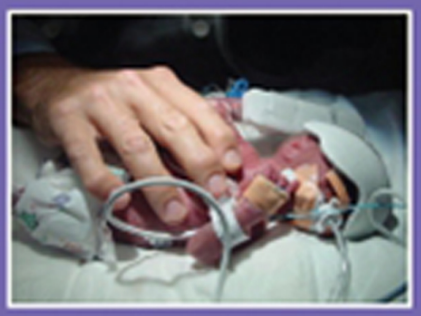
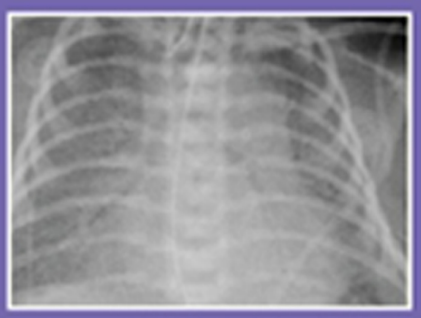
NEONATAL and PEDIATRIC RESPIRATORY CARE

FIFTH EDITION





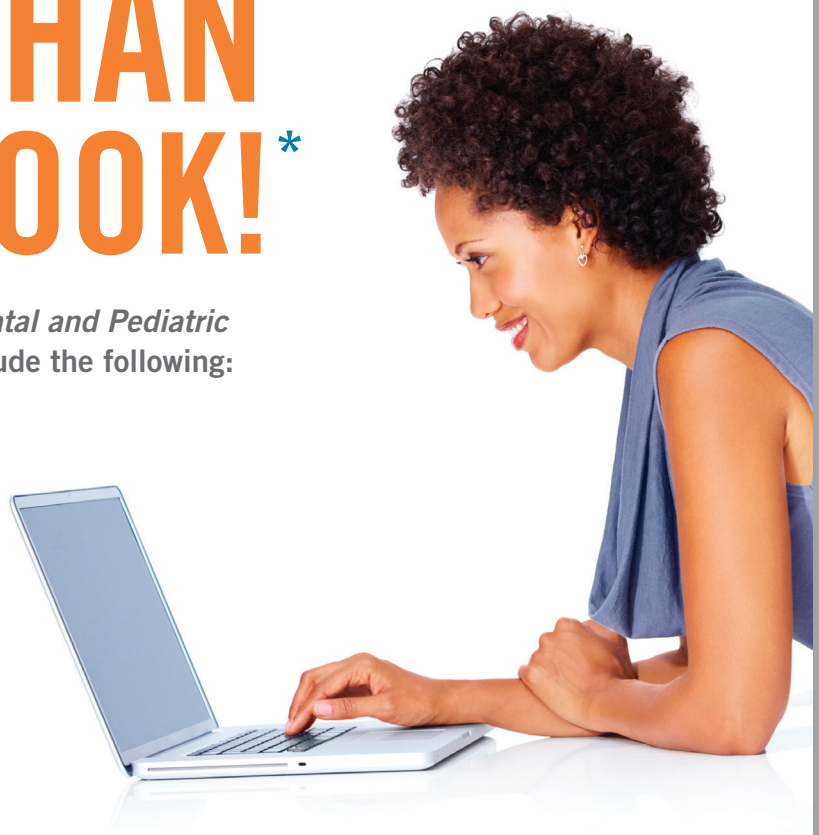
BRIAN K. WALSH

ELSEVIER

evolve

ELSEVIER

YOU'VE JUST PURCHASED MORE THAN A TEXTBOOK!*



Evolve Student Resources for *Neonatal and Pediatric Respiratory Care, Fifth Edition,* include the following:

- Case Studies
- Answers to Assessment Questions and Case Studies
- NBRC Neonatal/Pediatric Specialty (NPS) Exam Correlation Guide

Activate the complete learning experience that comes with each *NEW* textbook purchase by registering with your scratch-off access code at

http://evolve.elsevier.com/Walsh/

If you purchased a used book and the scratch-off code at right has already been revealed, the code may have been used and cannot be re-used for registration. To purchase a new code to access these valuable study resources, simply follow the link above.

Place Peel Off Sticker Here

REGISTER TODAY!

You can now purchase Elsevier products on Evolve!
Go to evolve.elsevier.com/html/shop-promo.html to search and browse for products.

* Evolve Student Resources are provided free with each *NEW* book purchase only.

2015v1.0

NEONATAL and PEDIATRIC RESPIRATORY CARE

FIFTH EDITION

BRIAN K. WALSH, PhD, RRT, RRT-NPS, FAARC
Professor, Health Professions
Director, Respiratory Therapy
School of Health Sciences
Liberty University
Lynchburg, Virginia

ELSEVIER

ELSEVIER

3251 Riverport Lane
St. Louis, Missouri 63043

NEONATAL AND PEDIATRIC RESPIRATORY CARE, FIFTH EDITION

ISBN: 978-0-323-47947-9

Notices

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary. Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility. With respect to any drug or pharmaceutical products identified, readers are advised to check the most current information provided (i) on procedures featured or (ii) by the manufacturer of each product to be administered, to verify the recommended dose or formula, the method and duration of administration, and contraindications. It is the responsibility of practitioners, relying on their own experience and knowledge of their patients, to make diagnoses, to determine dosages and the best treatment for each individual patient, and to take all appropriate safety precautions. To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

International Standard Book Number: 978-0-323-47947-9

Director, Content Development: Laurie Gower
Senior Content Strategist: Yvonne Alexopoulos
Publishing Services Manager: Julie Eddy
Senior Project Manager: Richard Barber
Design Direction: Bridget Hoette

Printed in Canada

Last digit is the print number: 9 8 7 6 5 4 3 2 1

To the students and future or current neonatal and pediatric respiratory care providers, may this book add knowledge to your wisdom. To the contributors and reviewers who continue to make this book better than the last edition, I could not have done it without you. Finally, to my children, Keagan and Trey, who continue to impress me and challenge me to be a better father.

Preface

Since the first edition was published in 1995, *Perinatal and Pediatric Respiratory Care* has been a foundational neonatal and pediatric respiratory care textbook. We are proud to continue that tradition with the fifth edition.

The fundamental role of the pediatric respiratory therapist (RT) continues to be redefined daily. RTs specializing in the care of children are an integral part of an autonomous health care team. As our health care system changes, these individuals will need to be highly professional, have critical thinking skills, and be more involved in critical roles as experts in critical and acute care, extracorporeal membrane oxygenation (ECMO), air and ground transport, discharge coordination, home care, education, healthcare quality, and research. All roles that encompass the respiratory therapy of children require an individual who remains current with the changing face of this wonderful and exciting profession. The proliferation of new surgical interventions, discoveries in applied translational and clinical research, devices and mechanical ventilator technologies, and strategies that are currently being implemented into practice require dynamic, self-driven clinicians, and lifelong learners who are dedicated to providing the highest quality care possible. Increases in premature and multiple births, as well as paradigm shifts in strategies focused at reducing hospital costs and healthcare spending, have led to the growth and development of many neonatal special care or intensive care units across the world. RTs working outside of free-standing children's and university hospitals, many of whom have typically cared for adults, are now often called to support newborns at high-risk deliveries or to manage pediatric patients in respiratory distress. With advance practice roles becoming the norm, practitioners are faced with more challenging decisions that require collaboration, teamwork, and sharp critical thinking skills. These attributes, coupled with a better understanding of evidence-based practice and technologically advanced equipment, will positively affect patient outcomes and raise future ethical debates.

