages ≥4 years). A total score of ≤9 is considered to be normal. 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.

Prognosis

- The prognosis is difficult to quantify, but in most instances, it is very good once the underlying etiologic origin has been identified and treated.

When to Refer

- Refer the patient to a sleep medicine specialist when the etiologic origin of the excessive somnolence is unclear or if it did not respond to treatment.
- Refer the patient to a pediatric pulmonologist, sleep medicine specialist, or otolaryngologist for evaluation and treatment of OSAS.

Resources for Families

- Hypersomnias (American Academy of Sleep Medicine). www.sleepeducation.org/sleep-disorders-by-category/hypersomnias
- Insomnia: Overview and Facts (American Academy of Sleep Medicine). www.sleepeducation.org/essentials-in-sleep/insomnia
- Excessive Sleepiness (National Sleep Foundation). sleepfoundation.org/excessivesleepiness/excessive-sleepiness-home

Clinical Pearl

- Include excessive somnolence in your differential diagnosis when evaluating patients for behavioral and neurodevelopmental disorders (eg, attention-deficit/hyperactivity disorder).

Chapter 102

Narcolepsy

Nadav Traeger, MD, FAAP, FCCP, DABSM

Introduction

- Narcolepsy is felt to be an intrusion of rapid eye movement (REM) sleep into wakefulness. The body is relatively atonic during REM sleep, which is when dreams occur. Thus, narcolepsy is characterized by excessive daytime sleepiness and symptoms of REM-sleep dissociation.
- The 2 diagnostic subtypes are
  - Narcolepsy type 1 (narcolepsy with cataplexy)
  - Narcolepsy type 2 (narcolepsy without cataplexy)

Etiology

- Narcolepsy type 1 is caused by a deficiency in central nervous system hypocretin (also known as *orexin*) levels, most likely caused by a selective loss of hypothalamic hypocretin-producing neurons. Patients with sleepiness and low or absent cerebrospinal fluid (CSF) hypocretin levels are classified as having narcolepsy type 1, even if they do not yet manifest cataplexy.
  - A strong association with certain human leukocyte antigen (HLA) subtypes (DR2/DRB1*1501, DQB1*0602, DQB1*0602) suggests the involvement of autoimmune destruction of the hypocretin-releasing brain regions.
  - 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 neurological disease.
- The genetic and environmental factors associated with narcolepsy type 2 are unknown.

Epidemiology

- Narcolepsy in childhood is underrecognized and underdiagnosed, often being mistaken for behavioral or mood disorders.
- Narcolepsy type 1 occurs in 0.02%–0.18% of people in the United States.
- The prevalence of narcolepsy type 2 is more uncertain and is thought to represent a minority (about 15%–25%) of the total narcoleptic population.
- Both sexes are affected, with a slight preponderance of male sex.

Clinical Features

Specific for Narcolepsy

- Excessive daytime sleepiness
  - This is the most common symptom and often the most debilitating.
  - The patient experiences repeated daily episodes of unintentional lapses into sleep.
  - Unlike patients with other sleep disorders (eg, obstructive sleep apnea syndrome [OSAS]), patients with narcolepsy typically wake up feeling 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.
  - Sleepy children can often have seemingly paradoxical symptoms more typical of mood or behavioral disorders (see Chapter 101, Excessive Somnolence).
- Cataplexy
  - This is the most specific symptom but is only present in narcolepsy type 1.
  - There are recurrent episodes of loss of muscle tone without loss of consciousness.
  - These are generally sudden, brief (<2 minutes), and bilaterally symmetrical.
  - They are typically triggered by strong emotions that are often positive (eg, laughter, surprise) but may be negative (anger).
  - There is great interpersonal variation. The degree of muscle weakness can range from very subtle (unsteady gait or drooping of the eyelids, jaw, or shoulders) to dramatic (generalized muscle atonia). While for some patients, cataplexy is triggered only by laughter, others may have multiple emotional triggers, and sometimes there is no clear relation to emotions. While some patients with narcolepsy experience multiple attacks per day, some experience them less than once a month.
  - 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.

Not Specific for Narcolepsy

- The following symptoms are not specific for narcolepsy and can occur with other sleep disorders and even in otherwise healthy individuals.
- Hallucinations—either hypnagogic (upon falling asleep) or hypnopompic (upon waking)—are vivid, dreamlike experiences (visual, auditory, and/or tactile) that occur during the transition between wakefulness and sleep.

These may be frightening and involve the perception that there is someone or something in the room. Unlike psychotic episodes, these rarely have complex auditory hallucinations or fixed delusions. Hallucinations are estimated to occur in about 20% of the general population.

- Sleep paralysis is the temporary inability to move voluntary muscles occurring during the transition between wake and sleep. The person is awake and conscious but unable to move at all (including limbs or even opening the eyes). This may last for a couple of minutes and can be very frightening. There may be a sensation of dyspnea because the accessory respiratory muscles (but not the diaphragm) can be affected.
- Sleep disruption: Nighttime awakening is a common complaint.

Associated Findings and Comorbidities

- Obesity, which often coincides with disease onset, occurs more than twice as often in patients with narcolepsy as it does in the general population.
- There is an increased frequency of sleep talking, periodic limb movements of sleep, sleep-disordered breathing (eg, OSAS), and REM sleep behavior disorder.
- There is an increased occurrence of anxiety and depressive symptoms, although they may not necessarily meet the full diagnostic criteria for disorders of depression or anxiety.
- Patients often experience social isolation and poor performance at school and at work.
- Driving may be avoided for fear of a motor vehicle accident. If the patient chooses to drive, he or she should be cautioned not to drive at night, for long distances, or when feeling drowsy.

Usual Clinical Course

- Typical onset is between ages 10 and 25 years (it occurs only rarely prior to age 4).
- For those who have narcolepsy type 1, sleepiness is usually the first symptom to manifest. Cataplexy usually occurs within 1 year of onset but, in rare cases, it may either precede the sleepiness or not occur until several decades later. The other symptoms (hypnagogic hallucinations, sleep paralysis, and disturbed nocturnal sleep) often manifest later in the course of the disease.
- In most cases, symptoms gradually develop over several years. When the clinical picture has fully developed, there are usually only minor fluctuations in severity.

Diagnostic Considerations

- Perform overnight polysomnography (PSG) (sleep study) to evaluate the patient for other sleep disorders, such as OSAS, and to ensure an adequate night's sleep prior to the Multiple Sleep Latency Test (MSLT).

- An MSLT should be conducted the day after PSG to measure the mean time to sleep onset during 4 or 5 nap opportunities and to observe the patient for the presence of REM periods during those naps.
- HLA typing may be helpful in evaluating those with suspected narcolepsy type 1. Of note, this test result will be positive in a sizable proportion of the general population (about 25% of white individuals, 12% of Japanese individuals, and 38% of black individuals are positive for DQB1*0602). Therefore, its usefulness lies in having a high negative predictive value for narcolepsy type 1 (ie, this may be helpful in ruling it out).
- CSF hypocretin-1 measurements are performed according to research protocols at some centers.

Treatment

- There is no cure for narcolepsy; treatment is directed at the symptoms and manifestations.
- Stimulants are used to treat the excessive daytime sleepiness. Wakefulness-promoting agents (modafinil, armodafinil) have fewer side effects than typical stimulant medications and are generally considered first-line treatment.
- Serotonin-norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, and/or tricyclic antidepressants are used to treat the symptoms of REM-sleep dissociation (cataplexy, hallucinations, and sleep paralysis).
- Sodium oxybate (also known as *GHB* or sodium γ-hydroxybutyrate) can be used to address all 5 of the cardinal narcolepsy symptoms.
- Good overall sleep habits
- Brief (<30 minutes) scheduled daytime naps
- Avoidance of caffeine, alcohol, and nicotine
- Exercising regularly
- Avoidance of activities that would be dangerous if the patient were to experience a sudden sleep attack

Prognosis

- Narcolepsy is a lifelong condition. Once symptoms appear, they tend to get worse over the first 2–3 decades and then remain stable thereafter.
- There is no cure, but there are medications to address the symptoms. Cataplexy can be controlled in most patients with medications. Unfortunately, none of the currently available medications will allow these patients to consistently maintain a normal state of alertness.

When to Refer

- Given the complexities of the diagnosis and treatment, the patient should be referred to a sleep medicine specialist or a neurologist any time this diagnosis is suspected.

Resources for Families

- Narcolepsy: Overview and Facts (American Academy of Sleep Medicine). www.sleepeducation.org/essentials-in-sleep/narcolepsy
- Narcolepsy Network. narcolepsynetwork.org

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Chapter 103

Parasomnias

Priya Prashad, MD

Introduction

- Parasomnias are undesirable physical events or experiences that occur during entry into sleep, within sleep, or during arousal from sleep.
- 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.

Etiology

- Parasomnia may occur during non–rapid eye movement (REM) sleep, during REM sleep, or during transitions to and from sleep.

Epidemiology

- Confusional arousals occur in 17.3% of children aged 3–13 years.
- Sleepwalking has an 18.3% lifetime prevalence.
- Sleep terrors are experienced by 1%–6.5% of children and 2.2% of adults.

Pathophysiology

- Arousal parasomnias have similar predisposing characteristics and triggers that are suggestive of a common pathophysiology.
- Parasomnias tend to run in families, so there may be a genetic factor.
- Parasomnias may be triggered by increased arousal from sleep, including obstructive sleep apnea (OSA), restless legs syndrome, periodic limb movement of sleep, or gastroesophageal reflux.
- Other triggers include sleep deprivation, illness, sleeping in a new or unfamiliar environment, and fever.
- These disorders are most common in childhood, particularly the preschool age, and usually resolve by adolescence.

Clinical features

Non-REM Sleep Disorders of Arousal

- Result from incomplete arousal from non-REM (NREM) sleep
- Occur at the transition from deep NREM (stage N3) sleep into the lighter stages of NREM sleep (N1 or N2) or from stage N3 into the awake state

- Most likely arise during the first third of nocturnal sleep because N3 sleep is most prominent early in the night

Confusional Arousals

- Confusional arousals occur mainly in infants and toddlers.
- They 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.
- The child appears confused (with eyes open or closed), very agitated, or even combative.
- Episodes may last 5–15 minutes before the child calms and returns to sleep.

Sleep Terrors

- These are more intense than confusional arousals.
- They begin with a loud scream and an intense look of fear, mydriasis, sweating, and tachycardia; episodes can last several minutes.
- The child is unaware of caregiver presence and will be confused and disoriented if awakened.
- Attempts to console the child may prolong or intensify the episode.
- Thrashing or other bodily movement is common.
- The child tends not to remember the episode in the morning.

Somnambulism

- Mild episodes, 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, although 1 type usually predominates.
- The patient may be found walking into a parent's room, bathroom, or different parts of the house; the patient can negotiate obstacles and seems to be awake.
- Some patients have injured themselves by attempting to walk downstairs, climb through windows, or leave the house.
- As with other arousal disorders, sleepwalkers are unaware of caregiver presence. They are difficult to awaken and may be confused on arousal, but no harm will result from awakening them.

Disorders of REM 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.

Nightmares

- May occur from an identifiable source, such as a frightening movie or video game, but more commonly occur from unspecific fears
- More common in children with posttraumatic stress disorder and anxiety
- Little confusion or disorientation involved; the child is often able to recall clear details upon awakening

REM Behavior Disorder

- Characterized by aggressive motor behavior as part of dream enactment
- Results from loss of muscle atonia during REM sleep and may lead to injury
- Occurs in <1% of adults (usually in men >50 years of age) and is even more rare in children

Other Parasomnias

- Bruxism: Involuntary and forceful clenching, grinding, or rubbing of the teeth during NREM sleep. Can be associated with anxiety and some neurodevelopmental disorders. Consider a dental evaluation, especially if associated with jaw pain.
- Rhythmic movement disorder (eg, head banging, body rocking): In some infants and toddlers, this starts at sleep onset and when attempting to go back to sleep. It generally resolves spontaneously by the age of 3–4 years.
- Nocturnal enuresis: The possibility of OSA should be considered in children who present with nocturnal enuresis, particularly if they have ≥1 of the following: habitual snoring or observed apneas, obesity, adenotonsillar hypertrophy and/or mouth breathing, or secondary enuresis.
- Sleep paralysis: Muscle atonia that normally occurs during REM sleep intrudes into wakefulness at sleep onset or when waking up from sleep and lasts for several seconds to minutes. 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. It is often associated with narcolepsy, anxiety, and sleep deprivation.

Differential Diagnosis

- Nocturnal seizures can mimic sleep terrors (Table 103-1).
- Sleep terrors can be easily confused with nightmares.

Diagnostic Considerations

When evaluating pediatric parasomnias, obtaining a detailed history from the parents (supported by home videos if possible) is of the utmost importance.

Table 103-1. Differential Diagnosis of Parasomnias

Feature	Sleep Terrors	Nightmares	Nocturnal seizures
Age of onset	Childhood	Childhood	Any age
Family history of similar events	May be present	Nonfamilial	May or may not be present
Time of occurrence	First third of the night	Final third of the night	Randomly throughout the night
Frequency of events	Can be separated by weeks or months	Nightly or separated by weeks or months	Nightly
Most common sleep stage at occurrence	Slow-wave sleep	REM sleep	Stages I or II of NREM sleep
Duration of event	5–30 min	<5 min	0.5–5.0 min
Description of events	Nonstereotypical movements	Little movement	Stereotypical movements
Postevent symptoms	None, no recollection of episode	Full alertness generally returns immediately on awakening	Postictal symptoms—headache, extreme grogginess, patient hard to arouse, as well as incontinence of urine and stool
Electroencephalographic abnormalities	None	None	Yes
Structural central nervous system lesion	No	No	Possibly

NREM, non-REM; REM, rapid eye movement.

Management/Prevention

- NREM-arousal parasomnias
  - — Guiding the child gently back to bed without awakening, placing extra locks on outside windows and doors, hanging a bell on the child's bedroom doorknob to alert parents of sleepwalking, and increasing the total sleep time by as little as half an hour a night may decrease or prevent episodes.
  - — Anticipatory awakening about 15–20 minutes prior to the usual time of occurrence may modify the sleep state and prevent the event.
  - — A low dose of a benzodiazepine (eg, clonazepam) may be used to treat persistent, severe, and frequent episodes.

- Nightmares
  - — Management includes reassurance and 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.
- REM behavior disorder
  - — Discontinue medication known to exacerbate REM behavior disorder (including selective serotonin reuptake inhibitors).
  - — Pharmacological treatments include melatonin and benzodiazepines, such as clonazepam.

Indications for Polysomnography

In children with frequent-arousal parasomnias, indications for nocturnal polysomnography (sleep study) include

- Habitual snoring, observed apneas, and/or daytime somnolence, behavioral problem, or mood disturbance, which are suggestive of underlying OSA as a potential trigger
- Leg discomfort or involuntary jerking movements during sleep, which are suggestive of restless leg syndrome or periodic limb movements of sleep
- Atypical features that raise concern for nocturnal seizures, including daytime neurological symptoms, highly stereotyped behaviors, older age group, multiple occurrences in a single night, and/or very frequent occurrences (eg, several nights each week) (see Table 103-1); in this case, the PSG should include a 16–18-channel electroencephalogram

Expected Outcomes/Prognosis

- Parasomnias are most effectively treated on an outpatient basis with a customized treatment plan and close follow-up.
- Parents 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.
- Symptoms will usually resolve as the child grows older.

When to Refer

- Patients with persistent and complex cases or those in whom the parasomnia is resulting in anxiety and fear, embarrassment, sleep avoidance and deprivation, insomnia and daytime sleepiness, depression, or physical injury should be referred to a pediatric sleep center.

Resources for Families

- Nightmares and Night Terrors (American Academy of Pediatrics). www.healthychildren.org/English/ages-stages/preschool/Pages/Nightmares-and-Night-Terrors.aspx

- Sleep Problems in Children (American Academy of Pediatrics). patiented.solutions.aap.org/handout.aspx?resultClick=1&gbosid=156710
- Sleep and Parasomnias (National Sleep Foundation). sleepfoundation.org/ask-the-expert/sleep-and-parasomnias

Clinical Pearls

- Asking the parent to record video of the suspected parasomnia can be helpful in establishing the diagnosis and differentiating a parasomnia from a seizure.
- Often, there is a history of sleepwalking or sleep talking in other family members of the child who is experiencing parasomnias.

Chapter 104

Circadian Rhythm Sleep Disorders

Deborah M. Brooks, MD, and Lee J. Brooks, MD, FAAP

Introduction

- Circadian rhythm basics
- Circadian rhythms are the body's (typically) 24-hour clock, controlled by the suprachiasmatic nucleus (SCN) in the brain.
  - The circadian clock is regulated or "set" primarily by visual cues of light from the eyes to the SCN (see Figure 104-1). This keeps the clock synchronized to the 24-hour day. Other time cues (zeitgebers) also influence the clock's timing—for example, meal, social, and exercise schedules.

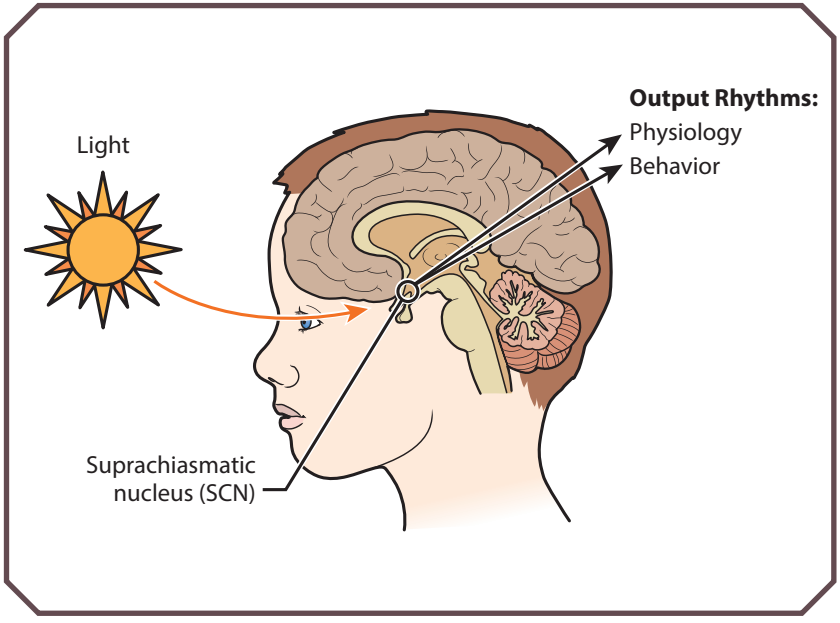

Figure 104-1. The suprachiasmatic nucleus is the body's "master clock" that uses light and other zeitgebers to control all of the body's clocks. https://www.nigms.nih.gov/education/pages/Factsheet_CircadianRhythms.aspx

  - The SCN regulates release of melatonin by the pineal gland. Melatonin is the main sleep hormone. It is secreted about 2 hours before natural sleep time, and levels are highest in the middle of the night.
- Circadian rhythm sleep disorders (CRSDs)
  - CRSDs are a timing problem with wake and sleep—either a problem with the internal body clock or a mismatch between the internal clock and the environment.
  - Symptoms include trouble falling asleep, trouble staying asleep, waking up too early, or poor quality of sleep—functioning must be impaired for it to be considered a disorder.
  - Common to these disorders is inflexibility: Even when physically tired or sleep deprived, sufferers cannot make up for lost sleep outside of their endogenous sleep times.
  - Types of CRSDs include
    - Advanced sleep phase
    - Delayed sleep phase
    - Jet lag
    - Shift work
    - Irregular sleep phase
    - Non–24-hour sleep-wake rhythm disorder

Advanced Sleep Phase

Basics

- Sleep and wake times are habitually early when compared with conventional times, such as in "morning people" or "larks."
- This is more common in older adults.

Etiology

- Possibly a shortened circadian rhythm

Symptoms

- Extreme sleepiness in the late afternoon or early evening
- Involuntary early-morning awakening

Delayed Sleep Phase

Basics

- Sleep and wake times are habitually later than conventional times, such as in "evening people" or "owls" (Figure 104-2).
- Earlier wake-up times can lead to daytime sleepiness and impaired work and school performance.

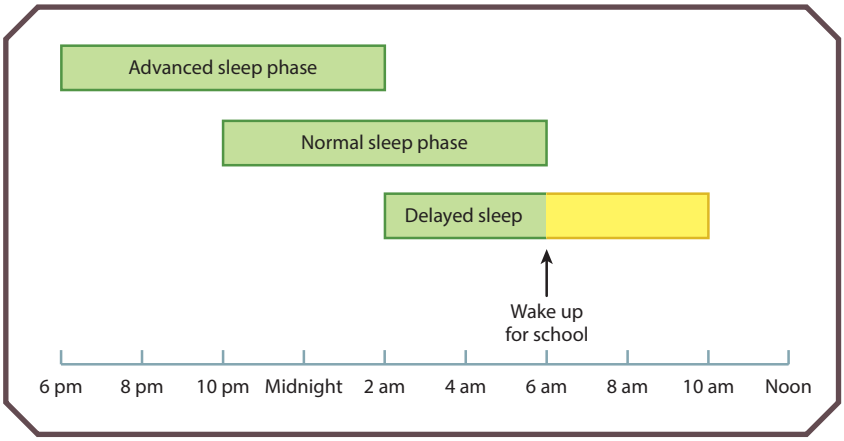

Figure 104-2. Normal sleep phase and variations.

- It is more common among adolescents and young adults, with a reported prevalence of 7%–16%.
  — Forty percent of affected individuals have a positive family history.

Etiology

- An etiologic origin is possibly an exaggerated reaction to the normal shift in the internal clock that is seen in adolescents after puberty.
- Because of the delay in falling asleep and yet still needing to get up at the required time for work or school, children or adolescents often experience excessive daytime drowsiness as a result of not getting enough sleep (this is most evident on weekdays). The delayed rhythm is coupled with a delay in the cycle of the night hormone melatonin, which lingers in the morning and makes it harder to wake up.

Symptoms

- The patient awakens late.
- Inability to fall asleep at the desired time usually manifests as insomnia complaints. It may be exacerbated by the social pressures teenagers feel to stay up late (eg, to do homework or to use the Internet or a cell phone).
- Inability to wake up at the desired time and excessive daytime sleepiness are usually the most common complaint because it is more readily evident to parents than the nighttime insomnia.

Jet Lag

Basics

- Jet lag occurs when long travel by airplane quickly puts a person in another time zone and the person must sleep and wake at times that are misaligned with his or her body clock.
  - The body clock is slightly longer than 24 hours. This makes it easier to travel westward than eastward because it is easier to delay sleep than to advance sleep.
- Jet lag affects all age groups.

Symptoms

- Disturbed sleep
- Decreased alertness and impaired daytime function
- Occasionally, gastrointestinal distress and general malaise
- Depressed mood, irritability, and anxiety

Shift Work

Basics

- This occurs when a person's work hours are scheduled during the normal sleep period.
- It is not common in children.
- The primary etiologic origin is the opposition of required sleep and wake times to one's endogenous circadian rhythm of sleep and waking.

Symptoms

- Sleepiness during the work shift
- Difficulty sleeping while others are awake
- Shortened sleep duration by 1–4 hours

Irregular Sleep Phase

Basics

- This is characterized by lack of a clearly defined circadian rhythm of sleep and waking.
- It is commonly associated with developmental disorders in children and in adults with neurodegenerative diseases and brain tumors or traumatic brain injury.

Etiology

- The etiologic origin is likely central degeneration of SCN neurons.
- Decreased exposure to or input of external synchronizing agents (zeitgebers), such as light and activity, results in a weakened central circadian rhythm.

Symptoms

- Sleep is fragmented into a series of at least 3 naps that occur throughout a 24-hour period.
- Total sleep time is usually normal for the patient's age.

Non–24-Hour Sleep-Wake Disorder

Basics

- This disorder is characterized by fluctuating periods of insomnia and/or excessive sleepiness that occur because the intrinsic circadian pacemaker is not entrained to a 24-hour light-dark cycle.
- Most individuals with this disorder are totally blind, and the failure to entrain circadian rhythms is related to the lack of light input to the SCN.
- Occasionally, the disorder is associated with mental retardation or dementia.

Symptoms

- A person's day length is longer than 24 hours. Sleep times get progressively later and later, so the person is eventually sleeping during the day until he or she cycles back to a nighttime bedtime.

Differential Diagnosis

- The presence of sleep disorders, including obstructive sleep apnea (OSA), narcolepsy, and restless legs syndrome, among others, needs to be considered.
- In addition to comorbid sleep disorders, psychiatric disorders—particularly depression and anxiety—are common in patients with nearly all types of CRSDs and should be considered in the differential diagnosis.
- Children and adolescents with a delayed sleep phase may experience depression and other psychiatric problems, including behavioral problems, as a result of daytime drowsiness and missing school. Daytime drowsiness can also lead to lowered academic performance from missed school days or tardiness and inattention. Dependency on caffeine, sedatives, or alcohol may also be seen.

Diagnostic Considerations

- The diagnosis of all CRSDs is based on a careful history and review of a sleep diary with actigraphy.
  - — In addition to the typical symptomatology, diagnosis of irregular sleep phase requires a history of a minimum of 3 irregular sleep-wake cycles in a 24-hour cycle, recorded for 14 days in a sleep diary and/or with actigraphy.
- Polysomnography (PSG) is not routinely indicated to establish the diagnosis. However, PSG is indicated to assess the presence of other comorbid sleep disorders, such as OSA syndrome and narcolepsy.

Management

- All patients and parents should be encouraged to practice sleep hygiene (see Chapter 96, Sleep Disorders: Evaluation and Prevention).
- Non–24-hour sleep-wake disorder
  - This disorder is treated via timed, exogenous melatonin administration. One method is to give the patient 3 mg of melatonin 1 hour before the desired bedtime. Entrainment typically occurs between 3 and 9 weeks. After entrainment, melatonin must be continued at a lower dose (0.5 mg) nightly to prevent relapse.
  - Tasimelteon, a melatonin receptor agonist, has been approved for use in adults with non–24-hour sleep disorder.
  - In patients with some remaining sensitivity to light, morning bright-light therapy (2,500 lux for 2 hours daily on awakening) may be effective.
- Irregular sleep phase
  - Bright-light therapy
    - Exposure to 3,000–5,000 lux of bright light for 2 hours every morning for 4 weeks has been shown to improve daytime alertness, decrease napping, consolidate nighttime sleep, and reduce nocturnal agitation.
  - Structured social and physical activity (9:00–10:30 pm and 7:00–8:30 pm daily for 2 weeks)
  - Minimizing noise and light during the scheduled sleep period and addressing issues such as nocturia (or nocturnal polyuria) and enuresis to reduce sleep disturbances at night
- Delayed sleep phase
  - Good sleep habits
    - Going to bed and waking up at the same times on weekends as on weekdays
    - Avoiding caffeinated products; avoiding other stimulants and products that can disrupt sleep (eg, alcohol, sleeping pills, nicotine)
    - Maintaining a cool, quiet, and comfortable bedroom and avoiding activities before bedtime that are stimulating (eg, computer games and television)
    - Avoidance of light at night
  - Shifting the bedtime schedule
    - Advancing the internal clock simply involves moving the bedtime a bit earlier on each night, until the desired bedtime is reached. For example, set the bedtime at midnight on one night, 11:45 pm on the next night, 11:30 pm on the following night, and so on. This is facilitated by concomitantly moving the waking time to allow this transition to occur with more control. These methods are best individualized with the help of a sleep specialist.

    - Delaying the internal clock involves moving the bedtime sequentially ≥1–3 hours later on successive nights until the desired bedtime is reached. This requires several days free from social activities and may be best attempted during a long school break or vacation period. The rationale behind this strategy is that it is much easier for the body to adjust to a later bedtime than an earlier one. Again, this is best accomplished with advice from a sleep specialist.
  - Bright-light therapy
    - Exposing the child to bright light for approximately half an hour in the morning helps to reset the body's internal clock. Reduced exposure to bright light in the evening also helps.
  - Taking melatonin about an hour before the desired bedtime may help shift the circadian clock.
- Advanced sleep phase
  - Sleep-wake scheduling
    - Time light exposure in the evening and avoid light in early morning hours.
  - Melatonin or hypnotics may be beneficial for sleep maintenance insomnia.
- Jet lag
  - Melatonin
    - For greatest effectiveness, melatonin should be taken at the target bedtime, optimally starting 3–4 days before departure.
  - Light therapy
    - Strategic exposure and avoidance of exposure to light have been used as an effective treatment approach.
  - Additional treatment options include maintaining home-based sleep hours for brief travel, short-term use of hypnotics for insomnia, and caffeine to alleviate daytime sleepiness.

Resources for Families

- What Is Delayed Sleep Phase Disorder? (National Sleep Foundation). sleepdisorders.sleepfoundation.org/chapter-5-circadian-rhythm-sleep-disorders
- What Are Circadian Rhythm Sleep Disorders? (Circadian Sleep Disorders Network). www.circadiansleepdisorders.org/defs.php
- Circadian Rhythm Sleep-Wake Disorder Symptoms (PsychCentral). psychcentral.com/disorders/circadian-rhythm-sleep-disorder-symptoms

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Part IX. Pediatric Respiratory Care

Associate Editor: Allen J. Dozor, MD, FCCP, FAAP

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Chapter 105

Delivery of Inhaled Medications

Ariel Berlinski, MD, FAAP

Introduction

- Aerosol therapy is administered to infants and children to treat many respiratory conditions (according to Food and Drug Administration–approved indications and off-label indications).
- Advantages of inhaled medications include
  - Providing topical action
  - Allowing drugs to begin working faster
  - Achieving high in situ drug concentration
  - Allowing the use of lower doses, thus decreasing the risk for side effects
- Upper-airway and intrapulmonary delivery is used for
  - Asthma (corticosteroids, long- and short-acting bronchodilators)
  - Cystic fibrosis (corticosteroids, long- and short-acting bronchodilators, antibiotics, hypertonic saline, dornase alfa)
  - Croup (epinephrine and corticosteroids)
  - Chronic lung disease of prematurity (corticosteroids, long- and short-acting bronchodilators)
  - Pulmonary hypertension (vasodilators)
  - Chronic airway infection associated with non–cystic fibrosis bronchiectasis
- Systemic delivery is used for
  - Diabetes (insulin)
  - Pain (opioids)

Types of Delivery Devices

- There are 3 main types of aerosol delivery devices.
  - Nebulizers
  - Metered-dose inhalers (MDIs)
    - Pressurized MDIs (pMDIs)
    - Soft mist
  - Dry-powder inhalers (DPIs)
- The advantages and disadvantages associated with each type of device are outlined in Chapters 106, 107, and 108.

Basic Concepts of Aerosol Medicine

Definitions

- Aerosols are a suspension of liquid (nebulizer and MDIs) or solid particles (DPIs) in a carrier gas.
- Aerosols are typically characterized by 3 different parameters.
  - A central tendency measurement known as *mass median aerodynamic diameter* (MMAD) represents the particle diameter that has half of the drug mass below and above its size.
  - For the dispersion measurement known as *geometric standard deviation* (GSD):
    - Most medical aerosols are polydisperse.
    - An aerosol with a GSD <1.2 is considered monodispersed.
  - The *respirable fraction* is the proportion of aerosol that lies between 1- and 5-μm diameter.
    - This particle size range is considered highly likely to be deposited in the lungs.
    - Some investigators suggest that using aerosols with smaller MMAD could enhance drug deposition in infants and young children.
    - It is not clear if this aerosol size is ideal for drug delivery through artificial airways (ie, tracheostomy).

Mechanisms of Aerosol Deposition

The process of aerosol deposition is mainly governed by 3 mechanisms.

Inertial Impaction

- This occurs when sudden changes in the direction of the flow take place.
- Fast-traveling aerosols, as well as those with large particle size (MMAD between 3 and 5 μm), deposit via this mechanism.
- It occurs mainly in the upper and large airways.
- Inhaling aerosols at a lower inspiratory flow rate will enhance intrapulmonary deposition.

Gravitational Sedimentation

- This is the main deposition mechanism for particles with an MMAD in the 0.5–3.0-μm range.
- The longer the residence time of the particles, the more likely that gravitational forces will determine deposition. This is why a breath-holding maneuver increases intrapulmonary deposition.

Brownian Diffusion

- Deposition occurs by random particle motion at the alveolar level.
- This is the main deposition mechanism for particles with an MMAD smaller than 0.5 μm. Many of these small particles are exhaled.

Factors That Affect Intrapulmonary Deposition

Factors that could affect intrapulmonary deposition are twofold (Box 105-1).

Aerosol-Related Factors

- Particle size
  - — Particles >10 μm are filtered by the nose.
  - — The larger the MMAD, the higher the upper-airway deposition.
  - — Particles with smaller MMAD tend to have more peripheral distribution than those with larger MMAD.
- Particle velocity
  - — This results from the interaction of velocity at which the particle is generated by the device and the patient's inspiratory flow.
  - — Fast aerosol is more likely to affect the upper airway.
- Hygroscopic properties
  - — Increase of the MMAD while traveling through a humid environment can occur in formulations that contain hygroscopic components.
- Drug viscosity and surface tension
  - — The addition of excipients with surfactant properties enhances drug delivery.
  - — More viscous fluids require longer nebulization times.

Box 105-1. Factors Affecting Intrapulmonary Drug Deposition

Aerosol Related	Patient Related
Particle size	Breathing pattern
Velocity	Age
Hygroscopic properties	Inspiratory flow rate
Drug viscosity and surface tension	Nasal vs mouth
Suspension vs solution	Anatomic differences
Use of add-devices	Cognitive abilities
	Behavior
	Acceptance of interface
	Contrivance
	Adherence
	Disease severity

Modified from Geller D, Berlinski A. Aerosol delivery of medication. In: Light MJ, Homnick DN, Schechter MS, Blaisdell CJ, Weinberger MM, eds. *Pediatric Pulmonology.* Elk Grove Village, IL: American Academy of Pediatrics; 2011.

- Suspension and solution formulations may behave differently.
  - — Ultrasonic nebulizers are not suitable to deliver suspensions.
  - — Aerosols generated by pMDIs with corticosteroid solution have a smaller MMAD than those from corticosteroid suspensions.
  - — Care for pMDI of corticosteroids formulated as suspension is different from those generated as solutions.
- Use of add-on devices
  - — Some of the plastic materials used to build the add-on device can build electrostatic force.
  - — A spacer or a valved holding chamber may be used.

Patient-Related Factors

- Breathing pattern
  - — The ability to perform a single inhalation versus a tidal breathing maneuver should be considered.
  - — Increasing inspiratory time increases intrapulmonary deposition.
  - — Large tidal volumes increase intrapulmonary deposition.
  - — Breathing patterns of distressed or crying children decrease intrapulmonary deposition.
- Age
  - — Intrapulmonary deposition increases with age.
- Inspiratory flow rate
  - — The use of low inspiratory flow maneuvers with nebulizers and MDIs enhances drug deposition.
  - — The use of high inspiratory flow maneuvers with DPIs enhances drug deposition.
- Nasal versus mouth inhalation route
  - — Young children are preferential nose breathers.
  - — The use of the nasal route decreases intrapulmonary deposition by 50% in older patients.
- Anatomic differences in young children compared to adults
  - — The larynx of infants is situated much higher, and the epiglottis is closer to the palate.
  - — The pharynx and supraglottic tissues are less rigid and more prone to inspiratory collapse.
  - — The tongue is relatively larger than the oral airway.
- Cognitive abilities
  - — Impaired or undeveloped cognitive abilities may limit the successful performance of the maneuvers and techniques that optimize intrapulmonary deposition (eg, breath hold).
- Behavior
  - — Crying markedly reduces intrapulmonary deposition.
- Acceptance of interface
  - — This is critical for infants and young children.

- Contrivance
  - This occurs when the patient knows how to use a device but uses it incorrectly, instead.
- Adherence
  - Enhanced with family-centered practices
  - Can be monitored with use of devices and, less precisely, by reviewing the refill history
  - Decreased when financial barriers exist
- Disease severity
  - Patients with more advanced lung disease tend to have more drug deposited in the central airways.
  - Patients with severe bronchospasm will have decreased intrapulmonary deposition.

Choosing the Appropriate Device

- A recent Cochrane review article demonstrated that pMDI with a valved holding chamber is at least as effective as nebulization when treating children with acute asthma.
- Many factors are involved in choosing the appropriate device for the patient.
  - Is the drug available for use with the device the physician intends to prescribe?
  - Has the drug been approved as a drug-device combination?
  - Is the practitioner knowledgeable regarding the use and care of the different devices?
  - What is the patient's and the family's preference?
    - Is it convenient?
    - Does it interfere with the patient's and the family's lifestyle?
    - Is the device easy to use and care for?
  - What is the patient's age and cognitive ability?
    - Can he or she follow commands?
    - Can he or she perform the required inhalation maneuver?
  - Is the drug or device covered by insurance, and can the family afford the copayments?

Clinical Pearls

- Generally, inhaled medications are preferred over oral medications with the hope that topical medications offer effectiveness with less risk for systemic side effects.
- Achieving adequate airway or pulmonary deposition of inhaled medications is more difficult than it first appears. There are many barriers.
- Choosing the appropriate inhalation devices and technique for each child is critical for success and changes as children age.
- Success requires a substantial time investment in patient or parent education—not just at a first visit, but repeatedly.

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Chapter 106

Small-Volume Nebulizers

Ariel Berlinski, MD, FAAP

Introduction

- Nebulizers convert a solution or suspension into an inhalable mist with the aid of a gas source.
- Many parents mistakenly refer to the required air compressor as the "nebulizer."
- Drugs usually delivered in pediatric patients include short-acting bronchodilators, anticholinergics, corticosteroids, epinephrine, and antibiotics.
- This platform is used for the off-label use of many drugs.
- The advantages and disadvantages to the use of nebulizers are shown in Box 106-1.

Box 106-1. Advantages and Disadvantages of the Use of Jet Nebulizers

Advantages	Disadvantages
Easy technique (tidal breathing)	Bulky, less portable than other systems
Can use at any age	Longer treatment times
Can use with any disease severity	Require cleaning and disinfection
Use with artificial airways	Noisy (may disturb infants)
High doses possible (ie, antibiotics)	Require a power source
Inexpensive	High variability between brands

Modified from Geller D, Berlinski A. Aerosol delivery of medication. In: Light MJ, Homnick DN, Schechter MS, Blaisdell CJ, Weinberger MM, eds. *Pediatric Pulmonology.* Elk Grove Village, IL: American Academy of Pediatrics; 2011.

Types of Small-Volume Jet Nebulizers

- Small-volume jet nebulizers typically have a loading capacity lower than 10 mL.
- There are 3 main types of small-volume jet nebulizers (Figure 106-1).
  - — Continuous output
  - — Breath enhanced
  - — Breath actuated
- Continuous-output jet nebulizers are the most commonly used because of their low cost and widespread availability.
  - — They generate and release aerosol during inspiration and expiration, thus generating large aerosol waste and exposing the caregivers.
  - — Adding a 15-cm corrugated tube distal to the patient increases drug delivery (reservoir effect).
  - — Disposable units should not be reused.
- Breath-enhanced nebulizers also generate and release aerosol during inspiration and expiration but increase their output during inspiration by means of air entrainment facilitated by one-way valve systems.
  - — Verify that the patient can open the valve and take advantage of the increased efficiency.
- Breath-actuated nebulizers deliver medication only during inspiration.
  - — Some devices are a modified form of continuous-output jet nebulizer with a one-way valve and a reservoir that is filled during expiration.
  - — Other devices have a spring-loaded one-way valve and produce aerosol only during inspiration.
    - ▪ Treatments will be longer, and either dose or treatment time might need to be reduced to avoid overdosing.
  - — Verify that the patient can open the valve and take advantage of the increased efficiency.

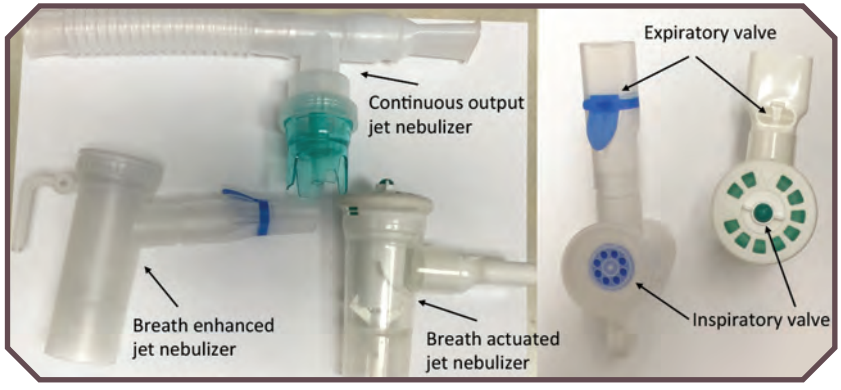

Figure 106-1. Examples of nebulizers.

Gas Source

- Compressors are used for home care; they generate a low and fixed flow at a low pressure.
  - — Compressors lose efficiency over time, so ask the patient if the treatment is taking longer than usual.
  - — Air filters used in the compressor need to be changed periodically.
- Central oxygen or air is typically used at institutions; the gas is delivered at high pressure, at an adjustable flow rate.
  - — Treatments are short and have more particles that are likely to be deposited in the lungs.