We believe that *Neonatal and Pediatric Respiratory Care,* fifth edition, will provide you with the tools and knowledge to improve the respiratory therapy of neonates, infants, and children regardless of your education, experience, or the environment in which you work.

AUDIENCE

Although principally designed as a textbook for the respiratory therapy student and practitioners new to the field, this book is also intended to be detailed enough to serve as a current desktop reference for the experienced practitioner engaged in mastering the practice of respiratory care in infants and children, regardless of professional discipline. This textbook may also serve as a study guide for the National Board for Respiratory Care's (NBRC) specialty examination concerning the respiratory care of neonatal and pediatric patients. For convenience, the Evolve Resources for this edition include a correlation guide for the NBRC's Neonatal/Pediatric Respiratory Care Specialty Examination.

NEW TO THIS EDITION

The publisher and editors of this textbook have taken a more focused approach to satisfying some of the essential features that are needed to help guide educators and students at the collegiate level. This fifth edition introduces the following:

- Revisions to all the chapters reflect the latest updates in scientific literature.
- Measurable learning objectives, key terms, and key points are included in each chapter. The objectives are designed to succinctly guide the student to key areas of importance and mastery of chapter content.
- Each chapter concludes with a series of multiple-choice assessment questions. Answers can be found on the Evolve website at http://evolve.elsevier.com/Walsh/neonatal.

LEARNING AIDS

EVOLVE RESOURCES—http://evolve.elsevier.com/walsh/neonatal

Evolve is an interactive learning environment designed to work in conjunction with this text. Instructors may use Evolve to provide an Internet-based course component that reinforces and expands the concepts presented in class. Evolve may be used to publish the class syllabus, outlines, and lecture notes; set up virtual office hours and e-mail communication; share important dates and information through the online class calendar; and encourage student participation through chat rooms and discussion boards.

Evolve allows instructors to post exams and manage their grade books online.

For the Instructor

For the instructor, Evolve offers valuable resources to help them prepare their courses, including the following:

- PowerPoint lecture for each chapter
- A test bank of approximately 800 questions in ExamView
- An image collection of the figures from the book available in PowerPoint presentations for each chapter
- National Board for Respiratory Care (NBRC) Neonatal/Pediatric Respiratory Care Specialty (NPS) examination correlation guide

For Students

For students, Evolve offers valuable resources to help them succeed in their courses, including the following:

- Answers to Assessment Questions and Case Studies
- Case Studies
- NBRC Neonatal/Pediatric Respiratory Care Specialty (NPS) examination correlation guide

For more information, visit http://evolve.elsevier.com/Walsh/neonatal or contact an Elsevier sales representative.

ACKNOWLEDGMENTS

I thank all the contributors to this edition of *Neonatal and Pediatric Respiratory Care*. It is their work that yet again laid the foundation for this edition. I thank them for their patience and the professional quality of each chapter's content. I also thank Sandra Hinski for her work writing the test bank and PowerPoint presentations for the accompanying Evolve instructor resources.

I thank the developmental publishing staff, especially Senior Content Development Manager, Ellen Wurm-Cutter, who tirelessly attempted to keep the contributors and me in line and on target for publication. I continue to be awed by her wonderful attitude and never-ending supply of positive instruction, despite many delays and changes along this journey. I also thank Yvonne Alexopoulos, Senior Content Strategist, for her calm patience and attention to detail.

Last, but by no means least, I especially thank my family and friends whom I largely ignored during the development of this edition.

Brian K. Walsh

Contributors

Arzu Ari, PhD, RRT, PT, CPFT, FAARC
Professor, Department of Respiratory Care and Texas State Sleep Center
Texas State University
Round Rock, Texas

Leo Andrew Benedict, MD
Research Fellow, Surgery
Children's Mercy Hospital
Kansas City, Missouri

Robert Chatburn, MHHS, RRT-NPS, FAARC
Clinical Research Manager, Respiratory Care
Cleveland Clinic
Professor, Department of Medicine
Lerner College of Medicine of Case Western Reserve University
Cleveland, Ohio

James B. Fink, PhD
Adjunct Professor, Respiratory Therapy
Rush Medical University
Chicago, Illinois
Chief Science Officer
Aerogen Pharma Corporation
San Mateo, California

Leslie Mariel Gonzalez, BSRC, RRT-NPS
ECMO and Advanced Technologies Specialist
ECMO and Advanced Technologies
Neonatal Transport Team Respiratory Therapist
Neonatal Intensive Care Unit
University Hospital
Registered Respiratory Therapist, Respiratory Care
University Health Systems
San Antonio, Texas

Benjamin Hamar, MD
Maternal-Fetal Medicine
Beth Israel-Deaconess Medical Center
Boston, Massachusetts

Anne Hansen, MD, MPH
Associate Professor of Pediatrics
Harvard Medical School
Medical Director, NICU
Boston Children's Hospital
Boston, Massachusetts

Olivia Lund Hoffman, MD
Clinical Fellow, Pediatric Critical Care Medicine
Department of Anesthesiology, Critical Care and Pain Medicine, Division of Critical Care Medicine
Boston Children's Hospital
Boston, Massachusetts

Katrina Hynes, MHA, RRT, RPFT
Supervisor, Pulmonary Function Laboratory
Mayo Clinic
Rochester, Minnesota

Hussam Sameer Inany, MD
Clinical Fellow, Pulmonary and Respiratory Diseases
Boston Children's Hospital
Harvard Medical School
Boston, Massachusetts

Robert L. Joyner Jr., PhD, RRT, RRT-ACCS, FAARC
Program Director, Respiratory Therapy Program
Salisbury University
Salisbury, Maryland

David Kaufman, MD
Professor, Pediatrics
University of Virginia School of Medicine
Charlottesville, Virginia

John Nagi Kheir, MD
Assistant Professor of Pediatrics
Harvard Medical School
Staff Physician, Cardiac Intensive Care Unit
Department of Cardiology
Boston Children's Hospital
Boston, Massachusetts

Nina Kowalczyk, PhD, RT(R)(CT)(QM), FASRT
Wexner Medical Center
The Ohio State University
Columbus, Ohio

Oren Kupfer, MD
Assistant Professor, Pediatrics
University of Colorado School of Medicine
Anschutz Medical Campus
Pediatric Pulmonologist
Children's Hospital Colorado
Aurora, Colorado

Michael Le, BS, RRT
ECMO Specialist, Respiratory Care / ECMO Program
Boston Children's Hospital
Boston, Massachusetts

Jonathan Levin, MD
Fellow, Newborn Medicine
Boston Children's Hospital
Boston, Massachusetts

Liza Li, PharmD, BCPS
MSICU Clinical Pharmacist
Boston Children's Hospital
Harvard Medical School
Boston, Massachusetts

Arin Lindquist Madenci, MD, MPH
Department of Surgery
Boston Children's Hospital
Department of Surgery
Brigham and Women's Hospital
Boston, Massachusetts

Thomas Mancuso, MD, FAAP
Associate Professor of Anaesthesia
Harvard Medical School
Senior Associate in Anesthesiology
Critical Care Medicine and Pain Management
Boston Children's Hospital
Boston, Massachusetts

Carl Mottram, RRT, RPFT, FAARC
Technical Director, Pulmonary Function Laboratory
Associate Professor of Medicine
Mayo Clinic
Rochester, Minnesota

Asha Gopalan Nair, MD
Instructor of Pediatrics
Harvard Medical School
Assistant in Cardiology
Boston Children's Hospital
Boston, Massachusetts

Linda Allen Napoli, MBA, RRT-NPS, RPFT
Senior Director
Respiratory Care, Neurodiagnostics, Pulmonary Function and Sleep Labs, ECMO, Apnea Monitoring
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Lauren Perlman, BS, RRT
C.A.P.E. and Home Ventilation Program
Respiratory Care Continuing Care Coordinator
Department of Anesthesia
Boston Children's Hospital
Boston, Massachusetts

Jordan Sage Rettig, MD
Department of Anesthesiology, Division of Critical Care Medicine
Boston Children's Hospital
Harvard Medical School
Boston, Massachusetts

Samuel Rice-Townsend, MD
Attending Surgeon, Department of Surgery
Boston Children's Hospital
Assistant Professor of Surgery
Harvard Medical School
Boston, Massachusetts

Craig D. Smallwood, PhD, RRT
Research Associate in Anesthesia
Harvard Medical School
Department of Anesthesia, Division of Critical Care Medicine
Boston Children's Hospital
Boston, Massachusetts

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

Lisa Tyler, MS, RRT-NPS, RRT-ACCS, RPFT, AE-C
Manager, Respiratory Care
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Karen Watters, MB, BCh, BAO, MPH
Attending in Otolaryngology
Otolaryngology and Communication Enhancement
Boston Children's Hospital
Assistant Professor, Otology and Laryngology
Harvard Medical School
Boston, Massachusetts

Christopher B. Weldon, MD, PhD
Assistant in Surgery, Department of Pediatric Surgery
Boston Children's Hospital
Assistant Professor of Surgery, Department of Surgery
Harvard Medical School
Boston, Massachusetts

Craig Wheeler, MS, RRT-NPS
Supervisor, Department of Respiratory Care/ECMO
Boston Children's Hospital
Boston, Massachusetts

Jessica White, PharmD
Boston Children's Hospital
Harvard Medical School
Boston, Massachusetts

Santina Zanelli, MD
Associate Professor, Pediatrics
University of Virginia
Charlottesville, Virginia

Reviewers

Catherine Bitsche, EdS, RRT-NPS, RCP
Program Director, Respiratory Therapy Program
Catawba Valley Community College
Hickory, North Carolina

Margaret-Ann Carno, PhD, MBA, MJ, CPNP, DABSM, FAAN
Professor, Clinical Nursing and Pediatrics,
School of Nursing
University of Rochester
Rochester, New York

Amy Ceconi, PhD, RRT, RPFT, NPS
Program Director, Respiratory Care Program
Division of Health Professions
Bergen Community College
Paramus, New Jersey

Bernard Lee, PharmD, BCPS, BCPPS
Pediatric Clinical Pharmacist, Pharmacy
Johns Hopkins All Children's Hospital
St. Petersburg, Florida

Diane Oldfather, MHEd, RRT
Registered Respiratory Therapist/Educator
Cardiopulmonary
Phelps County Regional Medical Center
Rolla, Missouri

Contents

This page intentionally left blank

Fetal Lung Development

1

Robert L. Joyner, Jr.

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. List the five stages of fetal lung development and the gestational age at which they occur.
2. Explain the key steps of each stage of fetal development.
3. Identify the gestational age during which extrauterine viability occurs, and explain why it cannot occur earlier.
4. Identify several conditions that lead to abnormal lung development and injury.
5. Discuss the role of the type II pneumocyte in surfactant production.
6. Discuss the various physiologic functions of surfactant.
7. Explain how fetal lung liquid differs from amniotic fluid and describe how it is cleared during and after labor.

Key Terms

fetal lung fluid
lamellar bodies
oligohydramnios
primary germ layers
pseudoglandular
pulmonary acinar units
pulmonary hypoplasia
saccules
secondary crests
surfactant

At birth, the lungs become the source for gas exchange between the external environment and the blood. External respiration through the lungs becomes essential to the survival of the newborn. Fetal lung development is progressive, and at birth the lungs have reached only that degree of morphologic, physiologic, and biochemical maturity required for basic functioning to support extrauterine life. In other words, lung development is not complete at birth: The newborn lung continues to undergo differentiation and growth well beyond birth.[1,2] Fetal lung development is not considered complete until the alveoli possess an adequate surface area for gas exchange. The pulmonary vascular system must also have sufficient capacity to transport an adequate amount of blood through the lungs for carbon dioxide and oxygen exchange. The alveoli need to be structurally and functionally stable and sufficiently elastic and resilient to endure the cyclical stretching associated with tidal breathing and crying.

What is known about the normal development of the human lung originates from Reid's anatomic description of the developing human lung.[3] From this description the following can be ascertained:

- The bronchial tree develops by week 16 of intrauterine life.
- After birth the alveoli develop in increasing numbers until the age of 8 years and increase in size until growth of the chest wall is finished.
- Preacinar arteries and veins develop after the airway has been established; intraacinar vessels develop after the alveoli are generated.

Although the criteria listed here are generally agreed on, research interest in the mechanics of fetal lung development continues to be kindled by the desire to prevent acute and chronic lung injury in premature infants. This interest is currently centered on the biochemical and genetic mechanisms of cellular repair in the immature lung that permit recovery of injured lungs in premature infants. Another topic of focus concerns the complex process of geometric growth and alveolar development.[4-6]

As stated earlier, birth does not signal the end of lung development. A remarkably complex process of growth occurs after birth, accommodating differing proportions of airway size, alveolar size, and surface area. A full-term infant, with an estimated 50 million alveoli, has the potential to add another 250 million alveoli and increase its total alveolar surface area from approximately 3 to 70 m^2 at maturity. More than 40 different cell types, with many different functions, are found in the lung. Adding to this complexity are growth factors, which are responsible for normal cell and structural development and affect various aspects of prenatal and postnatal lung function, growth, and structure.

PHASES OF LUNG DEVELOPMENT

Humans experience five well-recognized phases of lung development: embryonal, pseudoglandular, canalicular, saccular, and alveolar (Table 1-1).[7-9] What follows is a description and important milestones of progression for each phase of lung development.

EMBRYONAL PHASE

The embryonal phase includes primitive lung development and is generally regarded to encompass the first 2 months of gestation. The lung begins to emerge as a bud from the pharynx 26 days after conception (Figure 1-1). This lung bud elongates and forms two bronchial buds and the trachea, which then separate from the esophagus through the development of the tracheoesophageal septum. Further subdivisions occur in an irregular, dichotomous way until the end of the embryonal stage. By this time, the major airways have developed. Various growth factors and fibroblasts mediate morphogenesis of the tubular epithelium, which results in airway branching: 10 on the right and 9 on the left.[1] The left and right pulmonary arteries form plexuses even before the heart descends into the thorax. Left and right pulmonary veins start to develop at about week 5 as a single evagination in the sinoatrial portion of the heart.