Using the Nebulizer

Tips for Patients Using Nebulizers

- Tapping the nebulizer cup increases drug delivery.
- Use of single-dose vials is recommended because the use of a multidose containers has been associated with infection.
- Drug output markedly decreases after sputtering begins.
  - — Instruct the patient to stop the treatment after sputtering begins.
- The solution or suspension left in the nebulizer after a treatment is complete is called *residual volume*.
  - — It varies from 0.5 to 2.2 mL, depending on the nebulizer model.
  - — Increasing the loading volume to 4 mL will improve drug output of those devices with high residual volume but will also increase treatment time.
  - — Decreasing loading volume could result in minimal drug output.
    - ▪ Consider decreasing treatment time as a strategy for decreasing the delivered dose.
  - — Instruct the patient to maintain the nebulizer in the upright position.

Interface and Inhalation Technique

- While there may be less pulmonary deposition of medications when using a face mask instead of a mouthpiece, this difference is unlikely to have a significant clinical effect.
- Use of a face mask generates facial and ocular exposure.
  - — Dermatitis has been reported with the administration of corticosteroids.
  - — Anisocoria has been reported with the administration of anticholinergics.
- Most specialists suggest that children use a mouthpiece as soon as he or she can create a good seal.
  - — Poor seal of the face mask markedly reduces lung delivery.
  - — Blow-by technique is very inefficient and should be avoided.
  - — Front-loaded face masks are more efficient than bottom-loaded face masks, especially when the seal is not tight (Figure 106-2).

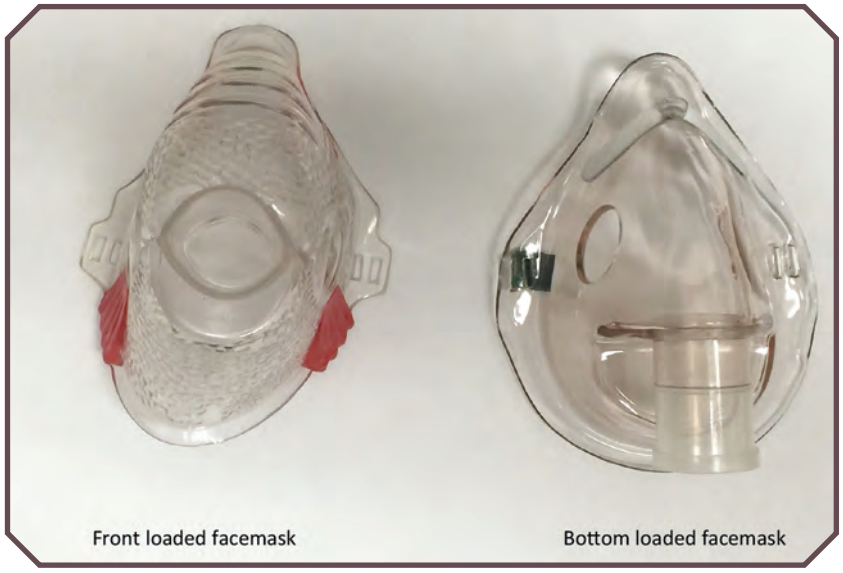

Figure 106-2. Examples of face masks used with small-volume nebulizers.

- Do not occlude the holes in the face mask, because doing so does not increase drug delivery and can result in rebreathing CO_2.
- Some masks and interfaces favor transnasal delivery. This could be an alternative for patients <18 months of age (obligate nose breathers).
- Since crying markedly reduces intrapulmonary deposition, patients might require desensitization to get them accustomed to using the mask.
- Instruct the patient to breathe slowly and deeply when possible.
- Instruct the patient to take his or her medication in the sitting position, when possible.

Cleaning

- Cleaning the nebulizer is important to prevent the device from malfunctioning.
- The tubing that connects the nebulizer and the compressor should not be submerged in water.
- Vinegar solutions are ineffective at killing *Pseudomonas aeruginosa.*
- After each use
  - — Perform proper handwashing.
  - — Disconnect the nebulizer from the tubing and disassemble the nebulizer.
  - — Clean the nebulizer, mouthpiece, and mask with water and dish detergent.
  - — Remove any visible secretions.
  - — Rinse the nebulizer, face mask, and mouthpiece with sterile water, which can be prepared by boiling tap water for 5 minutes.

- Remove excess water.
- Place the nebulizer on an absorbent towel to air-dry before storing it.

Disinfection

- Disinfecting the nebulizer is important to avoid contamination of the device.
- Once a day, after cleaning is completed, perform disinfection with any of these methods.
  - Cold methods
    - Soak the nebulizer and parts in either
      ~ 70% isopropyl for 5 minutes
      ~ 3% hydrogen peroxide for 30 minutes
    - Then, rinse it off with sterile water.
  - Heat methods (if recommended by the manufacturer)
    - Soak the nebulizer and parts in boiling water for 5 minutes.
    - Microwave the device while submerged in water in a microwave-safe receptacle for 5 minutes.
    - Wash the device in a dishwasher for 30 minutes, if the water is at least 70°C (158°F).
    - Use an electric steam sterilizer.
  - After the disinfection
    - Remove excess water.
    - Place the nebulizer on an absorbent towel to air-dry before storing it.

Other Types of Nebulizers

- Ultrasonic nebulizers
  - Should not be used to deliver budesonide or other medications that may be degraded by the heat generated.
- Vibrating mesh nebulizers
  - These are very efficient.
  - They are faster than jet nebulizers.
  - They generally have very low residual volume, which means a higher proportion of medication will be delivered to the patient. This is not so important with bronchodilators but may be important for delivering drugs with a narrow therapeutic index.
  - Cleaning of the device (mesh) is crucial for optimal performance.
  - The mesh is periodically replaced.
  - These devices are very expensive.
  - Many devices are prescribed as a drug-device combination of mesh nebulizers.
    - Aztreonam-Altera (PARI Pharma, Starnberg, Germany) for the treatment of *P aeurugina* infection in patients with cystic fibrosis
    - Iloprost–I-neb (Philips, Amsterdam, Netherlands) for the treatment of pulmonary hypertension

Resources for Families

- How to Use a Nebulizer (Medline Plus). medlineplus.gov/ency/patientinstructions/000006.htm
- A Patient's Guide to Aerosol Drug Delivery (American Association for Respiratory Care). www.aarc.org/wp-content/uploads/2014/08/aerosol_guide_patient.pdf

Clinical Pearls

- Inhalation technique and equipment maintenance should be frequently reviewed.
- Ask the patient whether the length of therapy is increasing, since this could represent compressor malfunction.
- If the patient uses a vial dose and the dose needs to be decreased by half, a half-vial dose should be mixed with same volume of normal saline solution so the final volume remains the same.
- Don't use an ultrasonic nebulizer to deliver corticosteroid suspensions.

Chapter 107

Metered-Dose Inhalers

Ariel Berlinski, MD, FAAP

Introduction

- Metered-dose inhalers (MDIs) are portable devices capable of delivering precise amounts of medication.
- Before the invention of the MDI, asthma medication was delivered by using a squeeze-bulb nebulizer that was fragile and unreliable. The particles generated were relatively large—probably too large for effective drug delivery to the lungs. Nonetheless, these nebulizers paved the way for inhalation drug delivery and provided the inspiration for the MDI, which was first developed in 1955.
- The portability and relative ease of use have propelled MDIs to be the most commonly used inhalation devices for asthma medications in children. They have in large part replaced the use of small-volume nebulizers, although some health care providers and parents continue to prefer nebulizers. Dry-powder inhalers, reviewed in chapter 108, have proven popular for the treatment of adolescents and adults but have limited use in younger children.
- There are 2 types of devices.
  - Pressurized MDIs (pMDIs)
  - Soft-mist inhalers (SMIs)
- The use of a pMDI has advantages and disadvantages (Box 107-1).

Pressurized MDI

- The components of pMDIs are shown in Figure 107-1, including:
  - A canister that contains drug, excipients, and propellants, stored under pressure. The canister has a metering valve.
    - Many pMDIs contain ethanol as their excipient and can transiently increase the breath alcohol exhalation test result.
  - A plastic actuator that consists of
    - Actuator seat: The interaction between the metering valve and this component is crucial for optimal drug delivery.
    - Nozzle
    - Mouthpiece
- Aerosols are released at high speed from the pMDI.

Box 107-1. Advantages and Disadvantages of Metered-Dose Inhalers

Advantages	Disadvantages
Compact, portable	Cleaning and priming instructions are specific for each product
Rapid delivery	Coordination of actuation and inhalation
Multidose convenience	The oropharyngeal dose is high if not used with a valved holding chamber or spacer
Can be used at any age (when used with valved holding chambers)	Intolerance of the tight face mask in young children
Most products have dose counters	Limited number of drugs available

Adapted from Geller D, Berlinski A. Aerosol delivery of medication. In: Light MJ, Homnick DN, Schechter MS, Blaisdell CJ, Weinberger MM, eds. *Pediatric Pulmonology.* Elk Grove Village, IL: American Academy of Pediatrics; 2011:913–932.

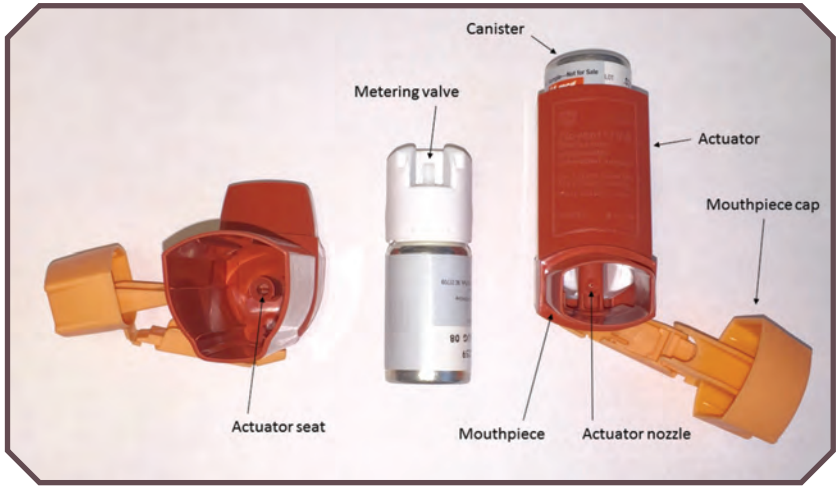

Figure 107-1. Components of pressurized metered-dose inhalers.

- The use of a spacer or a valve holding chamber (VHC) is suggested for pediatric patients when using a pMDI because it reduces oropharyngeal deposition.
  - Spacers may be used in patients who can perform a single inhalation and coordinate actuation and inhalation.
  - VHCs should be used in patients who have difficulty coordinating actuation and inhalation and/or who use the tidal breathing inhalation technique.
- Drugs commonly used in infants and children include short-acting bronchodilators, anticholinergics, corticosteroids, and corticosteroid long-acting bronchodilator combinations.
- Drugs are formulated as solutions or suspensions.
  - Shaking the canister before actuation and actuating the canister right after shaking are critical for drugs formulated as suspensions, such as fluticasone, but not so much for drugs formulated as solutions, such as beclomethasone.
- The use of pMDIs with an incorporated dose counter is very important to decrease the risk of patients using empty inhalers.
- Instruct patients to discard the pMDI when the counter reaches zero.
- If a counter is not available
  - For scheduled medications (corticosteroids): Discard the pMDI after 30 days if the total doses per canister were 120 and the drug was prescribed at 2 puffs twice daily.
  - For as-needed medications (short-acting bronchodilators): Patients should tally their use.
  - pMDI canisters should *never* be submerged to estimate their fullness.
- Priming and cleaning inhalers: Each device has slightly different directions on how they should be primed prior to use, as well as how often they should be cleaned. Patients and parents should be encouraged to read package inserts for each specific brand.

VHC Procedure

- Verify that there no foreign objects in the VHC.
- Couple the pMDI to the VHC and shake it for at least 5 seconds.
- For each child, 2 decisions must be made.
  - Should a mask or mouthpiece be used?
    - There is likely to be greater pulmonary deposition if a mouthpiece is used, but children must be willing and able to cooperate, which requires placement of a mouthpiece past their teeth and closure of their lips around the mouthpiece.
    - Young children, usually <5 years of age, or older children with developmental delays or oral defensive issues, generally do better with a masked holding chamber.

  - Once the interface is chosen, which inhalation technique should be used—tidal breathing or single breath?
    - It is important to determine which of the 2 techniques is appropriate for each child and to recognize that the optimal technique may change as a child grows older.
    - In general, the tidal breathing technique is appropriate for children <5–8 years of age, and the single-breath technique (which usually results in greater pulmonary deposition) is optimal for older children. The single-breath technique should be used when possible.
- Most young children should use a masked holding chamber with the tidal breathing technique, and most older children should use a holding chamber with a mouthpiece and the single-breath technique. However, there are exceptions. Some children may be able to master the use of a mouthpiece but must use tidal breathing, and some children may tolerate the treatment better when a mask is used, even at an older age, but they can properly perform the single-breath technique.
- The use of a mouthpiece is preferred to a face mask because it decreases oculofacial deposition and increases the amount of drug available for inhalation.
- The single-breath technique is preferred to the tidal breath technique because it increases lung deposition.
- Regardless of which inhalation technique is chosen, if there is a substantial delay between actuation and inhalation, pulmonary deposition will be reduced, as more medication deposits on the walls of the VHC. If using the tidal breathing technique, this delay is minimized if the child starts breathing before the inhaler is actuated.
- Delay between shaking and actuating the pMDI could result in variability of the inhaled dose of drug formulated as suspension.

Tidal Breathing Technique

- Gently place the mask against the face or insert the mouthpiece in the mouth, ensuring a good seal.
- Encourage the child to breathe quietly and normally for a few seconds before actuation and for at least 4–6 breaths after each spray.

Single-Breath Technique

- Instruct the child to exhale to the end of a normal breath.
- Insert the mouthpiece into the mouth, past the teeth, and instruct the child to close the lips around the mouthpiece to maintain a good seal.
- Immediately after each actuation, many children will be tempted to breathe in too quickly. Ideally, they will learn how to take a slow, deep breath all the way, until they can't breathe in any further.
- Many VHCs with a mouthpiece have a flow signal. If the chamber whistles, the patient is breathing in too quickly.

- After complete inhalation, the child should remove the inhaler, close the lips, and hold the breath for 5–10 seconds.
- Repeat the process for any additional prescribed actuation.

Soft-Mist Inhalers

- SMIs deliver more drug than pMDIs, especially at lower tidal volumes.
- SMIs release propellant-free aerosols (tiotropium).
- The speed of the aerosol is tenfold slower than the pMDI.
- The aerosol cloud lasts in suspension threefold longer than the pMDI.
- The device is marketed for use without a VHC. However, a patient who can't or won't perform the recommended inhalation technique should use a VHC.
- The only drug that currently has a U.S. Food and Drug Administration–approved pediatric indication is tiotropium (for asthma, ≥12 years of age).
  - A device that combines albuterol and ipratropium bromide is also commercially available but is marketed for treatment of chronic obstructive pulmonary disease.
- Devices need to be discarded 90 days after opened.
- The device has a dose indicator that turns red when 7 of 30 doses are available.
- Priming and cleaning are also necessary, just as in pMDIs. Patients and parents should be reminded to read all package inserts, as recommendations vary from brand to brand.

SMI Procedure

- Turn the base of the device clockwise until it clicks.
- Open the cap that covers the mouthpiece.
- Release the aerosol.
  - Exhale fully.
  - Close the lips around the mouthpiece.
  - While keeping the device in a horizontal position, begin to breathe slowly and press the dose-release button.
  - Do not block the lateral opening present in the mouthpiece.
  - Once inhalation is completed, a 5- to 10-second breath hold is suggested.

Resources for Families

- Using Your Metered Dose Inhaler (American Thoracic Society). www.thoracic.org/patients/patient-resources/resources/metered-dose-inhaler-mdi.pdf
- A Patient's Guide to Aerosol Drug Delivery (American Association for Respiratory Care). www.aarc.org/wp-content/uploads/2014/08/aerosol_guide_patient.pdf

Clinical Pearls

- MDIs are the most commonly used inhalation devices in children with asthma and have many advantages over small-volume nebulizers, even in very young children.
- They are more portable and are quick and easy to use, and many more medications are available in this form.
- Proper inhalation technique is critical for success and should be reviewed at each visit.
- Parents must be reminded of the importance of not using an empty MDI. Use of pMDIs with counters is preferred.
- Since most children with asthma use both controller and reliever MDIs, it is easy and common for patients and parents to confuse the two. Some specialists suggest placing easily read labels, in the parent or child's primary language, on each inhaler (controller or reliever).
- Verification of correct inhaler technique should occur at each visit if possible.

Chapter 108

Dry-Powder Inhalers

Ariel Berlinski, MD, FAAP

Introduction

- Dry-powder inhalers (DPIs) are devices than can deliver medications to the lungs without the need for a suspending medium.
- DPIs are mainly used in pediatric patients to treat asthma (bronchodilators, corticosteroids, and combination corticosteroid and long-acting bronchodilator) and cystic fibrosis (tobramycin).
- Currently, all devices available in the United States are passive and breath actuated.
- The inspiratory force (peak inspiratory flow) required of the patient to overcome the internal resistance of the device is responsible for the deagglomeration of the dry powder when it is released from the device.
  - A minimum inspiratory flow threshold is needed (30–40 L/min for most devices).
  - For most devices, the higher the inspiratory flow, the higher the intrapulmonary deposition of the drug.
- DPIs can deliver larger quantities of drugs than pressurized metered-dose inhalers.
- Many formulations use a carrier, such as lactose.
- The advantages and disadvantages of the use of DPIs are listed in Box 108-1.

Types of DPI Devices

- There are many configurations of DPI devices.
  - Single-dose devices (Figure 108-1)
    - These devices require placement of a capsule in the device.
  - Multidose devices (Figure 108-2)
    - Common reservoir
    - Individually packed blister strips or cartridge
    - Incorporated dose counters

Proper use of DPIs

Dose Preparation

- The dose to be inhaled has to be loaded in the device.
- For some devices, this step automatically occurs when the patient opens the device or removes the cap.

Box 108-1. Advantages and Disadvantages of the Use of Dry-Powder Inhalers

Advantages	Disadvantages
Compact, portable	Strong and consistent inspiratory effort is needed
Rapid delivery	High oropharyngeal deposition
Multidose with counters	Vulnerable to humidity
Breath actuated	Not suitable for younger children
No need for a valved holding chamber or spacer	Technique confusion is possible if used with other devices that require slow inhalation

Modified from Geller D, Berlinski A. Aerosol delivery of medication. In: Light MJ, Homnick DN, Schechter MS, Blaisdell CJ, Weinberger MM, eds. *Pediatric Pulmonology.* Elk Grove Village, IL: American Academy of Pediatrics; 2011:913–932.

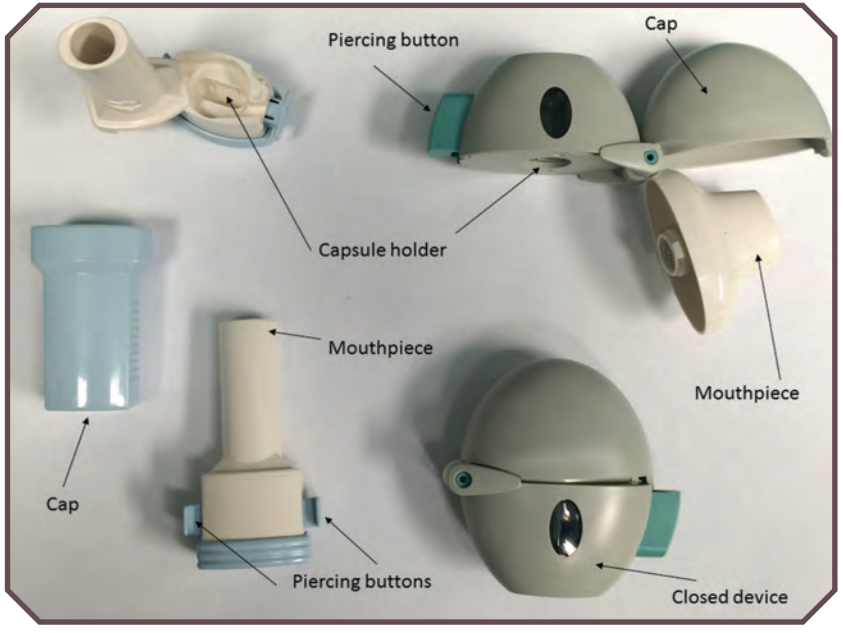

Figure 108-1. Examples of single-dose dry-powder inhalers.

Figure 108-2. Examples of multidose dry-powder inhalers.

- For other devices, loading the dose requires an extra step, such as pulling down a lever, twisting the base, or loading and piercing a capsule.