During the embryonal phase, the respiratory epithelium develops from an area of the endoderm referred to as the *foregut bud*. The endoderm is the innermost layer of the three **primary germ layers** (i.e., endoderm, mesoderm, and ectoderm). The foregut bud interacts with the bronchial mesoderm (the middle primary germ layer), and, through a number of complex embryonic development processes, this interaction eventually gives rise to the pulmonary interstitium, smooth muscle, blood vessels, and cartilage.[10] The mesenchyme, an extracellular matrix of undifferentiated embryonic connective tissue cells, determines the nature of airway branching by a complex interaction of epithelial cells with the bronchial mesoderm.[11] The mesenchyme and epithelium are separated from each other by a basal lamina containing type I collagen at the sites of airway branching.

The diaphragm also develops during the embryonal stage of lung development. Complete development of the diaphragm occurs by approximately week 7 of gestation.

Table 1-1 Classification of Phases of Human Intrauterine Lung Growth

STAGE	TIME OF OCCURRENCE	SIGNIFICANCE
Embryonal	Day 26 to day 52	Development of trachea and major bronchi
Pseudoglandular	Day 52 to week 16	Development of remaining conducting airways
Canalicular	Week 17 to week 26	Development of vascular bed and framework of respiratory acini
Saccular	Week 26 to week 36	Increased complexity of saccules
Alveolar	Week 36 to term	Development of alveoli

PSEUDOGLANDULAR PHASE

The pseudoglandular phase, named after the distinct glandular appearance of the developing lung, extends to week 16 of gestation, during which time the conducting airways continue to develop. In this phase there is extensive subdivision of the conducting airway system. The branching pattern that occurs in both lungs determines the pattern in the adult lung.[12] The subsequent growth of these airways is in size only. The most distal structures are the terminal bronchioles, which likely differentiate into the respiratory bronchioles and alveolar ducts.[13] The gas-exchanging part of the lung, consisting of the pulmonary acini, or terminal respiratory units, may also be laid down completely during the pseudoglandular phase. Various growth factors and chemical mediators also begin to transdifferentiate the primordial tracheal epithelium into the respiratory type II epithelial cells required for alveolar development.[1]

During the pseudoglandular phase, cilia appear on the surface of the epithelium of the trachea and the

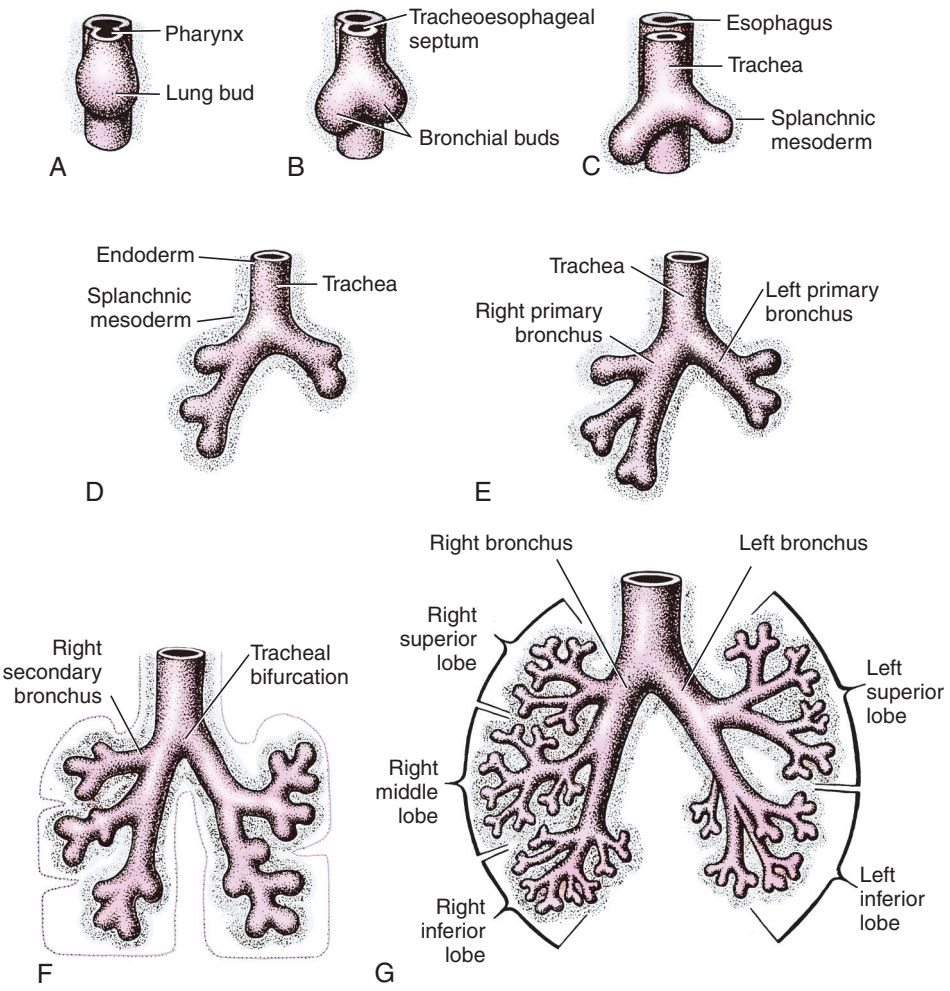


FIGURE 1-1 Embryonal stage of lung development. A to C, The trachea and major bronchi at 4 weeks; D and E, 5 weeks; F, 6 weeks; G, 8 weeks. (From Moore KL, Persaud TVN: *The developing human*, ed 5. Philadelphia, 1993, WB Saunders.)

mainstem bronchi at 10 weeks of gestation and are present on the epithelial cells of the peripheral airways by 13 weeks of gestation. Goblet cells appear in the bronchial epithelium at 13 to 14 weeks of gestation, and submucosal glands arise as solid buds from the basal layers of the surface epithelium at 15 to 16 weeks of gestation. Smooth muscle cells derived from the primitive mesenchyme surrounding the airways can be seen at the end of week 7 of gestation and by week 12 form the posterior wall of the large bronchi. The development of cartilage has been documented at 24 weeks of gestation and may be present earlier. Cartilage may be present in about 10 to 14 airway branching generations at 24 weeks gestation. The cartilage is immature at this stage. Lymphatics appear first in the hilar region of the lung during week 8 of gestation and in the lung itself by week 10. This phase has been termed **pseudoglandular** because random histologic sections show the appearance of multiple round structures resembling glands. They are separated from each other by mesenchyme and its derivatives. The cells lining the spaces are columnar and contain glycogen. By the end of this stage, airways, arteries, and veins have developed in the pattern corresponding to that found in an adult.

Maturation of the immune system begins before birth. By 14 weeks' gestation, T lymphocytes can be found in the respiratory system. Fetal immune responses to allergens develop early and can be detected in cord blood. The potential routes of exposure are via the placenta (transplacental) or the fetal gut (by the swallowing of amniotic fluid). However, the relative importance of the two is not fully understood.[3]

CANALICULAR PHASE

The canalicular phase follows the pseudoglandular phase and lasts from approximately 17 weeks to about 26 weeks of gestation. This phase is so named because of the appearance of vascular channels, or capillaries, that begin to grow by forming a capillary network around the air passages.[14] Some of the capillaries extend into the epithelium. The capillaries develop at 20 weeks of gestation and by 22 weeks have increased in number. Satisfactory gas exchange cannot occur

until the capillaries have sufficient surface area and are close enough to the airspaces for efficient gas transfer. This development, along with the appearance of **surfactant,** a surface-active phospholipoprotein formed by alveolar type II cells that is important in reducing alveolar surface tension and ultimately reducing the work required for breathing, is critical to the extrauterine survival of the immature fetus. The survival of the fetus becomes possible during the canalicular stage, at 22 to 24 weeks of gestation.

Pulmonary acinar units are also formed during the canalicular period (Figure 1-2). Each acinar unit (also referred to as an acinus) consists of a respiratory bronchiole (which contains no cartilage in its wall), alveolar ducts, and alveolar sacs. It follows that primitive lobules will have formed by the beginning of the canalicular phase. Each lobule contains three to five terminal bronchioles; approximately 25,000 terminal bronchioles exist in an adult lung. If the primitive acinar units are all formed by the end of the canalicular phase, this would imply that the full complement of 25,000 terminal bronchioles should be present by 28 weeks of gestation.

Thinning of the extracellular matrix, or mesenchyme, continues through the canalicular phase. By 20 to 22 weeks of gestation, two types of cells can be identified within the developing human lung. These distinct cell types are referred to as *type I pneumocyte* and *type II pneumocyte epithelial cells.* Within the canalicular phase the type II pneumocytes retain the cytoplasmic shape of their precursors and contain the concentric layers of lipid and protein important for the production of surfactant called **lamellar bodies.** The type I pneumocytes provide the structural apparatus that will become the alveoli and begin this process by flattening and elongating during this phase of development. The conducting airways have now developed smooth muscle.

By the end of the canalicular phase, the developing air–blood barrier is thin enough to support gas exchange. Blood vessels grow alongside conducting airways, which are also undergoing muscularization, to a peripheral position that is more distant than in the adult.[15] The bronchial artery system may be as critical for lung development as the pulmonary arteries, although the role of the bronchial arteries in lung differentiation and growth is not clear.[16] It has been suggested that the most peripheral parts of the developing lung are supplied only by the pulmonary arterial vasculature.[15] The epithelial cells at this point are capable of producing fetal lung liquid.

SACCULAR PHASE

The saccular phase was formerly believed to be the last stage of lung development before birth. However, because alveoli are now known to form before birth, the termination of the saccular period is arbitrarily set at 35 to 36 weeks of gestation. At the beginning of this phase, at about 26 weeks of gestation, the terminal structures are referred to as **saccules** and are relatively smooth-walled, cylindrical structures. They then become subdivided by ridges known as **secondary crests** (Figure 1-3). As the crests protrude into the saccules, part of the capillary net is drawn in with them, forming a double capillary layer.[17,18] Further septation between the crests results in smaller spaces, which have been termed *subsaccules.* Exactly when these subsaccular structures become alveoli is a matter of debate (Figure 1-4). Some have advocated that any structure bordered on three sides should be termed an alveolus. Alveoli can be seen as early as 32 weeks of gestation and are present at 36 weeks of gestation in all fetuses (Figure 1-5). During the saccular phase, there is a marked increase in the potential gas-exchanging surface area.

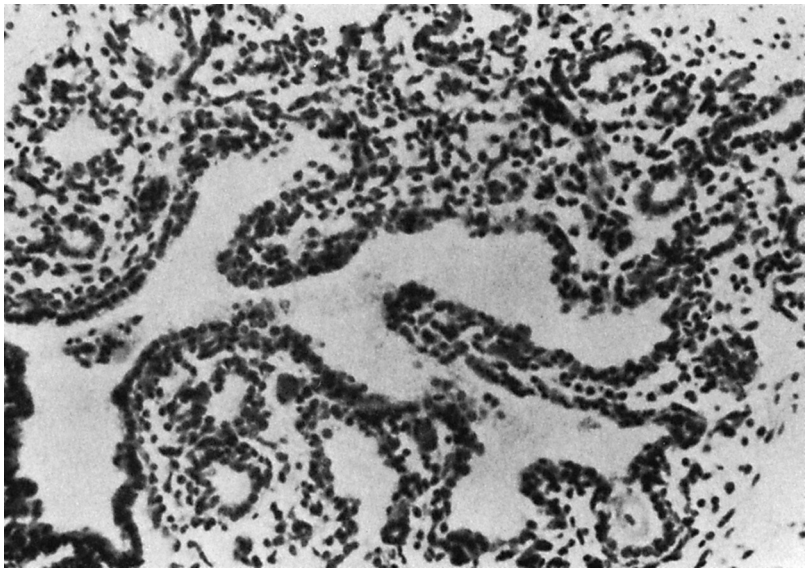


FIGURE 1-2 Canalicular stage of lung development at 22 weeks of gestation. A terminal bronchiole *(bottom left)* leads into a prospective acinus. Note that branches are sparse. (Langston C, Kida K, Reed M, et al. Human lung growth in late gestation and in the neonate. *Am Rev Respir Dis* 1984 Apr; 129(4):607-13.)

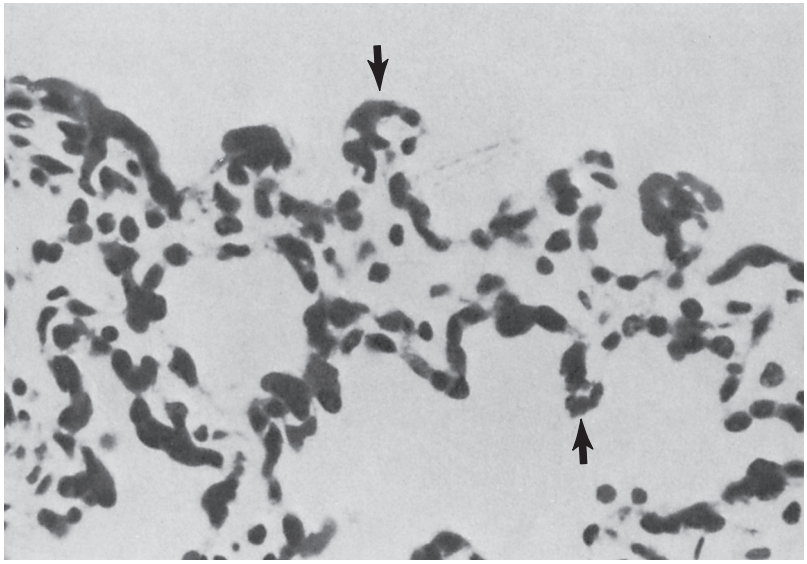


FIGURE 1-3 Saccular stage of lung development at 29 weeks of gestation. Secondary crests *(arrows)* begin to divide saccules into smaller compartments. (Langston C, Kida K, Reed M, et al. Human lung growth in late gestation and in the neonate. *Am Rev Respir Dis* 1984 Apr; 129(4):607-13.)