Breathing Maneuver

- Once the dose is loaded, the patient should exhale first and be careful not to do it inside the device.
- Next, the patient needs to seal his or her lips around the mouthpiece.
- Then, the patient should inhale forcefully as fast and as long as possible.
- The patient holds his or her breath for 10 seconds.
- Repeat if indicated.
- The patient should rinse his or her mouth with water and spit, after the treatment has been completed.

Counseling the Patient

- Devices should be stored in a cool and dry place.
- Patients should not blow inside the device.
- The device should not be tilted once it has been loaded.
- Patients should inhale forcefully from the start, as fast as they can and for as long as they can.
- Patients should be careful not to block the air vents of the device when handling it.
- Most multidose devices provide auditory feedback (a "click" sound) when the dose is loaded.
- Single-dose devices allow visual verification that the capsule was emptied.
- Multidose devices should be discarded once the dose counter reaches zero or after a specific length of time.
- Single-dose devices should be discarded when recommended by the manufacturer.
- Patients using single-dose devices need to remember to pierce the capsule.
- The device should be kept level during inhalation.

Choosing the Correct Device for the Patient

- Practitioners should realistically assess the ability of their patients to correctly use DPIs.
- Although age and cognitive abilities could be suggestive of the patient's ability to use a specific device, this assessment is not foolproof.
- Patients should demonstrate that they can follow correctly the necessary steps required to operate the device.
- In addition, patients need to demonstrate that they can generate the necessary inspiratory flow required for a specific device.
  - — Some drug and device manufacturers offer device-specific testers (Figure 108-3). The tester whistles when a threshold flow is reached.
  - — Use a peak inspiratory flow meter that allows you to set the resistance of the device you are planning to prescribe (Figure 108-3).
- Inhaler technique should be reviewed at every office visit.

Resource for Families

- A Patient's Guide to Aerosol Drug Delivery (American Association for Respiratory Care). https://www.aarc.org/wp-content/uploads/2014/08/aerosol_guide_patient.pdf

Clinical Pearls

- DPIs are a great choice for older children and adults who are able to demonstrate proper technique and are motivated to consistently do so, day in and day out.

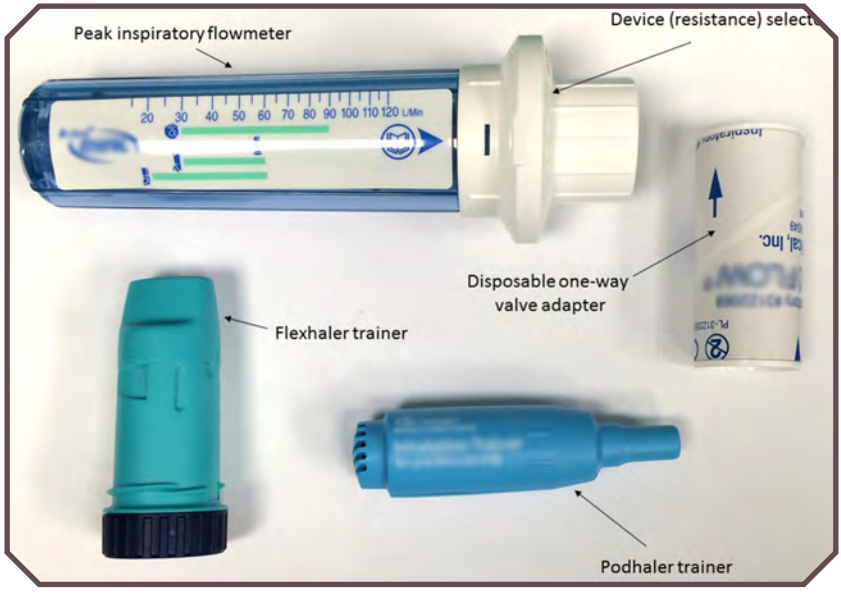

Figure 108-3. Examples of device trainers and peak inspiratory flow meter.

- While DPIs are approved for children ≥4 years of age, children <8 years of age may not consistently and reliably perform the required optimal technique.
- With optimal inhalation technique, most patients will taste little or no powder in their mouths. If they taste a lot of powder in their mouths, then pulmonary deposition and effectiveness may be decreased, and the risk of oral candidiasis (with DPIs that contain corticosteroids) may be increased.

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Chapter 109

Spacers and Holding Chambers

Ariel Berlinski, MD, FAAP

Introduction

Spacers and valved holding chambers (VHCs) have been developed to overcome several problems with pressurized metered dose inhalers (pMDIs).

- The aerosol emitted by pMDIs travels at high speed.
- High-velocity aerosols are more likely to be deposited in the upper airway by inertial impaction.
- A common error that occurs during inhalation of pMDi aerosols is to inhale too quickly.
- Local side effects of corticosteroids, such as thrush and hoarseness, are caused by oropharyngeal deposition.
- Coordination of actuation of the pMDI and inhalation is difficult to achieve by pediatric patients.

Spacers

- Spacers are valveless tubes that provide a distance between the pMDI and the patient's mouth.
  - — Aerosol speed decreases as it travels through the spacer.
  - — Particle size decreases because of evaporation of the propellant.
  - — Large particles impact against the airway walls.
  - — The use of a spacer does not prevent the patient from exhaling inside the tube.
- Commercially available and homemade spacers decrease oropharyngeal deposition.
- A pMDI of flunisolide with an incorporated spacer is available in the United States.
- Spacers should *only* be used in children who can perform a single-inhalation maneuver.

Valved Holding Chambers

- There are many types and brands of VHCs (Figure 109-1).
- VHCs incorporate one-way valves into their design, which allows
  - — Aerosol to be released from the VHC only during inhalation
  - — Diversion of exhaled air, thus preventing it from mixing with the aerosol present in the VHC
  - — Lack of the need for coordination of actuation-inhalation

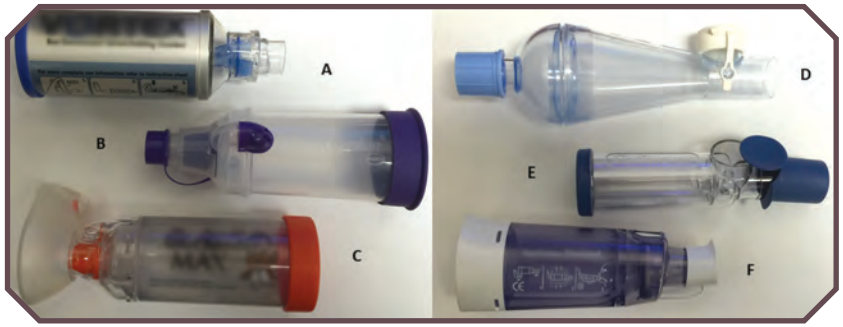

Figure 109-1. Examples of valved holding chambers (VHCs). A. This VHC is made of a metallic material and allows the use of the canister of the pressurized MDI (pMDI) without having to remove it from the plastic actuator. B. C. These nonelectrostatic plastic VHCs allow the use of the canister of the pMDI without having to remove it from the plastic actuator. D. E. These VHCs have a universal actuator and require the canister to be separated from the original actuator to use it. F. This nonelectrostatic plastic VHC allows the use of the canister of the pMDI without having to remove it from the plastic actuator.

- VHCs also provide the other benefits offered by spacers.
- Some VHCs use the exhaled air to provide feedback of a proper seal of the face mask or mouthpiece.
- Some VHCs incorporate a whistling signal that occurs when high inspiratory flows are used.
- The one-way valves should have low resistance. Verify that your patient can trigger the valve of the VHC.
- Most VHCs in the United States have an internal volume of <150 mL.
- The material used to build the VHC is very important.
  - Older VHCs were made of materials that could accumulate electrostatic force. Washing the VHC with water and ionic detergent and letting it air-dry before its first use and frequently thereafter mitigates this effect.
  - Newer VHCs are made of either metallic material or nonelectrostatic plastic (Figure 109-1).

Placement of the pMDI

- Some VHCs have a universal actuator and require the canister to be separated from the original actuator to use it (Figure 109-1).
- Other VHCs allow the use of the canister of the pMDI without having to remove it from the plastic actuator (Figure 109-1). This type of VHC should be prescribed when available.

Patient Interface

- Clinical outcomes are similar between VHC mask and VHC mouthpiece, but a mouthpiece is preferable for several reasons.
  - Use of a face mask generates ocular and facial exposure.

  - Dead space of the mask reduces drug delivery.
  - Poor mask fit markedly reduces drug delivery.
- The mouthpiece should be used as soon as the patient is able to seal his or her lips around it.
- VHCs that provide feedback of a good seal are preferred.

Inhalation Techniques

- Tidal breathing
  - In general, patients require ≤4 breaths to empty the volume of a small-volume VHC. More breaths might be needed for a small infant (<5 kg).
  - This technique is used with either a mouthpiece or a face mask.
  - Administering pMDI with a VHC to a sleeping infant or toddler is likely to result in awakening.
- Single-breath inhalation maneuver
  - This technique is mostly used with a mouthpiece interface.
  - The inhalation flow should be <30 L/min.

Procedure

- Verify that there are no foreign objects in the VHC.
- Shake the pMDI and couple it to the VHC.
- Place the mask against the face or insert the mouthpiece behind the teeth and obtain a good seal with the lips.
- Actuate the pMDI once and maintain the mask seal for 4–6 breaths.
- If a mouthpiece is used, the single-breath inhalation maneuver should be used when possible. If not, the tidal breathing maneuver is acceptable. See Chapter 107, Metered-Dose Inhalers, for more details.
- Repeat the process after shaking for any additional prescribed actuation.

Maintenance

- VHCs require weekly washing to prevent bacterial colonization.
- VHCs are typically changed once per year.

Resources for Families

- Using Your Metered Dose Inhaler (American Thoracic Society). www.thoracic.org/patients/patient-resources/resources/metered-dose-inhaler-mdi.pdf
- Valved Holding Chambers and Spacers (American Lung Association). www.lung.org/lung-health-and-diseases/lung-disease-lookup/asthma/living-with-asthma/managing-asthma/valved-holding-chambers-and.html
- A Patient's Guide to Aerosol Drug Delivery (American Association for Respiratory Care). www.aarc.org/wp-content/uploads/2014/08/aerosol_guide_patient.pdf

Clinical Pearls

- The availability of VHCs has made it possible for infants and children of any age to use metered-dose inhalers, which markedly decreases the time needed for each treatment and permits many more medications to be considered.
- Choosing the optimal VHC for each child, particularly whether a mask or mouthpiece is optimal, may be as important as choosing the specific medication.
- Proper cleaning and maintenance of VHCs are very important.
- Not all health insurance plans cover holding chambers, and prices can vary widely between pharmacies. They are available online, often at lower costs than what local pharmacies charge.

Chapter 110

Inhaled Antibiotics

Ariel Berlinski, MD, FAAP

Introduction

- Inhaled antibiotic therapy with currently available preparations is safe and effective in patients with cystic fibrosis (CF).
- Inhaled antibiotics are sometimes prescribed by pediatric pulmonologists and otolaryngologists for patients without CF who have chronic or recurrent airway infections. However, currently, the only approved indication in the United States is CF.
- Patients with bronchiectasis caused by CF or other etiologic origins (eg, primary ciliary dyskinesia, postinfectious disease) have chronic bacterial colonization with different organisms (eg, *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus* [MRSA]) and experience recurrent airway infections.
- Patients with tracheostomies also develop chronic bacterial colonization (eg, *P aeruginosa,* MRSA) soon after tracheostomy placement and experience recurrent airway infections.
- The inhaled route provides
  - High in situ drug concentration
  - Reduced systemic drug delivery
  - Minimal side effects
- Tobramycin and aztreonam are approved by the U.S. Food and Drug Administration (FDA) for the treatment of *P aeruginosa* in patients with CF.
- Amikacin, tobramycin, gentamicin, ceftazidime, colistin, vancomycin, and ciprofloxacin are used off-label as inhaled antibiotics. Many of these and more are in development but are not yet approved by the FDA.

Treatment Against *P aeruginosa* in Patients With CF

- All FDA-approved inhaled antibiotics are drug-device combinations (Figure 110-1).
- Currently approved formulations include
  - Tobramycin delivered via nebulizer
    - Treatment lasts 15 minutes
    - Is usually dosed at 300 mg twice daily (28 days "on" and 28 days "off") with a standard nebulizer
  - Tobramycin delivered via dry-powder inhaler
    - Supplied as 28-mg capsules (aluminum-blister packaged)
    - Is usually dosed at 4 capsules twice daily (28 days "on" and 28 days "off")

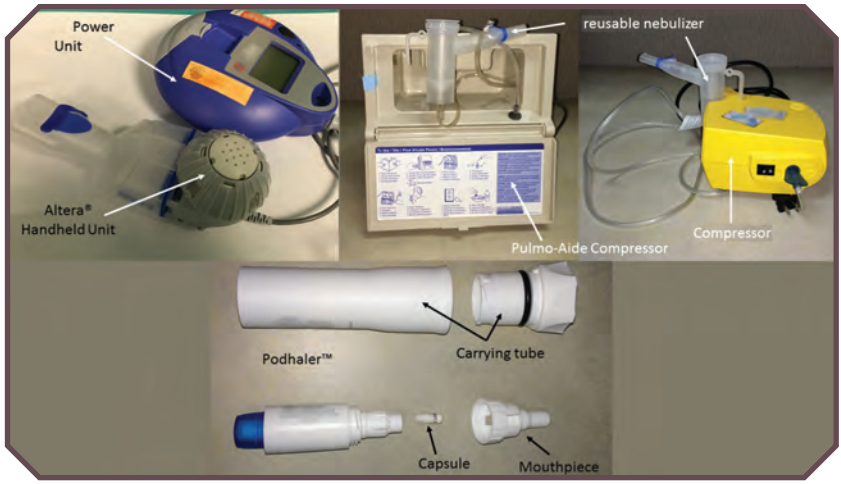

Figure 110-1. Examples of devices used for inhaled antibiotics.

  - — Aztreonam delivered via nebulizer
    - Treatment lasts 2–3 minutes
    - Supplied as lyophilized powder that needs to be reconstituted with 1 mL of sterile diluent before inhalation
    - Should be dosed 75 mg thrice daily
- Up-to-date information on FDA-approved drug-device combinations can be found in the FDA Orange Book (www.accessdata.fda.gov/scripts/cder/ob/default.cfm).
- The Cystic Fibrosis Foundation provides an overview of drugs currently in use (www.cff.org/Life-With-CF/Treatments-and-Therapies/Medications/Antibiotics).

Treatment Modalities

- Eradication therapy for *P aeruginosa* in patients with CF consists of 1 or 2 months of tobramycin nebulizer solution dosed at 300 mg twice daily.
- Chronic suppressive therapy for *P aeruginosa* in patients with CF
  - — Consists of 28 days "on" and 28 days "off" of either tobramycin or aztreonam
  - — Some patients alternate inhaled antibiotics.
    - Tobramycin and aztreonam
    - Tobramycin and any of the off-label formulations (see the "Off-Label Use" section)
    - Aztreonam and any of the off-label formulations (see the "Off-Label Use" section)
- Adjunct treatment of pulmonary exacerbation in patients with CF (off-label use; data on effectiveness are lacking)

Off-Label Use

- Off-label use consists of the use of intravenous formulations in the nebulizer for indications such as bacterial tracheitis in patients with chronic tracheostomy.
- The following antibiotics are used through the inhaled route.
  - Amikacin (250–500 mg twice daily; used also to treat nontuberculous mycobacterial infections)
  - Tobramycin (80 mg twice daily)
  - Gentamicin (20–80 mg twice daily)
  - Ceftazidime (1 g twice daily)
  - Colistin (75–150 mg twice daily; the solution tends to foam)
- Limitations of using these antibiotics include
  - Lack of safety data
  - Lack of characterization of aerosol output
  - Lack of guidance of which compressor or nebulizer should be chosen
    - Since none of the other antibiotics administered via the inhaled route are FDA approved, there is little guidance on which nebulizer or compressor is optimal.

Treatment Against MRSA in Patients With CF

- Treatment is vancomycin, administered with 250–500 mg twice daily.
- The effectiveness of this therapy has not been clearly proven and is not currently FDA approved.
- Practical aspects related to administration of inhaled antibiotics include the following.
  - The administration of inhaled antibiotics is known to cause bronchoconstriction.
  - Patients often receive inhaled albuterol 15 minutes before receiving the antibiotics, particularly if the inhaled antibiotic triggers coughing or bronchospasm.
  - Inhaled antibiotics should be given once the airway clearance therapies have been completed.
  - These antibiotics have well-described toxicities.
    - Nephrotoxicity (all aminoglycosides, colistin, and vancomycin)
    - Ototoxicity (all aminoglycosides)

Use of Inhaled Antibiotics in Patients With Conditions Other Than CF

- Most current practice is based on extrapolation of data obtained in patients with CF.
- Although inhaled antibiotics are frequently used in non-CF bronchiectasis, results are inconclusive, and pediatric data are lacking.
- Inhaled antibiotics are frequently used to treat bacterial tracheobronchitis in patients who have tracheostomies.

Resource for Families

- Inhaled Antibiotics (Cystic Fibrosis Foundation). www.youtube.com/watch?v=nYjmSy19Yd8

Clinical Pearls

- Inhaled antibiotics have been used by CF specialists for many decades, without FDA approval, in their struggle with chronic airway infections due to organisms that do not respond to oral antibiotics.
- In recent years, FDA approval has been achieved for inhaled antibiotics, with more likely on the way.
- Pulmonologists, infectious disease specialists, and otolaryngologists have gradually prescribed inhaled antibiotics for patients without CF, despite the lack of large well-designed clinical trials or regulatory approval.
- Like any inhaled medication, inhaled antibiotics can trigger coughing, hemoptysis, and bronchospasm.
- Without more study, it should not be assumed that there is no systemic absorption or potential systemic toxicity.

Chapter 111

Oxygen Therapy

Sankaran Krishnan, MD, MPH

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
- Hyperbaric oxygen: Delivery of oxygen under pressures that exceed atmospheric pressure
- High-flow oxygen: Delivery of oxygen at markedly higher flow rates than traditional flow rates used for oxygen therapies

Causes of Hypoxia and Hypoxemia

The causes of hypoxia and hypoxemia can be broadly grouped into 4 categories:

- Ventilation-perfusion mismatch: Resulting from differential ventilation and perfusion of the lungs, such as pneumonia, bronchiolitis, and atelectasis
- Hypoventilation:
  - — Central or neurogenic conditions, such as central hypoventilation syndromes, encephalopathies, or opioid or sedative overdose
  - — Neuromuscular conditions, such as spinal muscular atrophy, myopathies, myasthenia gravis
- Diffusion defect: Diseases or conditions that affect the alveolar-capillary barrier, such as interstitial lung disease
- Cytotoxic: Diseases or conditions that affect cellular respiration, such as cyanide toxicity

Determinants of Oxygen Delivery to Tissues

- The oxygen dissociation curve (Figure 111-1) illustrates the relationship between partial pressure of oxygen (Po_2) and the percentage of hemoglobin saturation with oxygen (Spo_2).
- The relationship between Po_2 and Spo_2 is not linear, but S-shaped. At higher Po_2 levels, the curve flattens out, indicating that at higher Po_2 levels, there is little incremental increase in Spo_2.
- Fever, acidosis, and increased levels of diphosphoglycerate reduce the affinity for hemoglobin with oxygen, creating a "shift to the right" for the curve, which leads to unloading of O_2 to the tissues.