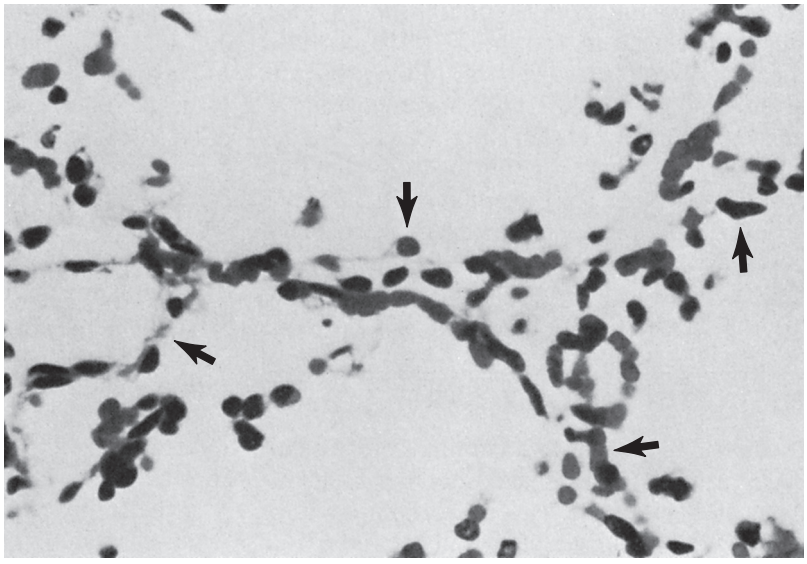


FIGURE 1-4 Alveolar stage of lung development at 36 weeks of gestation. Note the double capillary network *(solid arrows, center and right)* and the single capillary layer *(arrow at left).* (Langston C, Kida K, Reed M, et al. Human lung growth in late gestation and in the neonate. *Am Rev Respir Dis* 1984 Apr; 129(4):607-13.)

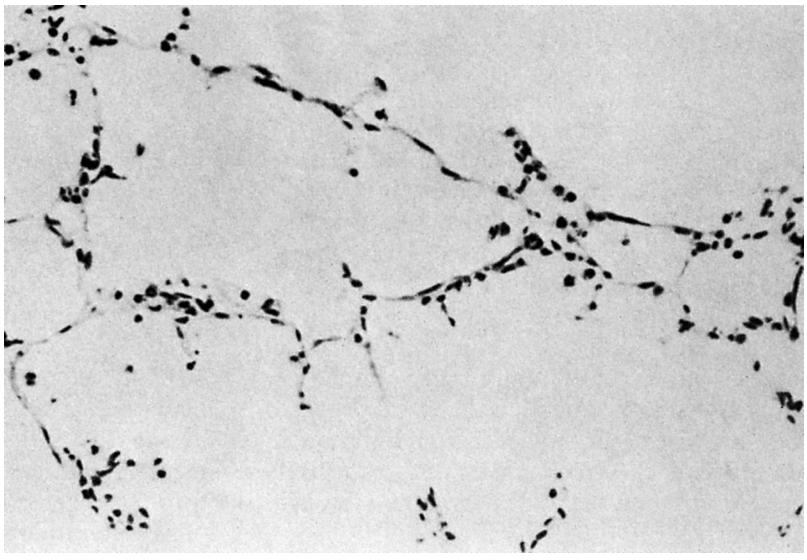


FIGURE 1-5 Alveolar stage of lung development at 36 weeks of gestation: Thin-walled alveoli are present. (Langston C, Kida K, Reed M, et al. Human lung growth in late gestation and in the neonate. *Am Rev Respir Dis* 1984 Apr; 129(4):607-13.)

ALVEOLAR PHASE

Distinction between the saccular and alveolar phases is somewhat arbitrary. Hislop, Wigglesworth, and Desai[19] claim that alveoli are present at 29 weeks of gestation; Langston and coworkers[7] believe that 36 weeks of gestation is the earliest point at which subsaccules and alveoli can be distinguished. Alveolar maturation and proliferation are primarily a postnatal event, extending beyond birth with rapid growth up to 18 months postgestation.[1] Alveologenesis is characterized by a complex interaction of epithelial, fibroblast, and vascular growth factors with extracellular matrix components.

At birth, the number of alveoli is highly variable, ranging from 20 million to 150 million. The accepted mean number of alveoli, as described in the literature, is also variable, given as 50 million by Langston and colleagues[7] and 150 million by Hislop, Wigglesworth, and Desai.[19] It has been estimated that only 15% to 20% of the adult number of alveoli are present at birth, and thus alveologenesis is largely a postnatal event. Hislop, Wigglesworth, and Desai[19] believe that almost half the total number of alveoli are present at birth. The important point is that alveolarization is rapidly progressing during the period of development from late fetal to early neonatal life and may be complete by a year or so after birth.

POSTNATAL LUNG GROWTH

Normal lung growth is a continuous process that begins early in gestation and extends through infancy and childhood. Major structural development occurs in late gestation and continues over the first few years of postnatal life.[20,21] As stated earlier, estimates of alveolar number at birth vary widely, and the average of 50 million is generally accepted. These alveoli provide a total gas-exchanging surface of approximately 3 to 4 m^2. More than 80% of the eventual total number of alveoli—about 300 million—form after birth. Lung volume increases 23-fold, alveolar number increases 6-fold, alveolar surface area increases 21-fold, and lung weight increases 20-fold. Lung volume increases disproportionally to alveolar number.

As the human infant doubles in body weight by 6 months and triples by 1 year, oxygen uptake increases proportionally; this is achieved by an increase in alveolar growth. The area of the air–tissue interface increases in a linear relationship to body surface area.[22] Alveolar volume and alveolar surface area increase in proportion to each other. However, alveolar number and alveolar diameter do not change proportionally. Most of the postnatal formation of alveoli in an infant occurs over the first 1.5 years of life.[23,24] Thereafter the lung continues to grow in proportion to body growth.

Boyden and Tompsett[25] have described a mechanism of alveolar formation that includes extension of the gas-exchange region by transformation of the respiratory bronchioles into alveolar ducts and terminal bronchioles into respiratory bronchioles. Lateral pouches from these transformed respiratory bronchioles form new alveoli. It has been proposed that new alveolar formation occurs in this manner into later childhood and that this is the likely mechanism for new alveolar formation throughout life. At 2 years of age, the number of alveoli varies substantially among individuals. After 2 years of age, males have more alveoli than do females. After the end of alveolar multiplication, the alveoli continue to increase in size until thoracic growth is completed.[21]

FACTORS AFFECTING PRENATAL AND POSTNATAL LUNG GROWTH

Success of each phase of lung development, as previously defined, requires the precise interaction of numerous complex physiologic mechanisms; the result is the production of a flawless maturing lung at birth. Understandably, problems occasionally arise in the developmental process of the fetal lung that can affect prenatal lung growth. Development of the initial structures of the pulmonary tree occurs in the embryonal stage. It is during this period that errors in development may result in laryngeal, tracheal, or esophageal atresia, or stenosis may develop.[26] **Pulmonary hypoplasia,** an incomplete development of the lungs characterized by an abnormally low number or size of bronchopulmonary segments or alveoli, can develop during the pseudoglandular phase.[27] If the fetus is born during the canalicular phase (i.e., prematurely), severe respiratory distress can be expected as the inadequately developed airways and insufficient and immature surfactant production by alveolar type II cells lead to the constellation of problems known as *infant respiratory distress syndrome*.[28]

Developmental abnormalities of other organ systems can also affect lung development in the fetus. For example, abnormalities of the chest wall or renal hypoplasia can result in varying severities of pulmonary hypoplasia, the latter known as Potter's syndrome.[29,30] Additionally, some complex genetic disorders may also affect lung growth.[31]

Other clinical factors have been cited as causing diminished lung growth. These conditions can be divided into four categories:

1. Chest wall compression as occurs in diaphragmatic hernia—that is, an abnormal opening in the prenatal diaphragm that allows some of the abdominal organs to move into the chest and exert pressure on the developing lungs; chest wall abnormalities; and probably hydrops fetalis—that is, abnormal fluid accumulation in the fetus, often resulting in hydrothorax and ascites—have all been implicated in diminished lung growth.[32]
2. **Oligohydramnios,** a reduced quantity of amniotic fluid present for an extended period, with or

without renal anomalies, is associated with lung hypoplasia.[33-35] The mechanisms by which amniotic fluid volume influences lung growth remain unclear. Possible explanations include mechanical restriction of the chest wall, interference with fetal breathing, and/or failure to produce fetal lung liquid. These clinical and experimental observations possibly point to a common denominator, lung stretch, as being a major growth stimulant.