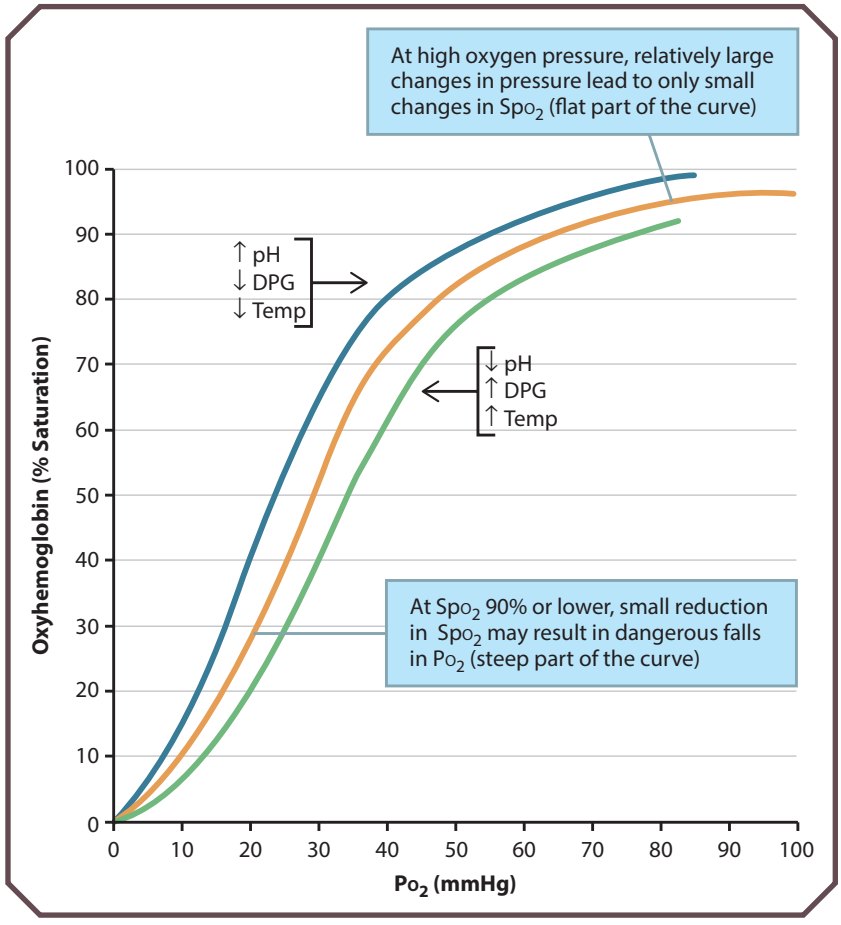

Figure 111-1. The oxygen dissociation curve. DPG = diphosphoglycerate, Po_2 = partial pressure of oxygen, Spo_2 = percentage of hemoglobin saturation with oxygen.

Oxygen Administration

- Oxygen delivery devices are compared in Table 111-1.
- Traditionally, maximum flows of 0.5–1.0 L/min for delivery of oxygen via a nasal cannula are used in newborns, and 2–4 L/min for older children and adults are used to prevent discomfort and drying of the nasal mucosa and other nasal mucosal complications.
- Oxygen is one of the most common interventions in respiratory disorders. However, if administered incorrectly, it can have clinically significant deleterious effects on the lung and other organs; therefore, like any prescribed medication, risks and benefits must always be carefully considered.
- Oxygen therapy should be monitored and dosage adjusted as per need, with the goal of timely discontinuation.

Table 111-1. Oxygen Delivery Devices, Maximal Flow Rates, and Maximal Fraction of Inspired Oxygen Achievable				
Device	**Maximal Flow rate**	**Maximal FIO_2 Achievable**	**Flow**	**Entrainment of Room Air**
Nasal cannula	0.5–4 L/min	Variable	Variable	Yes
Simple face mask	6–10 L/min	30%–60%	Variable	Yes
Partial rebreathing mask	10–12 L/min	50%–60%	Variable	Yes
Nonrebreathing mask	10–12 L/min	≤95%	Relatively fixed	No
Oxygen hood	10–15 L/min	80%–90%	Relatively fixed	No
Oxygen tent	10–15 L/min	30%–50%	Variable	Yes
Venturi mask	Variable	Variable, predictable	Fixed	Yes

FIO_2, fraction of inspired oxygen.

- Oxygen can be administered by using variable-flow or fixed-flow devices, at low or high flow rates. In variable flow systems, oxygen delivery is a function of entrainment of room air from the patient's own inspiratory flow rate and volume, mixing with the delivered oxygen.

Adverse Effects of Oxygen Therapy

- Retinopathy of prematurity in neonates born preterm
- CO_2 narcosis: Oxygen administration only corrects hypoxemia and not ventilatory failure with increased CO_2. It is particularly important in those who have hypoventilation from neuromuscular weakness, where injudicious O_2 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 O_2 therapy, especially at high inspired concentrations (fraction of inspired oxygen), can lead to pulmonary fibrosis and perhaps increase the risk for atelectasis.

Home Oxygen Use

- Oxygen for home use is typically delivered via nasal cannula for long-term use.
- Oxygen is also delivered to children with tracheostomies via "trach collar."

- In adults, oxygen has occasionally been delivered via placement of a catheter into the airway of patients without a tracheostomy ("transtracheal"). This method has not gained traction in children.
- It can be used continuously or as pulsed (on-demand) therapy.
- There are three forms of domiciliary O_2 delivery (Table 111-2).
  - — Compressed oxygen cylinders (large ["H/K" type], medium ["E" type], and portable types).
  - — O_2 concentrators, stationary or portable. While there are exceptions, oxygen concentrators do not typically deliver oxygen at concentrations >40%.
  - — Liquid oxygen

Use of Oxygen While Flying

- Current U.S. Federal Aviation Administration rules do not permit travelers to carry their own oxygen tanks or liquid oxygen aboard commercial aircraft. Instead, patients may use a Department of Transportation–approved battery-powered portable oxygen concentrator.
- A prescription from a health care provider is necessary.
- These portable concentrators are available for rent from most home-care providers.
- Travelers are expected to bring enough 12-cell batteries for 1.5 times the anticipated duration of the flight.
- 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 O_2 saturations.

High-Flow Oxygen Therapy

- High-flow oxygen therapy is most often referred to as high-flow nasal cannula (HFNC) and is a relatively new noninvasive ventilation therapy delivered via a variety of devices.
- Current literature is limited, but it has been suggested that HFNC may be a relatively safe, well-tolerated, and feasible method for delivering oxygen to children with few adverse events reported.
- High flow is usually defined as a flow rate of ≥4 L/min but ranging from 4 to 20 L/min, with some studies reporting flows as high as 70 L/min.
- High-flow oxygen therapy may reduce the need for less tolerated and more invasive respiratory supports, such as continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) and mechanical ventilation.
- In children, HFNC has been most frequently used for infants and young children who are hospitalized with bronchiolitis, particularly in patients who have respiratory distress despite receiving oxygen therapy who do not tolerate CPAP or BiPAP.
- There are reports of HFNC use in congenital heart disease, obstructive sleep apnea, and pulmonary edema.

Table 111-2. Delivery Methods for Home Oxygen Use							
Delivery Method and Use Time	**Availability**	**Reliability**	**Cost**	**Power: Wall Current**	**Stationary Weight and Use Time**		
Concentrator	Common	Good with regular service	Low cost, but the cost of electricity is borne by the patient	Required	Stationary, 35–50 lb; continuous use	Portable, 2–4 lb (delivers continuous or pulsed O_2); use time variable on portable devices, based on battery life and charging	—
Compressed Gas	Common	Good but gauges may become inaccurate	Moderate	Not required	"H" cylinder, 200 lb; use time, 2.5 d	"E" cylinder, 22 lb with cart; use time, 5 h	"M6" cylinder, 4.5 lb; use time, 12 h
Liquid	Limited	Generally good but connector may freeze	High	Not required	Reservoir, 120 lb; use time, 8.9 d	Small reservoir, 6 lb with no conserver; use time, 4 h	Portable, 3.4 lb with conserver; use time, 10 h

Data from the American Thoracic Society clinical practice guideline on Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease.

- To date, there is limited evidence for the safety, effectiveness, or relative cost analysis of HFNC, but this may change over the next few years.
- The use of HFNC in clinical practice continues to increase, particularly in inpatients. It is too soon to tell if home use will increase.

Possible Mechanisms of Action of HFNC

The mechanisms of action of HFNC are incompletely understood, because the flow rates delivered are greater than the normal minute ventilation of patients. Some possible effects of HFNC 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

Pressure Generated by HFNC

- The amount of pressure generated by HFNC 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 demonstrated 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 HFNC

- Studies in children outside the neonatal period and in adults have shown HFNC to be more comfortable and associated with less dyspnea and mouth dryness than oxygen delivered via face mask.
- Improved patient tolerance may be one of the reasons for the increasing use of high-flow oxygen therapy, despite the lack of conclusive evidence for clinical effectiveness.

Adverse Effects and Safety of HFNC

- Most studies demonstrate no or minimal adverse events.
- There are anecdotal reports of pneumothorax in younger infants, with flows exceeding 10 L/min, abdominal distention, and nasal bleeding.
- Unlike CPAP, there is no regulatory pressure relief valve; pressure effects may be seen if there is a minimal leak or no leak.

Resources for Families

- Oxygen Therapy for Children (American Thoracic Society). www.thoracic.org/patients/patient-resources/resources/oxygen-therapy-children.pdf
- Oxygen Therapy for Children (World Health Organization). apps.who.int/iris/bitstream/10665/204584/1/9789241549554_eng.pdf
- When Baby Needs Oxygen at Home (American Academy of Pediatrics). www.healthychildren.org/English/ages-stages/baby/preemie/Pages/When-Baby-Needs-Oxygen-At-Home.aspx

Clinical Pearls

- Home oxygen therapy can be helpful in the care of children with a wide variety of chronic respiratory diseases.
- Oxygen therapy is not benign and should only be prescribed when all risks and benefits are considered, with adequate supervision and monitoring.
- Pediatric pulmonologists should be involved in the care of all children prescribed home oxygen.
- HFNC is a relatively new approach, which is predominantly used in hospitals; recently, it appears to be finding its place in the homes of select patients. The safety of home high-flow oxygen therapy remains unclear.

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Chapter 112

Tracheostomy Care and Complications

Renée B. Stromsness, MD, FAAP, and Manisha Newaskar, MBBS

Introduction

- The most common indications for tracheostomy are anatomic upper-airway obstruction and chronic respiratory failure caused by pulmonary or neuromuscular conditions (see Box 112-1).
- Forty percent to 70% of pediatric tracheostomies are performed in children <1 year of age.
- Optimal care requires an interdisciplinary team, which may include the primary care physician, otolaryngologist or surgeon, pulmonologist, speech therapist, home nursing staff, and family members well trained in tracheostomy care.

Box 112-1. Indications for Tracheostomy in Children

Upper-Airway Obstruction

- Foreign body
- Laryngeal or pharyngeal cysts or neoplasms
- Craniofacial disorders, such as macroglossia or micrognathia
- Epiglottitis
- Severe laryngotracheomalacia
- Bilateral true vocal cord paralysis
- Subglottic stenosis
- Facial or laryngeal trauma
- Laryngeal edema after burns

Prolonged Ventilatory Support

- Chronic respiratory failure
- Neuromuscular diseases
- Bronchopulmonary dysplasia
- Guillain-Barré syndrome
- Coma with respiratory dysfunction

Choice of Tube

- Neonatal, pediatric, and adult tube sizes vary by length and radius or curvature (Figure 112-1). Tubes can be customized.
- Tubes can be made of silicone, polyvinyl chloride, and, uncommonly, metal.
- Silicone tracheostomy tubes are safe for magnetic resonance imaging, but they may cause signal scatter.
- Uncuffed tubes are generally preferred for children to allow for vocalization by air leak around the tube.
- Cuffed tubes are used for patients who require mechanical ventilation with high pressures or who are at risk for aspiration.
  - Cuff pressures are kept below 20 cm H_2O to prevent necrosis injury to the airway epithelium.
  - Air cuffs are inflated with air; water cuffs are inflated with sterile water (not saline).
- Fenestrated tubes are used for adults to promote translaryngeal airflow but are not commonly used for children because of a higher propensity to form granulomas.

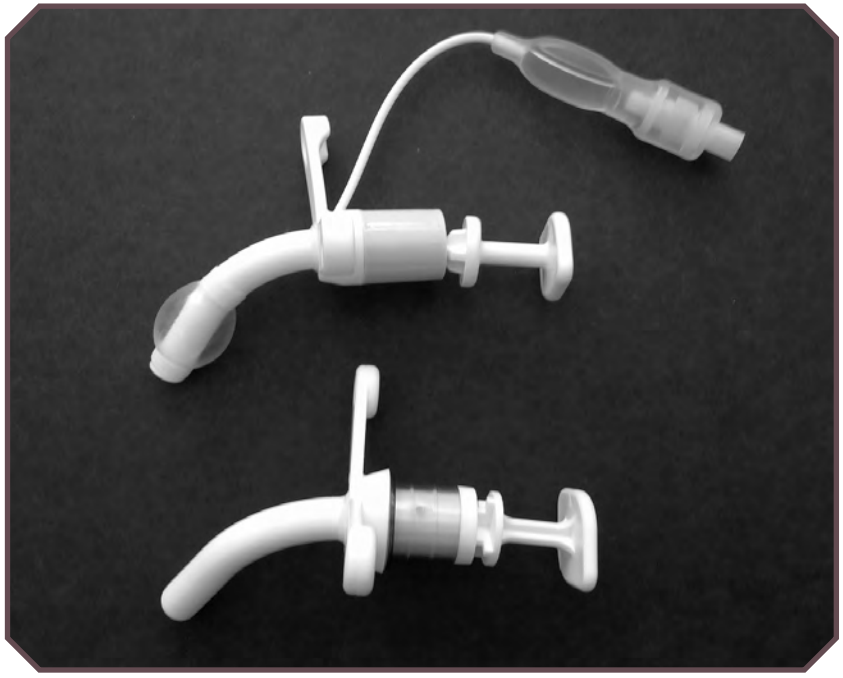

Figure 112-1. Cuffed and uncuffed tracheostomy tubes.

Altered Physiology After Tracheostomy

- Airway clearance is impaired, leading to increased risk of infection.
  - Scar tissue disrupts the normal ciliary function of the anterior trachea at the tracheostomy site.
  - Cough clearance is less effective because the compressive phase of glottic closure before forced expiration is bypassed with the tracheostomy in place.
- The sense of smell is impaired because of decreased airflow through the nose.
- Speech is impaired because of decreased airflow past the vocal cords.
  - To achieve speech without augmentative communication devices, the tube must not exceed two-thirds of the tracheal lumen.
  - A speaking valve can be used to augment speech, depending on the severity of upper-airway obstruction.
- Humidification of inspired air is bypassed.
  - This can lead to desiccation of secretions, damage to mucous glands, mucous plugging, and impaired ciliary function unless external humidification is provided.
  - External humidification with cool mist or heat and moisture exchangers is needed.
- Swallow function is impaired, leading to a risk of dysphagia.
  - The tube limits superior excursion of the larynx with deglutition.
  - The tube may inhibit the normal laryngeal reflex that prevents aspiration.
  - The tube may contribute to mass effect on the esophagus posteriorly.

Management

Home Care

Caregiver Education

- Education of the child's caregivers is an important step in the successful transition from hospital to home that should be individualized to the child and family.
- Some institutions require training of ≥2 adult caregivers who will provide constant care to the child. If appropriate, older siblings could be included in this process.
- Hands-on caregiver teaching should start at the bedside as soon as the tracheostomy is placed.
- Education should include
  - Technical skills, such as tracheostomy tube and tie changes, appropriate suctioning techniques, stoma care, and cardiopulmonary resuscitation training
  - Decision-making skills, such as recognizing signs and symptoms of respiratory problems and troubleshooting

- Caregivers should demonstrate proficiency before the patient is discharged from the hospital.

Home Supervision and Monitoring

- Constant supervision by an adult trained in tracheostomy care is required. If at any time after hospital discharge a trained adult caregiver is not available, the child should be readmitted until a trained caregiver is available.
- Skilled home nursing care is often prescribed, both during the transitional adjustment time after hospital discharge and when trained family members cannot be available.
- For high-risk tracheostomy-dependent patients (eg, with a critically narrow airway), 24-hour nursing support may be necessary.
- A pulse oximeter should be considered for children at high risk for complications.
- Apnea monitors do not indicate airway obstruction and may not be appropriate for monitoring patients with tracheostomies.

Tracheostomy Supplies for Home

- Essential supplies must be available in the home and are usually supplied via prescription from a durable medical equipment company before hospital discharge (Box 112-2).
- Home care equipment should be tested in the hospital before discharge.

Box 112-2. Tracheostomy Home Care Supplies

- **Extra trach tube, same size**
- **Extra trach tube, 0.5 or 1 size smaller**
- **Suction machine and tubing**
- **Suction catheters and olive tip**
- **Resuscitation bag with trach adapter and face mask**
- **Scissors**
- **External humidification (nebulizer, compressor, or heat and moisture exchanger)**
- **Trach ties**
- **Clean jar of water**
- **Normal saline for suctioning**
- **Cotton swabs and gauze**
- **Oxygen with tubing (if ordered)**
- **Breathing monitor, such as a pulse oximeter (if ordered)**

Tracheostomy Care at Home

- Changing tracheostomy tubes
  - The frequency of tube change ranges from daily to monthly, depending on the tube and the patient; weekly changes are most common.
  - Advantages of frequent tube changes include
    - Keeping caregivers well practiced in changing the tube
    - Decreasing airway infection or granuloma formation
    - Reducing the risk of tube occlusion by thick secretions
  - Consider changing the tubes daily or every other day if the child experiences increased tracheal secretions.
- Tracheostomy ties
  - Ties should be replaced during tube changes or when soiled.
  - Soft hook and latch material causes minimal irritation of the skin.
  - Ties should be tight enough to minimize the movement of the tube without causing skin breakdown. Allow enough slack for a finger to be inserted underneath the tie.
- Suctioning of the tracheostomy tube
  - Attention to clean technique is very important.
  - Wash hands before and after each suctioning procedure.
  - After suctioning, the catheter should be flushed with tap water until secretions are cleared from the lumen.
  - The catheter should be wiped with alcohol and allowed to air-dry, then stored in a clean, dry area.
- Wear and tear of tracheostomy tubes
  - Tubes made of polyvinyl chloride (PVC) become rigid with repeated use and may develop cracks or splits; therefore, tubes should be inspected before insertion.
  - PVC tubes can be used for 6–12 months before stiffening and should be replaced every 6 months.
- Cleaning of the tracheostomy tube
  - Clean tubes with mild liquid detergent and water.
  - Rinse them thoroughly and air-dry them completely.
  - Store them in a clean plastic bag after air drying.

Humidification Devices

- External humidification can be delivered by a heated humidifier, jet nebulizer, or heat and moisture exchanger (HME), also known as an "artificial nose."
- An HME device can contribute to resistance and dead space; the patient must undergo evaluation with the device before using it routinely.

Speaking With Tracheostomy

- Speech can be facilitated with the use of a speaking valve for certain patients.
  - Must be awake, interactive, and medically stable

  - Should tolerate deflation of the tracheotomy tube cuff
  - Must not have excessive thick secretions or high tracheal pressures
- A speech-language pathologist should be consulted as soon as possible to assist with the care of every child with a tracheostomy.

Routine Medical Care

- Regular follow-up with a primary care physician, otolaryngologist, and pulmonologist is indicated for children with chronic tracheostomies.
- At follow-up visits, assess the patient for an ongoing need for a tracheostomy tube and for complications.
- Routine evaluation with rigid or flexible bronchoscopy can be performed to assess underlying airway pathologic findings and tube size and position, detect and treat complications, and determine readiness for decannulation.

Expected Outcomes/Prognosis

Complications

- Twenty-five percent to 50% of children develop complications after tracheostomy.
- Complications are more common in younger children and those with long-term tracheostomies (Box 112-3).

Box 112-3. Late Postoperative Complications of Pediatric Tracheostomy

- Suprastomal collapse
- Tracheal wall granuloma
- Tracheoesophageal fistula
- Depressed scar
- Laryngotracheal stenosis
- Tracheal wall erosion
- Catastrophic hemorrhage
- Tracheomalacia
- Tube obstruction or displacement
- Decannulation failure
- Recurrent tracheitis, bronchitis, or pneumonia
- Death

From Sherman JM. American Thoracic Society statement: care of the child with a chronic tracheostomy. *Am J Respir Crit Care Med.* 2000;161:297–308. Reprinted with permission of the American Thoracic Society.

- Tracheal lesions, such as granulomas, fistulas, and erosions, can develop from rubbing of the tube against the tracheal wall. The suprastomal area is particularly prone to collapse and granuloma formation (Figure 112-2).
- Infection, particularly tracheitis, may 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 quickly become colonized with bacteria, such as *Pseudomonas aeruginosa*.

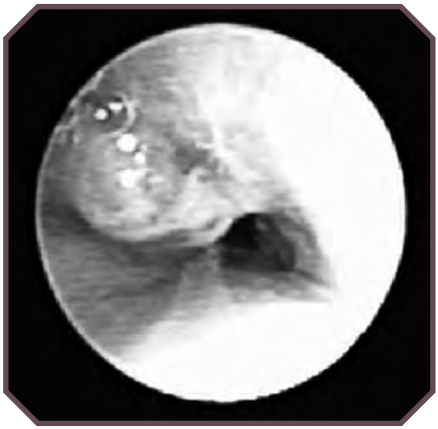

Figure 112-2. Bronchoscopic image shows the suprastomal granulation tissue proximal to the tracheostomy tube, obstructing approximately 50% of the airway lumen.