3. Diminished respiration has been shown to have a severe effect on lung growth. This effect could be mediated through a lack of stretch of the developing lung parenchyma.[36]
4. A variety of hormonal or metabolic abnormalities may alter lung growth and structure. Leprechaunism, associated with abnormal carbohydrate metabolism, results in dysmorphic lungs with a decreased number of terminal bronchioles, dilated alveolar ducts and saccules, and enlarged airspaces.[37] Experimental diabetes produced by streptozotocin administration to 3-week-old rats resulted in diminished airspace size, increased alveolar number, and a marked effect on pulmonary connective tissue metabolism.[38,39]

An example of altered lung development is seen in children with Down syndrome. Although fetal lung growth is normal, postnatal lung growth is characterized by larger and fewer alveoli than normal.[40]

ABNORMAL LUNG DEVELOPMENT

Structural development of the lung may be altered by a number of conditions affecting the lungs in utero or by postnatal events.[41,42] Complex relationships exist among humoral, hormonal, and physical forces acting on the developing lung, altering its growth in ways that are poorly understood. Growth retardation of the fetal lung may affect size and weight but not maturation of airways and alveoli, whereas malnutrition may slow functional rather than structural maturation.[41]

Timing or dating of adverse events influencing fetal lung development is important in considering the approach to treatment and prognosis. Abnormalities occurring in the embryonic period are often associated with renal agenesis or dysplastic kidneys; branching of the lungs may also be affected. Abnormalities occurring later in development, such as diaphragmatic hernia, may affect the lungs during the pseudoglandular period, or before 16 weeks of gestation, and thereby decrease airway branching. If abnormalities occur during the second trimester of pregnancy, completion of pulmonary vascularization and acinar development may not proceed, and hypoplasia in the gas-exchanging area may result. Problems occurring in the perinatal period, such as premature birth and bronchopulmonary dysplasia, may alter subsequent alveolar growth and differentiation, ultimately leading to a decrease in alveolar number.

PULMONARY HYPOPLASIA

Pulmonary hypoplasia, or failure of the lungs to develop in utero, is a relatively common abnormality of lung development, with a number of clinical associations and anatomic correlates. Hypoplasia may be considered to be present when there are too few cells, too few alveoli, or too few airways. The incidence of pulmonary hypoplasia diagnosed at autopsy is between 10% and 25% of all cases.[42-45]

The best-studied condition associated with hypoplasia is diaphragmatic hernia. The incidence of diaphragmatic hernia is about 1 in 4000 births. The range of abnormalities reported is wide and is probably related to variations in the severity and timing of the onset of lung compression.[46] Compression of the lung before 16 weeks of gestation causes incomplete branching of the conducting airways, terminal airways, or both. Early and severe compression results in severe hypoplasia that can reduce the weight of the affected lung to less than half that of the contralateral lung. The affected lung demonstrates fewer, smaller alveoli; a decreased surface area for gas exchange; and a proportional decrease in pulmonary vasculature.

Other forms of lung compression may result in hypoplasia. Causes include osteogenesis imperfecta, hypophosphatasia,[47] and thoracic dystrophies. In addition, chest wall anomalies, pleural effusion, ascites, intrathoracic tumors, and extralobar sequestration may cause lung compression.

Pulmonary hypoplasia occurs in oligohydramnios as a result of leakage of amniotic fluid. It was first described by Potter in association with renal agenesis.[33] Experimental evidence supports the conclusion that the amount of lung liquid present in the fetus is a major determinant of lung growth, because chronic tracheal drainage produces pulmonary hypoplasia and tracheal ligation produces lungs with increased tissue mass.[48] It has been shown that experimental oligohydramnios causes pulmonary hypoplasia, which varies in severity depending on its timing.[43,49]

Several experimental studies suggest that lung growth alteration may be caused by various hormonal imbalances.[50-54] Changes caused by endocrine effects may cause lung compression or diminished lung liquid and respiration. Glucocorticoid administration has been shown to accelerate lung maturation but may also affect lung growth. Type II epithelial cell maturation is induced both functionally and anatomically by this drug. Depending on the dose, glucocorticoids may reduce the rate of DNA synthesis and thus produce hypoplasia. Thyroidectomy in fetal sheep produces pulmonary hypoplasia and diminished type II cell differentiation. Maternal growth hormone apparently plays little role in fetal growth, but the effect of maternal administration of growth hormone on fetal lung growth has not been studied. Maternal experimental diabetes results in diminished tissue maturity in the fetus.[55]

ALVEOLAR CELL DEVELOPMENT AND SURFACTANT PRODUCTION

As the primordial epithelium evolves, the epithelial lining undergoes cellular division and differentiation into the highly specialized type I and type II pneumocytes. Type I pneumocytes are flat (squamous) cells serving as a thin, gas-permeable membrane for the diffusion of gases and as a barrier against water and solute leakage.[56] They account for more than 97% of the alveolar surface area, primarily as a result of their size, shape, and large cellular surface.[57]

Despite its smaller surface area, the cuboidal-appearing type II pneumocyte is the principal cell involved in surfactant production, storage, secretion, and reuse. Surfactant storage occurs in the lamellar bodies inside type II pneumocytes. An additional function of the type II pneumocyte is its ability to differentiate into type I pneumocytes.[58]

Type II pneumocytes contain the precursors required for surfactant synthesis and osmiophilic lamellar bodies that function as the storage apparatus for the synthesized surfactant.[9,57] Through a continuous process of exocytosis, the lamellar bodies release their contents of tubular myelin into the alveolar hypophase (the thin liquid lining of the internal surface of the alveoli). The liberated tubular myelin unravels and disperses to form a monolayer at the air–liquid interface.[58]

The primary role of mammalian surfactant is to lower the surface tension within the alveolus, specifically at the air–liquid interface. This allows the delicate structure of the alveolus to expand when filled with air. Without surfactant, the alveolus remains collapsed because of the high surface tension of the moist alveolar surface. Surfactant is composed predominantly of an intricate blend of phospholipids, neutral lipids, and proteins. See Chapter 14 for more information about surfactant composition.

Of clinical relevance during late gestation, analysis of amniotic fluid for the concentration of phosphatidylglycerol and phosphatidylcholine has been shown to be a sensitive indicator of the state of fetal lung maturity.[59] In addition, various chemical and mechanical stimulatory mechanisms leading to increased surfactant precursor (and presumably mature surfactant) production have been identified and include, but are not limited to, β-adrenergic agonists, prostaglandins, epidermal growth factor, and mechanical ventilation.