- Catastrophic bleeding as a result of erosion of the tracheostomy tube into a major vessel is rare but is more common with patients with severe scoliosis or other clinically significant airway structural abnormality.
- Any recurrent or clinically significant bleeding should be promptly evaluated by a pulmonologist or otolaryngologist.
- A tube that is too short may pop out easily. The length may need to be increased as the child grows.
- Obstruction or displacement of the tube can lead to life-threatening airway obstruction and even death.
  - Caregivers should be comfortable with suctioning, replacing the tube, and providing positive pressure resuscitation through the tube, mask, or upper airway, should such an event take place.

Decannulation

- This is achieved for about 50%–70% of patients.
- It should be performed if the initial indication for tracheostomy placement has resolved.
- The patient should demonstrate the ability to maintain a patent airway and adequate respiratory physiology independent of the tube.
- The mean time to decannulation ranges from 4 to 21 months on the basis of the original indication.
- The process of decannulation includes the following.
  - Laryngoscopy and bronchoscopy are performed to evaluate the airway for the presence of granulation tissue, suprastomal collapse, hypopharyngeal collapse, or tracheomalacia.

- A capping trial is performed in the specialist's office. If capping is tolerated, the specialist provides instruction on short capping trials at home under supervision, with a plan to advance as tolerated.
- The tube can be progressively downsized, although this approach is limited in very small children because of the proportionately larger increase in airway resistance and mucous plugging of the smaller tube.
- Once the patient is tolerating extended periods of capping, an overnight polysomnogram should be performed with a capped tracheostomy to assess the adequacy of gas exchange prior to decannulation.
- Decannulation should be attempted as an inpatient procedure if the patient passes these evaluations and tolerates capping for 24 hours per day.
- The patient should be monitored in the hospital for 24–48 hours after decannulation to observe the presence of any obstructive symptoms.

When to Refer

- The parent is experiencing difficulty with tracheostomy tube change.
- There is bleeding through tracheostomy tube.
- There is large granulation tissue around the tracheostomy stoma.
- The patient is no longer tolerating the speaking valve when it was previously tolerated (this suggests obstruction above the tube).

Resources for Families

- 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

Clinical Pearls

- If a tracheostomy tube comes out accidentally and resistance is noted when replacement is attempted, insert the backup smaller size of cuffless tube.
- If a tracheostomy tube comes out accidentally in a hospital setting and resistance is noted when replacement is attempted with tubes the same size and smaller, a smaller, cuffless endotracheal tube could be temporarily placed.

Chapter 113

Airway Clearance Devices and Techniques

Karen A. Hardy, MD

Introduction

- Healthy children are able to clear their airway with cough and mucociliary escalator.
- Some children do not clear secretions normally and need airway clearance techniques to prevent complications. Table 113-1 specifies the types of children who need airway clearance techniques.

Signs and Symptoms of Retained Secretions

- Chronic and productive cough, wet sounding
  - — May be weak and obviously ineffective
  - — May be strong, as in patients with cystic fibrosis (CF)
- Recurrent pneumonia or atelectasis
- Respiratory distress may be clinically evident if the muscles are normal.
  - — Note that a hypotonic patient may not be able to show the same degree of increase in work of breathing.
- Desaturation occurs with hypoventilation.

Associated Findings

- Bulbar dysfunction: drooling, lack of gag, dysarthria
- Recurrent or chronic aspiration
- Neuromuscular diseases
- Any of the diagnoses listed in Table 113-1

Clinical Course Without Treatment

- Recurrent infections, tracheitis, bronchitis, pneumonia with fever, respiratory distress
- Symptoms worsen in weak children who can rapidly deteriorate without obvious distress
- Hypoxemia
- Repeated admissions for acute treatment and antibiotics
- End-stage lung disease with respiratory failure

Table 113-1. Who Needs Airway Clearance Techniques and Why

Anatomic or Functional Abnormality	Diagnostic Category	Pathophysiology
Mucociliary Escalator		
Cilial dysfunction	Primary ciliary dyskinesia	Cilia immotile or dyskinesia
Abnormal airway surface liquid or mucous layer	Cystic fibrosis	Reduced airway surface liquid; thick and viscous mucus layer; increased inflammatory mediators; increased levels of destructive compounds (elastases, proteases)
	Pseudohypoaldosteronism	Increased volume of airway surface liquid; intermittent airway obstruction and infection as young children, typically <6 years
	Asthma	Abnormal and increased mucus Airway edema
Cough Clearance		
Respiratory muscle dysfunction		
Neuromuscular disease	Duchenne muscular dystrophy	Combined respiratory motor defects with abnormal inspiratory pressure generation and/or expiratory pressure generation; bulbar dysfunction with aspiration and/or gastroesophageal reflux
	Spinal muscular atrophy type I	See Duchenne muscular dystrophy
	Spinal muscular atrophy type II	Combined respiratory motor defects with abnormal inspiratory pressure generation and/or expiratory pressure generation
	Congenital myopathies	See Duchenne muscular dystrophy
Neuromotor disease	Cerebral palsy	Inability to sense secretions in the airways or pharynx, bulbar palsies, 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 the bellows function
	Meningomyelocele (spina bifida)	Bellows dysfunction and progressive scoliosis

Table 113-1. Who Needs Airway Clearance Techniques and Why, *continued*

Anatomic or Functional Abnormality	Diagnostic Category	Pathophysiology
Neurological disease	Bulbar palsy	Inability to control oral secretions and/or swallow, may include direct aspiration
	Encephalopathy	See bulbar palsy
Unstable airways	Airway malacia	Airways collapse with dynamic pressure changes during inspiration and/or expiration
	Tracheoesophageal fistula	See airway malacia and direct airway damage from aspiration
	VATER syndrome	See tracheoesophageal fistula
	Bronchiectasis (bronchiolitis obliterans, cystic fibrosis, immuno-deficiency, primary ciliary dyskinesia, postinfectious, tuberculosis)	See airway malacia
Obstructed airways	Tracheal stenosis	Inadequate lumen for secretion clearance
	Scoliosis	Airway rotational deformities ("kinking") and muscle imbalance that can be progressive

VATER, vertebral defects, anal atresia, tracheoesophageal fistula with esophageal atresia, and radial and renal anomalies.

Determining Need

- Perform pulmonary function testing with maximum inspiratory pressure and maximum expiratory pressure to measure combined respiratory motor strength and ability to cough and clear secretions.
- Chest radiography can be used to look for evidence of bronchiectasis and recurrent areas of complications.
- Chest computed tomography can be used to diagnose bronchiectasis (it's a fast procedure and often, no sedation is required).
- Sniff nasal inspiratory pressure is a less commonly used method that appears to a sensitive measure of respiratory muscle strength in patients with Duchenne muscular dystrophy.

Prescribing an Airway Clearance Technique

- Some techniques, noted herein, are easy to learn. Others are more complicated and are best taught by a pulmonologist or a specially trained respiratory therapist.

- Examples of correct technique are easily found online, from device manufacturers and major children's hospitals, CF centers, and the Cystic Fibrosis Foundation.
  - — Independent methods (no equipment or assistance needed)
    - ▪ Directed cough and huff or forced exhalation maneuver (easy to learn)
    - ▪ Active cycle of breathing techniques (easy to learn)
    - ▪ Autogenic drainage (hard to learn)
  - — Dependent methods (personnel required)
    - ▪ Chest physical therapy or postural drainage and percussion (easy to learn)
      - ~ The American College of Chest Physicians no longer recommends chest physical therapy because alternative methods are equally or more effective. However, it remains an important technique for young infants who are unable to perform other techniques.
    - ▪ Manual cough assist (easy to learn)
  - — Handheld or small devices
    - ▪ Manual percussors
    - ▪ Bubble positive expiratory pressure (PEP) (easy to learn)
    - ▪ PEP valve
    - ▪ Flutter valve
    - ▪ Vibratory therapy system (eg, Acapella [Smiths Medical, Minneapolis, MN])
  - — Large machinery required
    - ▪ High-frequency chest compressors or "VESTs"
    - ▪ Cough-assist device
    - ▪ Intrapulmonary percussive ventilator

Independent Techniques

Huff Cough Maneuver

Huff cough or forced expiratory maneuver can help to decrease the compression of airways.

- Step 1: Inhale.
- Step 2: Hold breath for approximately 3 seconds.
- Step 3: Exhale forcefully with a slightly open glottis.

Active Cycle of Breathing Technique

- Relaxation breaths or "belly breaths"
  - — Step 1: The patient should lie supine to learn the techniques, then graduate to doing them in any position.
  - — Step 2: Place a favorite stuffed animal (for younger children) or 1 hand (for older children) on the abdomen and 1 hand on the chest to enable visual and palpable feedback.

  - — Step 3: Breathe in and watch the stuffed animal "take a ride," or feel and see the hand on the abdomen move.
  - — Step 4: Breathe out and contract the belly muscles to push or squeeze the air out.
- Chest or thoracic expansions
  - — Step 1: Breathe in and feel the chest fill and rise.
  - — Step 2: Breathe out and see or feel the chest return to baseline.
- Combine these as a cycle of breathing.
  - — Perform relaxed belly breathing to start.
  - — Then, alternate between belly, thoracic, belly, and huff, and repeat the cycles.
- This independent skill can be mastered and then used any time in any position, although it requires attention to be the most effective.

Autogenic Drainage

- Step 1: Begin in the sitting position.
- Step 2: Breathe in via the nose (warm, filter, and humidify the air) and out via the mouth.
- Step 3: Breathe a number of breaths at each of 3 levels: small, medium, and large.
- Step 4: Suppress active coughing and move the secretions with airflow.
- Step 5: When the patient listens and feels the rattle of the moving secretions early in exhalation, it is time to move up to the next level of breathing.

Dependent Techniques

Chest Physical Therapy

- Position the patient in positions that encourage gravity drainage while clapping on the chest with either a hand or a cupped palm.

Manual Cough Assist

- The patient should be recumbent.
- Place the heel of the hand just below the xiphoid.
- Thrust from the abdomen toward the diaphragm in concert with patient efforts to cough.

PEP Techniques

Bubble PEP

Use a container with a narrow neck, such as a plastic water bottle.

- Step 1: Place a large straw into the container to rest on the bottom and still leave ≥6 inches out of the neck of the bottle.

- Step 2: Fill the bottle with liquid to 15 cm. The liquid should be potable if the child is young and he or she might drink it rather than blow it. Older children enjoy using soap and making overflowing bubbles. Place the setup into a large pan if soap is used.
- Step 3: Breathe in from room air.
- Step 4: Hold the breath for about 3 seconds.
- Step 5: Place the lips tightly around the straw.
- Step 6: Breathe out (making bubbles if using soap) for a slow count of 5–10 seconds.
- Step 7: Take a few relaxed belly breaths and repeat for a total of 10 breaths.
- Step 8: Take a break and return later. Aim for 100 breaths divided into shorter intervals during the day.

PEP Valves

- Use the same respiratory pattern as explained in the previous section, but blow into the handheld device.
- Observe that the correct pressure is achieved throughout exhalation, with the indicator included in the setup.

Oscillating PEP Devices

- High-frequency oscillations may be added to PEP. The oscillations produced by the devices throughout exhalation are passed along the airway walls and loosen the mucus.
- The flutter valve produces these oscillations with the flutter of a steel ball that sits in a cone-shaped pipe. Exhaled air pushes the ball up in the cone until air escapes and the ball reseats, producing a vibrating air flow.
- The vibratory therapy system (eg, Acapella [Smiths Medical]) and the oscillation PEP device (eg, Aerobika [Monaghan Medical, Plattsburgh, NY]) are popular devices designed to produce vibrations as patients breathe in and out.
- How to use:
  - Use a mouthpiece (requires adequate muscle strength to form a tight seal) or a mask over the nose and mouth.
  - Inhale for 3 seconds.
  - Hold the breath.
  - Exhale for 5–10 seconds while generating PEP and oscillations.

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*.
- Fixed pressure can be used, or variable short intervals at gradually increasing frequency can be cycled to help clear all airways.

- 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 the mucus.
- 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 the routine use of vests.

Cough-Assist Device

This device generates both positive and negative pressure breaths.

- Step 1: Select the patient interface. Use of a mask is common, but the cough-assist device can also be applied via adapter to an endotracheal tube or tracheostomy tube.
- Step 2: Set the inspiratory time according to the patient's comfort or similar to the patient's own breathing.
- Step 3: Set the exhalatory time to be longer than the inspiratory time. Encourage patients to cough, if they are able, with the suction phase of the treatment.
- Step 4: Permit a pause time for the patient to take a single breath or a few small breaths, and then proceed with the next clearance breath.
- Step 5: If the patient is unable to expectorate, suction after movement of secretions into the mouth.

Intrapulmonary Percussive Ventilator

- Positive pressure with controlled but rapid inspiratory and expiratory phases is delivered with continuous aerosol.
- A mask or mouthpiece is used (the cheeks must be supported if using a mouthpiece), and the patient breathes while the machine delivers the controlled small "breaths" over the patient's own breathing.
- How to use:
  - Step 1: Sit comfortably.
  - Step 2: Load liquid (albuterol, saline, or hypertonic saline) into the aerosol chamber.
  - Step 3: Place the mask over the patient's mouth and nose, or place the mouthpiece into the patient's mouth, and tighten or hold the patient's cheeks.
  - Step 4: Turn on the machine.
  - Step 5: The patient should breathe slowly and regularly.

Upkeep and Cost Considerations

- Upkeep and cost considerations are shown in Box 113-1 and Table 113-2, respectively.

Box 113-1. General Care of Airway Clearance Therapy Equipment

Vest

- Sponge clean with mild detergent and dry dust machine.
- Use germicidal wipes.
- Clean weekly.

Positive expiratory pressure devices

- Create a water-vinegar solution that has a ratio of 1 part vinegar to 2 parts water.
- Place the mouthpiece in to soak for 20 minutes.
- Let it drain and dry on a clean towel. Angle the device on the towel for best drainage.

Table 113-2. Cost Comparisons of Airway Clearance Therapy Equipment

Equipment Type	Device Cost	Respiratory Therapy Training (approximately 1 h per session)
Chest physical therapy	$0	1–2 sessions
Huff	$0	1 session
Active cycle of breathing technique	$0	2 sessions
Autogenic drainage	$0	4–6 sessions
Positive expiratory pressure valve	$23	1 session
Flutter valve	$71	1 session
Vibratory therapy system[a]	$38	1 session
Percussion mechanism device[b]	$40	1 session
Vest	$4,000–$14,000	1 session
Cough-assist device	$430–$1,500	2–3 sessions
Intrapulmonary percussive ventilator	$4,00–$7,000	1 session

[a] For example, Acapella (Smiths Medical, Minneapolis, MN).

[b] For example, Quake (Thayer Medical, Tucson, AZ).

Selection of Airway Clearance Techniques

- Consult a pulmonologist, other physician, or respiratory or physical therapist skilled in these applications in children for advice on the best method for the individual patient and for initial patient training.
- Simple methods such as manual cough assist, belly breathing, active cycle breathing, and bubble PEP are easily taught and learned in the primary care office.
- Infants or very young children typically require assistance and dependent methods of airway clearance techniques, traditionally by using chest physical therapy or large machines.
- Vest jackets have been developed for infants with a chest size of ≥19 inches.
- Multiple options are available, and therapies may be modified to suit maturity level and lifestyle.
- Offering patients input and choice of techniques can increase patient adherence.
- Other enhancers of airway clearance can include exercise, using a pogo stick, jumping on a trampoline, horseback riding, playing wind instruments, and singing and vocal training.

Inhaled Medications and Airway Clearance Techniques

- Bronchodilators are often prescribed to be given just prior to performing airway clearance techniques, particularly in children with asthma or increased airway hyperresponsiveness.
- If the patient has airway malacia, albuterol may worsen the airway tone.
- Pulmonologists often prescribe a variety of other inhaled agents, including saline at various concentrations (normal, 3%, 7%) and recombinant human DNase, usually to be used prior to performing airway clearance techniques with the goal of hydrating or thinning secretions to aid clearance. For the most part, clear evidence of safety and effectiveness have been limited to patients with CF.

Resources for Families

- Airway Clearance (Cystic Fibrosis Foundation). www.cff.org/Life-With-CF/Treatments-and-Therapies/Airway-Clearance
- Managing Treatments: Airway Clearance (Johns Hopkins Cystic Fibrosis Center). www.hopkinscf.org/living-with-cf/managing-treatments/airway-clearance
- Airway Clearance Techniques (University of Rochester Medical Center). www.urmc.rochester.edu/medialibraries/urmcmedia/childrens-hospital/pulmonology/cystic-fibrosis/documents/airwaytechniques.pdf

Clinical Pearls

- A wide selection of independent and dependent techniques is available to improve airway clearance in patients.
- Use chest physical therapy 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 techniques such as cough, breathe in, breathe out, and blow. Preschool-aged children can learn diaphragmatic breathing and the huff cough.
- Most pulmonary and respiratory specialists and hospital personnel become skilled in the application of these techniques and can assist generalists in decision-making regarding the selection and refinement of airway clearance skills.
- Weaker patients with poor cough are best managed with manual cough assistance or the cough-assist device.
- Skilled performance of autogenic drainage is associated with improved oxygenation and minimization of work to expectorate.
- Pressure loss into the mouth is prevented by tightening the cheek muscles or holding them with the thumb and fingers to compress the cheeks.
- The Cystic Fibrosis Foundation has developed comprehensive new guidelines on airway clearance techniques, which is a good reference for patients with CF or other diseases that cause bronchiectasis and productive cough.

Chapter 114

Continuous Positive Airway Pressure

Priya Prashad, MD, and Nadav Traeger, MD, FAAP, FCCP, DABSM

Introduction

Continuous positive airway pressure (CPAP) is a form of noninvasive respiratory support that delivers a constant positive pressure via an interface that covers the nose and/or mouth at a pressure sufficient to maintain a patent airway and thus eliminate snoring and obstructive sleep apnea (OSA). Other indications are listed in the following section.

Indications

CPAP is used for treatment in the following ways.

- As a secondary treatment modality for patients with clinically significant residual OSA after adenotonsillectomy or other upper airway or craniofacial surgery
- As a primary treatment modality for OSA in patients who are not surgical candidates because of other medical issues (eg, severe obesity, bleeding diathesis, atlantoaxial instability) and/or who have small tonsils and/or adenoids
- For OSA when either the patient or the parents prefer a nonsurgical option
- For hypoventilation and/or OSA caused by neuromuscular weakness rather than an anatomic issue (bilevel positive airway pressure [BiPAP] is more commonly used for this purpose; see Chapter 115).
- For preterm neonates whose lungs have not fully developed, who have respiratory distress syndrome, or who have bronchopulmonary dysplasia
- For patients who have clinically significant lower-airway obstruction due to tracheomalacia or bronchomalacia who may benefit from using CPAP to stent these airways open
- For patients with a variety of chronic obstructive lung diseases for lung recruitment and to aid with airway clearance of secretions

Settings

- CPAP machines can be set at 1 single pressure, typically between 4 and 20 cm H_20. Typically, the machine is set at the lowest pressure that resolves all obstructive events, as well as snoring.
- Expiratory positive airway pressure is the background pressure applied at a continuous rate (eg, 9 cm H_20).

- O_2 is the amount of oxygen that can be added to the inspired air. For most patients with OSA syndrome, supplemental O_2 is not needed. This parameter may be displayed in liters per minute or as a fraction (as in the fraction of inspired oxygen) or a percentage.
- *Humidification* refers to the relative amount of humidity added to inspired air, adjusted for comfort.

Equipment

- The CPAP machine (pressure generator) is connected to an interface via tubing. It blows air and thus creates positive pressure air through the interface into the nose and/or mouth, thus preventing the upper airway from collapsing during sleep.
- The most effective way to determine the correct pressure and mask is an in-laboratory overnight sleep study (CPAP titration).
- Interface options for CPAP include nasal masks, full-face masks that cover the nose and mouth (see Figures 114-1 and 114-2), total face mask (which covers the entire face), nasal pillows, and oral masks. These are available in a variety of sizes, shapes, and styles.

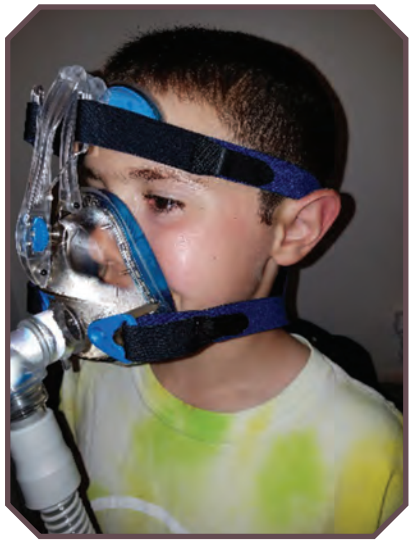

Figure 114-1. Full-face mask.

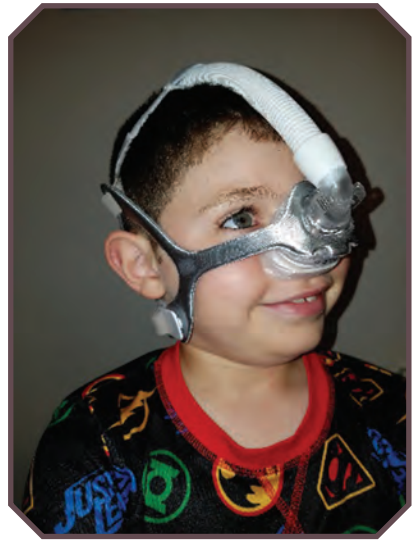

Figure 114-2. Nasal mask.

- Increasingly, medical device manufacturers have begun designing smaller masks for pediatric patients.
- These interfaces come attached with straps (headgear) that keep them in place.
- Some adult sleep centers prescribe nasal masks and headgear to children, which are designed for "small" or "petite" adults. For older children and teens, this solution may work, but it typically does not work for infants or young children. Masks should be replaced on an as-needed basis.

Insurers have different schedules as to how often they will pay for a CPAP mask replacement.

- Conventional nasal or ventilatory CPAP (Figure 114-3) can be administered via a CPAP machine, BiPAP machine, or home ventilator.
- Another type of CPAP is bubble CPAP (Figure 114-4).

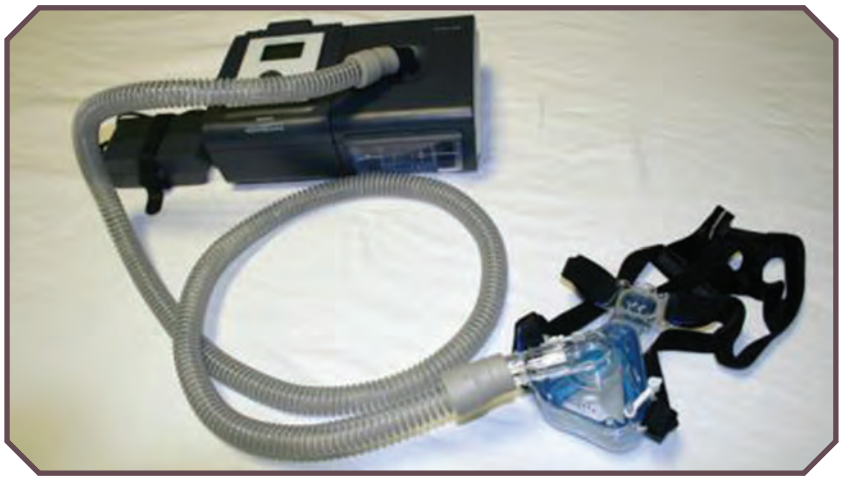

Figure 114-3. Conventional continuous positive airway pressure mask. From Children's Hospital of Philadelphia. Sleep Center Health Resources. Available at http://www.chop.edu/centers-programs/sleep-center/health-resources

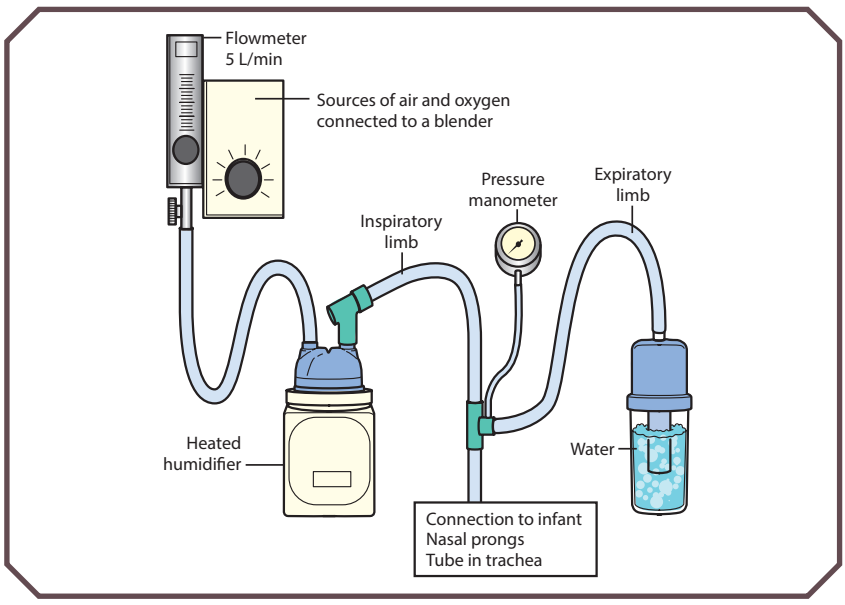

Figure 114-4. Bubble continuous positive airway pressure. From http://www.seattlechildrens.org/research/integrative-brain-research/our-labs/neonatal-respiratory-support-technologies-team/sea-pap/

— Bubble CPAP is used to treat neonates with respiratory distress syndrome by supporting spontaneous breathing with delivery of a continuous, pressurized gas flow to a neonate's airway.
— The gas is usually humidified air, mixed with oxygen, delivered though a nasal mask or nasal prongs.
— The depth to which the tubing is immersed underwater determines the pressure generated in the airways of the neonate.

Adverse Effects

Table 114-1 outlines the possible adverse effects from the use of CPAP.

Table 114-1. Potential Adverse Effects of CPAP

Adverse Effects	Prevention and Alleviation Strategies
Claustrophobia	A common problem with CPAP initiation, this usually improves with becoming accustomed to using the mask and machine or using a mask with less facial coverage.
Skin irritation	Insert a soft layer to create a barrier between the face and CPAP mask; avoid overtightening the straps; clean the mask regularly to prevent buildup of facial oils and rubbing; replace a poorly fitting mask.
Skin allergies	Most CPAP masks today are latex free, but a few patients may be allergic to the silicone in the mask, which can be alleviated by trying an alternative mask.
Nasal congestion	Increase the level of humidification or use a nasal saline or nasal steroid spray at bedtime.
Nasal, oral, or eye dryness	Increase the level of humidification, eliminate mask leaks, or switch from a nasal mask to a full-face mask if the child mouth breathes.
Risk of aspiration	Remove the CPAP mask when the child is vomiting if he or she is wearing a full-face mask and limit the use of full-face masks in pediatric patients who are more prone to gastrointestinal illnesses or are physically unable to pull them off.
Intolerance of air pressure	The air pressure from CPAP can make exhaling difficult or cause a choking or suffocating sensation. Use the "ramp" feature on the CPAP machine to slowly "ramp up" from a lower air pressure to the preset recommended pressure or use exhalation pressure relief, which provides a brief decrease in pressure during exhalation to reduce the effort required to overcome it.
Mask removal during sleep	For some CPAP machines, an alarm can be set to alert the caregiver if the mask comes off. This problem usually improves with becoming accustomed to using the mask and pressure, trying a different mask, or using the machine's humidifier.
Midface hypoplasia (underdevelopment of the maxilla bone)	A rare but serious adverse effect in pediatric patients where long-term pressure from the mask causes deformations or lack of proper growth of the facial bones, this can be prevented by using a mask with less facial coverage and monitoring the facial growth regularly.

CPAP, continuous positive airway pressure.

Contraindications

- Respiratory arrest
- Cardiovascular instability
  - Cardiac arrest
  - Hypotension
  - Uncontrolled arrhythmias
- Multiorgan system failure
- Somnolence, impaired mental status, uncooperative patient
- Severe upper gastrointestinal bleeding
- High risk for aspiration; inability to clear respiratory secretions
- Recent upper gastroesophageal surgery
- Recent facial surgery, trauma, or deformity
- Unable to fit the mask
- Undrained pneumothorax

Dealing With Nonadherence

- A major issue with CPAP therapy is poor adherence. A desensitization protocol to lessen claustrophobia and facial aversion can help a child become acclimated to the mask and pressure. When performed soon after treatment initiation, it can prevent later noncompliance.
- Many insurers will monitor adherence with the use of a memory card or a remote data monitoring system. They will deny payment and take away equipment in those who display poor adherence. This routinely happens in adult patients and is occurring increasingly in pediatric patients.
- Because of a tendency by patients and caregivers to overestimate CPAP and BiPAP usage, it is best for clinicians who manage these devices to rely on objective recorded usage rather than subjective reported usage.
- Most pediatric sleep specialists recommend a repeat CPAP titration ideally every 6–12 months after therapy begins because frequent changes in fat distribution, facial structure, or head size can result in a need to keep adjusting CPAP or bilevel pressure.

When to Refer

- Patients who use CPAP or BiPAP should undergo frequent follow-up with a physician who is well versed in its use (eg, a board-certified pediatric sleep medicine specialist or a pediatric pulmonologist) to monitor adherence and address adverse effects.

Resources for Families

- CPAP: Overview (American Academy of Sleep Medicine). www.sleepeducation.org/essentials-in-sleep/cpap
- Sleep Apnea and Your Child (American Academy of Pediatrics). patiented.solutions.aap.org/handout.aspx?resultClick=1&gbosid=156547

Clinical Pearls

- CPAP is an effective form of therapy for children with a wide variety of disorders that cause airway obstruction.
- There are many barriers to the adherence and effective use of CPAP.
- It is strongly suggested that a sleep medicine specialist or pulmonologist be closely involved with the initiation and management of CPAP therapy, because there may be a lot of trial and error involved in finding the optimal interface and difficulties with adherence.
- Many children who are prescribed CPAP may eventually require increased ventilatory support, including BiPAP and/or home mechanical ventilation.

Chapter 115

Bilevel Positive Airway Pressure

Nadav Traeger, MD, FAAP, FCCP, DABSM, and Priya Prashad, MD

Introduction

- Bilevel positive airway pressure (BiPAP) is a form of noninvasive respiratory support that delivers 2 levels of positive pressure.

Uses/Indications

- The same indications apply to BiPAP as to continuous positive airway pressure (CPAP; see Chapter 114), but some patients may tolerate BiPAP better because it has a lower exhalation pressure and a lower mean airway pressure.
  - Treatment of clinically significant residual obstructive sleep apnea (OSA) after adenotonsillectomy or other upper airway/craniofacial surgery
  - Treatment of OSA when either the patient or the parents prefer a nonsurgical option
  - Treatment of OSA in those who are not surgical candidates because of other medical issues (eg, severe obesity, bleeding diathesis, atlantoaxial instability) and/or who have small tonsils and/or adenoids
- In addition, BiPAP is used in situations where pressure support is needed—that is, as a means of providing noninvasive ventilation for treatment of hypoventilation or central apneas.
- BiPAP is used in hospitals for treatment of acute respiratory failure; the device settings are chosen and adjusted on the basis of clinical response, pulse oximetry values, and blood gas analyses.
- BiPAP is used at home for the treatment of chronic respiratory failure; the device settings are chosen and adjusted mostly on the basis of overnight polysomnography (sleep study) results, in addition to clinical response.

Device Settings

- BiPAP machines may have a number of different settings. The common ones are listed here.
  - Inspiratory positive airway pressure (IPAP): The pressure applied during patient-triggered breaths, similar to pressure support

  - Expiratory positive airway pressure (EPAP): The background pressure applied in between patient-triggered breaths, analogous to CPAP or positive end-expiratory pressure
  - Mode: Typical options are *S* (spontaneous), *S*/*T* (spontaneous/timed), or *T* (timed)
  - Rate: The minimum number of breaths per minute
  - Ramp: The number of minutes the device will take to gradually reach the selected settings from the minimal settings. This feature is used for patient comfort to allow the patient to fall asleep while the device is still at lower pressures.
  - O_2: The amount of oxygen added to the inspired air. It may be displayed in liters per minute or as a fraction (as in the fraction of inspired oxygen) or a percentage.
  - Humidification: The relative amount of humidity added to inspired air, adjusted for comfort
- Other settings that may be available include
  - Rise time: How fast (in seconds) it takes the pressure to increase from EPAP to IPAP
  - Inspiratory time: The amount of time (in seconds) spent in each inspiration (may be minimum or maximum, depending on machine and mode)
  - Exhalation relief: Some models have this option, where the pressure drops a bit at the end of an exhalation, making it easier to breathe out against this lower pressure, adjusted for comfort.
  - Triggering: The amount of change in flow or pressure needed to be generated by the patient to trigger the IPAP
  - Mode: Some additional BiPAP modes are used in special circumstances. These include autotitrating BiPAP for OSA, average volume-assured pressure support for periodic hypoventilation, and adaptive servo-ventilation for breathing pattern disorders, such as Cheyne-Stokes breathing and complex sleep apnea.

Interfaces

- BiPAP is generally delivered with either a nasal mask or a full-face mask that covers the nose and mouth (see Figures 114-1 and 114-2 in Chapter 114, Continuous Positive Airway Pressure). Other options include a total face mask (which covers the entire face) and nasal pillows.

Adverse Effects

The potential adverse effects of BiPAP are the same as those for CPAP (see Table 114-1 in Chapter 114, Continuous Positive Airway Pressure).

Contraindications

- Respiratory arrest
- Cardiovascular instability
  - Cardiac arrest
  - Hypotension
  - Uncontrolled arrhythmias
- Multiorgan system failure
- Somnolence, impaired mental status, uncooperative patient
- Severe upper gastrointestinal bleeding; frequent vomiting
- High risk for aspiration; inability to clear respiratory secretions
- Recent upper gastroesophageal injury
- Recent facial surgery, trauma, or deformity
- Unable to fit mask
- Undrained pneumothorax

When to Refer

- Given the complexities of managing the device and underlying medical issues, patients who require the use of BiPAP should be referred to a pediatric pulmonologist or a sleep medicine specialist.

Resources for Families

- CPAP: Overview (American Academy of Sleep Medicine). www.sleepeducation.org/essentials-in-sleep/cpap
- Sleep Apnea and Your Child (American Academy of Pediatrics). patiented.solutions.aap.org/handout.aspx?resultClick=1&gbosid=156547

Clinical Pearls

- BiPAP is an effective form of therapy for children with a wide variety of disorders that cause airway obstruction.
- There are many barriers to adherence and effective use of BiPAP.
- It is strongly suggested that a sleep medicine specialist or pulmonologist be closely involved with the initiation and management of BiPAP therapy, because there may be a lot of trial and error involved in finding the optimal interface and difficulties with adherence.
- When BiPAP is used to treat OSA, the general concept is to set the EPAP at a level that eliminates obstructive apneas and the IPAP at a level that eliminates obstructive hypopneas, desaturations, and snoring.
- When used to treat hypoventilation, the general concept is that minute ventilation will correlate with the pressure difference between the IPAP and EPAP (the larger the difference, the larger the tidal volume of each breath) and the inspiratory rate (for which a minimum can be set).

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Chapter 116

Home Mechanical Ventilation

Howard B. Panitch, MD

Introduction

- Home mechanical ventilation (HMV) is used to support patients with chronic respiratory failure (CRF).
- The aim of HMV is to increase quality of life, reduce morbidity and mortality, and reduce health care costs (Box 116-1).
- The demographics of children receiving HMV have evolved since its introduction with the polio epidemics of the 1940s and 1950s, reflecting both the diseases that lead to CRF and the attitudes toward providing ventilatory support to children with chronic progressive conditions like Duchenne muscular dystrophy and spinal muscular atrophy.
- The number of children who receive HMV continues to increase, with estimates in 2011–2012 being 4.2–6.7 per 100,000 children <18 years of age.
- Methods of support have also shifted, with an increasing number of children receiving noninvasive ventilation versus ventilation via tracheostomy.

Box 116-1. Goals of Home Mechanical Ventilation

- **Extend life and enhance its quality**
- **Reduce morbidity**
- **Improve physiological function**
- **Achieve normal growth and development whenever possible**
- **Reduce health care costs**

Pathophysiology of CRF

- *CRF* is defined as the need for ≥4 hours per day of mechanical ventilatory support for ≥1 month, despite efforts to wean the patient from support.
- CRF can result from inadequacy of the respiratory pump, including the respiratory muscles, rib cage, and abdominal wall; abnormalities in the respiratory drive; extrathoracic and central airway lesions; and pulmonary parenchymal and vascular lesions (Box 116-2).

Box 116-2. Conditions That Necessitate Chronic Mechanical Ventilation

- Respiratory pump disorders
  - —Neuromuscular and central nervous system conditions
    - Myopathies
    - Spinal cord injuries
    - Encephalopathies
    - Botulism
    - Metabolic disorders
  - —Thoracic insufficiency syndrome
    - Chest wall malformations
    - Kyphoscoliosis
- Abnormalities of the respiratory drive
  - —Congenital central hypoventilation syndrome
  - —Brainstem lesions
- Extrathoracic and central airway lesions
  - —Upper-airway obstruction
    - Laryngomalacia
    - Craniofacial abnormalities
  - —Tracheobronchomalacia
- Pulmonary parenchymal and vascular lesions
  - —Bronchopulmonary dysplasia
  - —Chronic aspiration
  - —Interstitial lung disease
  - —Congenital heart disease
  - —Congenital abnormalities
    - Diaphragmatic hernia
    - Pulmonary hypoplasia
    - Tracheoesophageal fistula
  - —Bronchiectasis

- Pump failure results in hypercapnia, while parenchymal disease causes hypoxemia.
- Suitability for HMV is more a function of the degree of medical stability and the extent of support available than the underlying cause of the CRF.

Clinical Features of CRF

- CRF can arise from an acute illness from which the child does not completely recover or a gradual progression of a chronic disease, such as cystic fibrosis or neuromuscular disease.
- CRF can progress in a stereotypical way in children with neuromuscular disease, beginning with sleep arousal and fragmentation, followed by sleep hypoventilation and, ultimately, diurnal respiratory failure.

- In children with chronic respiratory diseases, CRF can be exacerbated by acute viral illness, uncontrolled bronchospasm, or aggressive weaning from the ventilator.
- Inadequate respiratory support can result in growth and developmental delay or failure.
- Episodic or chronic hypoxemia from inadequate support can also lead to pulmonary hypertension, cor pulmonale, and right-sided heart failure.
- Infants and young children who require >16 hours per day of ventilatory support usually undergo tracheostomy placement; older children can be supported with noninvasive ventilation, even when they require support 24 hours per day.

Indications and Eligibility

- Suitability for HMV requires medical stability, caregiver support, an adequate home environment, commitment by third-party payers to support the endeavor, and a medical team to provide necessary care and guidance (Box 116-3).
- Two adults must agree to learn all aspects of the child's care.
- Health care professionals must be identified, including a primary care physician, a skilled nursing agency, a durable medical equipment (DME) company, and a local ambulance service.
- If the child lives a distance from the tertiary care center, an emergency care facility should also be identified if stabilization of the child may be necessary.
- The home is assessed by the DME company to determine whether there is adequate space and electrical service for all HMV equipment and accessories.

Management

- Before discharge, negotiations with the insurance company, state Medicaid, or model waiver programs must ensure payment for durable and disposable equipment and establish hours of skilled nursing care and other therapies and services.
- Skilled nursing care should be arranged for any infant or child *(a)* who would experience life-threatening respiratory compromise if the ventilator interface became displaced, disconnected, or obstructed by secretions and *(b)* who could not correct the problem without assistance.
- The amount of nursing care will vary from 8 to 24 hours per day on the basis of the complexity of the child's condition and other comorbidities, the demands on nonskilled caregivers (employment, other children at home), family preference, and point in the child's overall course (having nursing care 24 hours per day is reasonable for the first 1–2 weeks after initial hospital discharge to ease the transition to the home, with a reduction in nursing care hours thereafter).

Box 116-3. Patient Eligibility

- Medical stability
  - —Clinical
    - Positive trend on the growth curve
    - Stamina for periods of play
    - No frequent fevers or infections
  - —Physiological
    - Stable airway
    - Pa_{O_2} ≥60 mm Hg in F_{IO_2} ≤0.4
    - P_{CO_2} <50 mm Hg
    - Frequent ventilator changes not required
    - Individualization: Many of these guidelines can be modified to facilitate the discharge of a child who wishes to go home and receive hospice care, for example.
- Social, environmental
  - —Family members willing to
    - Help care for the patient
    - Be included in the planning and selection of professional caregivers
    - Commit to the plan
  - —Home environment
    - Enough space
    - Access (eg, ramps for children confined to wheelchairs)
    - Adequate heat, electricity, and water
    - Working telephone
    - Area resources (emergency room, ambulance service)
- Reimbursement by third-party payers, Medicaid, and Model Waiver Programs to fund the following:
  - —Durable medical equipment
  - —Disposable supplies
  - —Nursing salaries
  - —Occupational, physical, speech, feeding, and developmental therapists
- Organizational: home ventilation team
  - —Members
    - Medical, nursing, respiratory therapy, social services, nutrition, support services
  - —Functions
    - Coordinate care with community medical caregivers
    - Review treatment plans
    - Advocate for patient and family
    - Provide medical direction
    - Guarantee access to tertiary care

F_{IO_2}, forced expiratory volume in 1 second; Pa_{CO_2}, partial pressure of carbon dioxide, arterial; Pa_{O_2}, arterial oxygen pressure.

- A comprehensive set of medical orders must be established and periodically reviewed.
- Care of the ventilator-dependent child is best accomplished by a team of caregivers (see Box 116-3).
- It is strongly suggested that children treated with HMV be followed up by a comprehensive medical home and comanaged by a respiratory subspecialist and a primary care provider.
- Medical tasks can be divided among members of the medical team (Box 116-4), and decisions should be made by using a family-centered care approach.
- Routine follow-up care is accomplished primarily through home nursing and respiratory assessments with frequent telephone communication, along with ongoing interventions by speech, occupational, physical, and developmental therapists (Box 116-5).
- The frequency of routine office visits, home visits, or scheduled hospital admissions for special testing will depend on the child's underlying disease, the severity of illness, and the trajectory of the child's course regarding weaning.
- Newer ventilators can deliver support in either pressure control or volume control modes: There are no data in general to suggest superiority of 1 mode over the other.
- Pressure control mode may perform better in the presence of a large leak around the tracheostomy tube.
- When selecting the model of ventilator to be used, the needs of the patient should be taken into account (the need for continuous flow, the ability to provide pressure support ventilation, trigger and cycle sensitivities, the degree of portability), as well as the familiarity of the home care providers (nurses and respiratory therapists) with the equipment (Box 116-6).

Box 116-4. Physician Services for Ventilator-Assisted Children

- **Acute and chronic ventilator management**
- **General health**
  - **Immunizations**
  - **Developmental assessment**
  - **Growth and nutritional assessments**
- **Acute illnesses**
- **Care plan oversight**
- **Subspecialty care**
- **Family support**
- **Advocacy**

Box 116-5. Medical Interventions Performed in the Home

- Patient monitoring and assessments
  - —Capnography
  - —Oximetry
  - —Physical assessments
  - —Laboratory evaluation comprising
    - Sputum culture and Gram stain
    - Serum chemistry values
    - Blood count
    - Drug levels
- Adjustments of the care plan
  - —Weaning trials
  - —Changes in medications or nutrition
- Acute interventions during illness
  - —Oral or inhaled antibiotics
  - —Parenteral (intramuscular) diuretics
  - —Temporary increase in ventilator support

Box 116-6. Basic Equipment and Supplies for Invasive Mechanical Ventilation

- Two ventilators, heaters, and circuits
- Oxygen delivery system
- Monitors (pulse oximeter, capnograph, occasionally a cardio-respiratory monitor)
- Portable and stationary suction machines
- External battery
- Gas-powered generator (if frequent power outages occur)
- Tracheostomy tubes
- Suction catheters
- Speaking valves as tolerated
- Gastrostomy tubes
- Syringes
- Phlebotomy equipment (if home nursing agency personnel will draw blood)
- Lukens traps

- Some ventilators can be used in both invasive and noninvasive modes; some bilevel positive pressure (BiPAP) generators or "respiratory assist devices" are also used invasively, although they may not have the same alarms and modes of support that ventilators do.
- Most BiPAP machines do not have an internal battery, and only a few can be used with external batteries; all portable ventilators have an internal battery and can be used with portable batteries.
- Most BiPAP generators and some portable ventilators record interactions with patients, including tidal volume, minute ventilation, percentage of leak, percentage of spontaneous breaths, and pressures achieved; these can be downloaded via modem or memory card for review.
- A second (backup) ventilator should be provided to any child who cannot tolerate being off of ventilatory support for ≥4 hours per day or who lives >1 hour away from the DME company.
- Pulse oximetry is the preferred monitoring device beyond intrinsic ventilator alarms.
- Ventilator and external monitor alarms alone should not be relied on to identify problems: The best surveillance is an alert, well-trained adult directly observing the child.
- Weaning from ventilatory support is not a goal but is rather a natural outcome of growth and development.

Complications

- Several problems and complications can arise that are related to tracheostomies (Box 116-7).
- "Tracheitis" can be treated with oral and/or inhaled antibiotics.
- If the child's clinical course is not following an expected trajectory, consider microaspiration, uncontrolled bronchospasm, or episodes of hypoxemia.

Box 116-7. Complications Related to Tracheostomy

- **Inadvertent displacement or obstruction**
- **Increased risk of lower respiratory infections**
- **Increased risk of aspiration**
- **Swallowing dysfunction**
- **Granuloma formation**
- **False tract**
- **Acquired tracheal stenosis**
- **Suprastomal tracheomalacia**
- **Traumatic tracheoinnominate fistula**
- **Traumatic tracheoesophageal fistula**
- **Persistent tracheocutaneous fistula after decannulation**
- **Reduced balance**
- **Reduced upper-extremity strength**

- Children with neuromuscular weakness and ineffective cough will require a regimen of airway clearance to prevent recurrent episodes of atelectasis or pneumonia.
- In addition to care related to CRF, the child's underlying condition that led to CRF will require appropriate treatment.

Expected Outcomes/Prognosis

- Prognosis is generally good: The survival incidence from 19 single-center studies involving 621 children followed up for 4.5–25 years was 57%–100%.
- Liberation from mechanical ventilation has been reported in 30%–56% of patients.
- Outcomes are in part dependent on the underlying disease, with those having chronic lung disease or airway problems more likely to be liberated from mechanical ventilation than those with central nervous system (CNS) or neuromuscular diseases.
- Among patients with neuromuscular disease, HMV results in increased survival and decreased frequency and duration of hospital stays.
- Causes of death can be a natural progression of the underlying disease, complications related to tracheostomy, or the result of nonpulmonary comorbidities.
- The presence of a tracheostomy increases the risk of death or catastrophic CNS injury.
- Patients' self-perception of their quality of life is greater than most health care professionals' estimates.
- Care of ventilator-dependent children at home is stressful for families, and caregiver stress increases over time.

Comanagement

- A recent care statement from the American Thoracic Society endorses a model of comanagement between the primary care physician and a physician who specializes in respiratory care (Box 116-8).
- The role of the primary care physician will vary, depending on prior training, level of comfort, regional customs, proximity of the patient to the tertiary care center, and influence of managed care.
- A subspecialist designated to care for the ventilator-assisted child must have expertise in chronic ventilator management, be available for acute care issues and emergencies, perform periodic re-evaluations, provide subspecialty-specific care, participate in multidisciplinary conferences regarding patient care, and provide medical case management.

Box 116-8. Possible Roles in the Medical Home

Primary Care Provider	Subspecialist
General health maintenance	Chronic ventilator management
Acute illnesses	Acute ventilator management
Developmental assessments	Nutritional assessments
Family support	Subspecialty care
Immunizations	Care plan oversight
Community resources	Communication with durable medical equipment company

When to Admit

- Admission to the hospital should be considered when acute illness results in respiratory deterioration that cannot be readily corrected by making adjustments in ventilatory support or if any of the caregivers are uncomfortable with the child's status.
- Practical limitations of care delivery, including the amount of supplemental oxygen required to maintain adequate oxygen saturation at pulse oximetry during an acute illness or exhaustion of caregivers and lack of skilled nursing care, could dictate the need for hospitalization.

Resources for Families

- Aaron's Tracheostomy Page. www.tracheostomy.com
- SSI Child Disability Starter Kit (U.S. Social Security Administration). www.ssa.gov/disability/disability_starter_kits_child_eng.htm
- Disability Rights Pennsylvania. disabilityrightspa.org
- Pennsylvania Health Law Project. www.phlp.org
- Special Kids Network. www.specialkidsnetwork.org

Clinical Pearls

- The focus of HMV is to promote growth and development; weaning is not a focus but is instead a byproduct of improved respiratory health.
- With adequate caregiver training, acute illnesses can often be treated at home, and hospitalizations can be avoided.
- Clear delineation of responsibilities between primary care providers and subspecialists can enhance the delivery of services to patients.
- Respite care services for families are critical in preventing caregiver exhaustion and burnout.

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Chapter 117

Diaphragm Pacing by Phrenic Nerve Stimulation

Iris A. Perez, MD, FAAP, Sheila S. Kun, RN, BSN, MS, and Thomas G. Keens, MD, FAAP

Introduction

- Diaphragm pacing is a mode of ventilatory support in which the patient's own diaphragm acts as the respiratory pump.
- It is an alternative method of ventilating patients with congenital central hypoventilation syndrome, as well as those with high spinal cord (C1-C2) injury.
- It provides daytime ventilatory support for those who are dependent on a ventilator 24 hours a day, which allows for mobility and independence from the ventilator during the day.
- It can be the sole ventilatory support for stable patients who are ventilator dependent only during sleep, which permits tracheostomy decannulation.
- Although diaphragm pacing is only available at a few specialized centers, the primary care clinician should be aware of potential patients where pacing may be useful.

Components

- A diaphragm pacer system involves the following 4 components (Figure 117-1):
  - Electrodes that are surgically implanted bilaterally on the phrenic nerves
  - Receivers that are surgically implanted bilaterally on the abdomen or chest
  - Antennae
  - External battery-operated portable transmitter
- The external transmitter generates electric energy similar to radio frequency via an external antenna, which is placed on the skin over the receiver.
- The receiver converts the energy to electric current, which is then conducted to the phrenic nerve, stimulating diaphragm contraction.

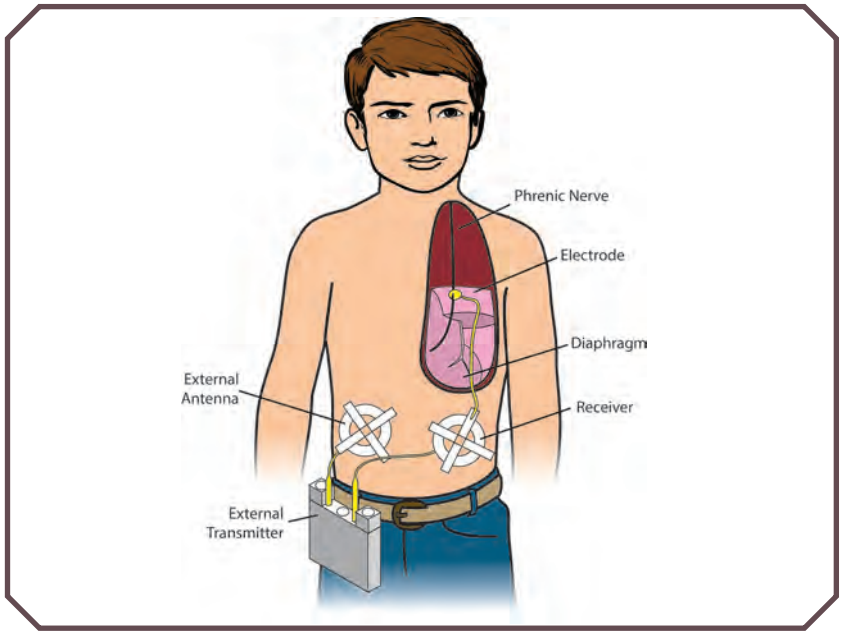

Figure 117-1. Diaphragm pacer components are shown. An electrode is implanted on the phrenic nerve, which is connected via lead wire to a receiver implanted subcutaneously in the upper abdomen, with an external transmitter connected to an external antenna taped over the receiver. Note that these components are bilateral. From Kasi A, Perez IA, Kun SS, Keens TG. Congenital central hypoventilation syndrome: diagnostic and management challenges. *Pediatric Health, Medicine, and Therapeutics.* 2016;7:99–107.

Indications and Eligibility

- Because diaphragm pacing uses the patient's own diaphragm as the ventilator pump, an ideal candidate must have intact phrenic nerves, normal diaphragm function, and little or no lung disease.
- Diaphragm pacing is contraindicated in those with phrenic nerve injury, diaphragm paralysis, obesity, and patients with conditions that require magnetic resonance imaging. Patients with a C3-C5 spinal cord injury may not be candidates if the phrenic nerve bodies have been injured.
- In obese patients, the high amount of adipose tissue increases the distance between the antenna and the receiver of the diaphragm pacer, resulting in increased variability in the signal received by the receiver.
- In 1 center, the mean age at diaphragm pacer implantation surgery is 9.6 years. For those who are dependent on a ventilator 24 hours a day, the diaphragm pacers can be considered in the toddler age range to allow for mobility.

Surgical Implantation

- Diaphragm pacers are surgically implanted on the phrenic nerves thoracoscopically.
- The pacers are tested intraoperatively, so neuromuscular blocking agents are not administered for the surgery.
- The diaphragm pacers are not used right away; therefore, the patients go back on their previous mode of ventilatory support after surgery.

Risks and Complications of Surgery

- Immediate postoperative complications after a diaphragm pacer implantation surgery are uncommon.
- The risk of atelectasis and pneumonia occurs because the lungs are collapsed during thoracoscopic implantation of the phrenic nerve electrodes. During the postoperative period, these risks can be reduced by optimizing airway clearance and upsizing the tracheostomy tube to minimize leak from the stoma and provide adequate tidal breaths.
- Most patients have the chest tubes removed at the conclusion of the surgery. However, persistent pneumothoraces that require the retention of chest tubes in the immediate postoperative period can occur in some patients.
- Patients undergoing the diaphragm pacer surgery are usually treated intraoperatively with antibiotics to decrease the risk of infection.
- The perioperative period is a vulnerable time for patients with congenital central hypoventilation syndrome (CCHS). They are extremely sensitive to the effects of central nervous system depressants and general anesthesia. When patients with CCHS receive sedating medications in the preoperative and postoperative periods, they must be connected to their ventilator.
- In 1 center, the mean hospital stay after diaphragm pacer implantation surgery is 5.7 days (maximum, 9 days), and the mean intensive care unit stay is 4.3 days (maximum, 9 days).

Initiation of Diaphragm Pacing

- At 1 center, diaphragm pacing is started 6–8 weeks after surgery to allow for healing. However, this timing may vary from center to center. Patients are admitted to the hospital to initiate pacing, where the settings are established and adjusted. Some centers may initiate pacing on an outpatient basis.
- On the night of pacing initiation, the pacers are turned on both sides, whether the patient is awake or asleep, with the goal of beginning to train the diaphragm. The patient is not receiving ventilation during diaphragm pacing.

- The patient is connected to continuous pulse oximetry and end-tidal CO_2 monitoring; the diaphragm pacer settings are adjusted to maintain oxygen saturation at pulse oximetry (Spo_2) in the desired range—for example, Spo_2 ≥95% and pulse oximetry and end-tidal CO_2 <40 mm Hg (the target range may vary among centers).
- Pacing is initially used for only 1–1½ hours during the night. After this time period, the patient goes back on the usual ventilatory support.
- The time on pacers is gradually increased by 30–60 minutes each week to train the diaphragm and prevent fatigue. This is usually done at home.
- In general, full pacing during sleep requires 2–3 months to establish. Once on full-night pacing with the tracheostomy open, if the patient does well for 3 months, a plan for decannulation can be considered.

Diaphragm Pacing Without Tracheostomy

- With proper patient selection, diaphragm pacing without tracheostomy can be achieved in patients with CCHS who require ventilatory support only during sleep. Sample criteria for diaphragm pacing without tracheostomy are listed in Box 117-1.
- A suggested protocol for tracheostomy decannulation is outlined in Figure 117-2 and Box 117-2.

Troubleshooting for Patients and Families

- If the diaphragm pacer malfunctions suddenly, this is most commonly unilateral.
- Most sudden unilateral pacer malfunction is caused by an external equipment problem.
- Be sure the battery on the nonworking side is good (this is shown by the battery power indicator on the pacer transmitter); if in doubt, change the batteries.

Box 117-1. Criteria for Pacing Without Tracheostomy

CCHS necessitates ventilatory support only during sleep.

The patient does not require daytime naps.

A stable medical course requires infrequent hospitalizations.

The patient does not require full-time ventilatory support during minor, acute respiratory illnesses.

The patient accepts that diaphragm pacing is not as secure a method of ventilation, and intubation may be required for serious illness.

CCHS, congenital central hypoventilation syndrome. From Diep B, Wang A, Kun S, et al. Diaphragm pacing without tracheostomy in congenital central hypoventilation syndrome patients. *Respiration.* 2015;89(6):534–538.

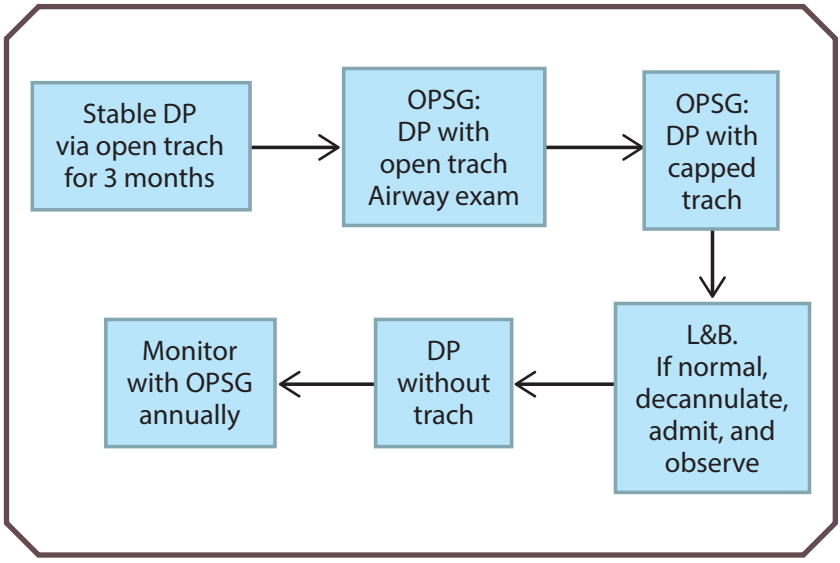

Figure 117-2. Protocol for tracheostomy decannulation at Children's Hospital Los Angeles. DP = diaphragm pacing, L&B = laryngoscopy and bronchoscopy, OPSG = overnight polysomnography.

Box 117-2. Protocol for Decannulation

Establish adequate ventilation with diaphragm pacing by using open tracheostomy for ≥3 months.

Downsize the tracheostomy.

Conduct an overnight sleep study with diaphragm pacing and capped tracheostomy tube.

If SpO_2 <95% and pulse oximetry and end-tidal CO_2 <40 mm Hg, consider administering supplemental O_2 via nasal cannula.

If OSA is present, consider decreasing the tidal volume in the diaphragm, pacer settings, tonsillectomy and/or adenoidectomy, and treatment of nasal allergies; repeat the sleep study.

If SpO_2 >95% and pulse oximetry and end-tidal CO_2 <40 mm Hg, the airway should be evaluated by an otolaryngologist; if it is normal, proceed to decannulation.

Observe the patient overnight in the hospital after decannulation.

OSA, obstructive sleep apnea; Spo_2, oxygen saturation at pulse oximetry. From Diep B, Wang A, Kun S, et al. Diaphragm pacing without tracheostomy in congenital central hypoventilation syndrome patients. *Respiration.* 2015;89(6):534-538.

- Be sure the antenna is centered over the receiver. This may be more difficult than it seems, especially in patients who have gained weight.
- Check the antenna to be sure there are no obvious breaks in the wire.
- Stimulate the nonworking side with the antenna from the working side. Reset the tidal volume setting to the value on the nonworking side. If there is a contraction, the problem is probably with the antenna. Change to a new antenna and try again.
- If the new antenna does not work with the original nonworking side, there may be a problem with the transmitter, which will require further investigation.
- If there is no contraction with the confirmed functioning side, try to turn up the tidal volume setting until the patient feels a contraction or pain in the shoulder or near the receiver site. If this does not solve the problem, there may be a problem with internal components that will require further investigation.
- Be sure that patients can be adequately ventilated with one-sided pacing by using a pulse oximeter and/or end-tidal partial pressure of carbon dioxide monitor. If they can, then further evaluation can wait. If they cannot, then they should go to a hospital to get some other form of ventilatory support.

Resources for Families

- Diaphragm Pacing by Phrenic Nerve Stimulation (American Thoracic Society). www.thoracic.org/patients/patient-resources/resources/diaphragm-pacing-online.pdf
- Introduction to Diaphragm Pacing (Children's Hospital Los Angeles). www.youtube.com/watch?v=ZbhPbcd4yrI
- Diaphragm Pacing Troubleshooting Tips (Children's Hospital of Los Angeles). www.youtube.com/watch?v=gI174Yv2yUs

Clinical Pearls

- Diaphragm pacing remains rare, but its use is increasing.
- Currently, only a few centers have substantial experience with pacing, and it is strongly suggested that primary care providers consult with such centers if their patient is contemplating this technology.
- Parents of children with CCHS are highly motivated to move toward diaphragm pacing in the hopes of removing their child's tracheostomy. However, there is no guarantee that decannulation will be successful.
- The greatest challenge is the development of obstructive apnea or upper-airway obstruction, particularly during sleep.

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