FETAL LUNG LIQUID

Fetal lungs are secretory organs that make breathing-like movements but serve no respiratory function before birth. They secrete about 250 to 300 mL of liquid per day. Thus the fetal airways are not collapsed but filled with fluid from the canalicular phase until delivery and the initiation of ventilation. This liquid flows from the terminal respiratory units through the conducting airways and into the oropharynx, where it is either swallowed or expelled into the amniotic sac. The presence of **fetal lung fluid** is essential for normal lung development. This luminal fluid is high in chloride and low in bicarbonate, with a negligible concentration of protein.[60,61] Active transport of chloride ions across the fetal pulmonary epithelium generates an electric potential difference and causes liquid to flow from the lung microcirculation through the interstitium and into the airspaces.[62] The pulmonary circulation, rather than the bronchial circulation, is the major source of this liquid. The balance between production and drainage of this liquid has an important effect on lung development. During fetal breathing, there is a small but steady movement of fluid outward from the trachea. The net movement of fluid away from the lungs has been measured at about 15 mL/hr and was about five times higher during periods of fetal breathing movements than during apnea.[63] Prolonged outflow obstruction expands the lungs and leads to a decrease in type II cells.[64] In contrast, unimpeded removal of lung liquid decreases lung size, increases apparent tissue density, and stimulates proliferation of type II cells.[48]

The clearance of fetal lung fluid is essential for normal neonatal respiratory adaptation. However, several studies have shown that both the rate of liquid formation and the volume within the lumen of the fetal lung normally decrease before birth.[65-67] It is unknown what causes the reduction in fetal lung secretions before birth. Hormonal changes, which occur in the fetus just before and during labor, may have an important role in triggering this process. The influence of catecholamines on fetal lung liquid volume has been investigated. It has been shown that injecting β-adrenergic agonists into pregnant rabbits reduces the amount of water in the lungs of their pups.[68] Epinephrine has been shown to inhibit secretion of fetal lung liquid.[69] Other hormones, such as arginine vasopressin and prostaglandin E_2, which are secreted around the time of birth, may reduce production of lung luminal liquid.[70,71]

Removal of lung liquid continues after birth. When breathing begins, air inflation shifts residual liquid from the lumen into distensible perivascular spaces around large pulmonary blood vessels and bronchi. Accumulation of liquid in these connective tissue spaces, which are distant from the sites of respiratory gas exchange, allows time for small blood vessels and lymphatics to remove the displaced liquid with little or no impairment of neonatal lung function at this critical juncture.[72,73] The clearance of the fluid from the interstitial spaces occurs over many hours.

Key Points

- Each developmental phase of the fetal lung is defined by its characteristic anatomic growth and maturation.
- A thorough understanding of each stage of fetal lung development is an important basis for identifying problems that occur during fetal lung development and helping prepare for the delivery and care of a premature infant.
- Fetal survival outside the uterus becomes possible at approximately 24 weeks of gestation. Survival outside the uterus before this is not possible, because the pulmonary capillary system is not sufficient to support gas exchange.
- Abnormal lung development can occur at any point during gestation.
  - Early developmental problems can be associated with abnormalities of other organ systems (e.g., renal agenesis associated lung branching abnormalities).
  - Other developmental problems can occur as through the direct obstruction of proper gestational growth (e.g., congenital diaphragmatic hernia with direct compression to the developing lung inhibits normal growth).
- By 22 weeks of gestation the cytoplasm within the alveolar type II cells begins to contain lamellar bodies, which are important in the production of surfactant.
- Surfactant produced by alveolar type II cells is a phospholipoprotein important for reducing alveolar surface tension. This reduction in surface tension reduces the work of breathing in a spontaneously breathing newborn.
- Fetal lung fluid is secreted by cells of the fetal airways. This fluid flows from the distal terminal airways toward the pharynx and eventually is either swallowed or expelled as a constituent of the amniotic fluid.
- During the birthing process, production of fetal lung fluid is slowed, and after birth the fetal lung fluid is cleared by the lymphatic system of the lung.

Assessment Questions

See Evolve Resources for answers.

1. Which of the following are phases of human lung development?
   - **I.** Embryonal
   - **II.** Canalicular
   - **III.** Blastocystic
   - **IV.** Chorionic
   - **V.** Saccular

   A. I, III, and III
   B. I, II, and V
   C. II and IV
   D. III and V
   E. I, IV, and V

2. The initial lung bud emerges from which of the following?
   A. Esophagus
   B. Trachea
   C. Umbilical cord
   D. Pharynx
   E. Mesoderm layer

3. The bronchial tree is formed at which gestational phase of lung development?
   A. Embryonal
   B. Canalicular
   C. Pseudoglandular
   D. Saccular
   E. Alveolar

4. The alveolar epithelial lining undergoes cell division into type I and type II pneumocytes. Which of the following correctly describe the pneumocytes?
   - **I.** Type I pneumocytes account for more than 97% of the alveolar surface area.
   - **II.** Type II pneumocytes form a gas-permeable membrane for diffusion of gases.
   - **III.** Surfactant production occurs in the lamellar bodies of type II pneumocytes, which release surfactant by exocytosis.
   - **IV.** Type I pneumocytes are responsible for surfactant production and storage.
   - **V.** Type I pneumocytes are squamous shaped and optimized for gas exchange; type II pneumocytes are cube shaped and may differentiate into type I cells.

   A. I, II, IV, and V
   B. I, III, and V
   C. I, IV, and V
   D. II, IV, and V
   E. III and IV

5. What are the minimal developmental features required for an immature human fetus to survive outside the uterus?
   - **I.** 32 weeks of gestation
   - **II.** Sufficient alveolar and vascular surface area for gas exchange
   - **III.** Sufficient endoplasmic reticulum production
   - **IV.** 22 to 24 weeks of gestation
   - **V.** Near completion of the canalicular stage of lung development

   A. I, II, III, and IV
   B. I and V
   C. II, III, and V
   D. II, IV, and V
   E. III, IV, and V

6. Which of the following best describe(s) fetal lung liquid?
   A. It lowers surface tension within the alveoli.
   B. It maintains the structure of the airway lumen and developing alveoli, preventing complete collapse.
   C. With fetal breathing movement it continuously flows out of the lungs and is swallowed or excreted into the amniotic fluid.
   D. A and B
   E. B and C

7. Estimates of the exact number of alveoli at birth vary widely, but investigators agree that:
   - **A.** The surface area of gas exchange increases inversely with age.
   - **B.** Normal structural development is complete before the first breath.
   - **C.** Normal lung growth is a continuous process that extends into adulthood.
   - **D.** Gas-exchange surface area grows proportionally with an increase in oxygen consumption and body surface area.
   - **E.** Extension of gas exchange occurs with transformation of alveolar ducts and terminal bronchioles into respiratory bronchioles.
8. Which is the lung development stage formerly believed to be the last stage before birth, and characterized by relatively smooth-walled, cylindrical structures subdivided by ridges known as *secondary crests*?
   - **A.** Alveolar phase
   - **B.** Saccular phase
   - **C.** Terminal phase
   - **D.** Trophoblast phase
   - **E.** Canalicular phase
9. Pulmonary hypoplasia is a relatively common abnormality of lung development with a number of clinical associations, including which of the following?
   - **A.** Lung tissue compression
   - **B.** Oligohydramnios
   - **C.** Maternal diabetes
   - **D.** All of the above
   - **E.** A and C only
10. Which of the following statements represent Reid's laws of human lung development?
    - **I.** The bronchial tree develops by week 16 of intrauterine life.
    - **II.** Preacinar vasculature develops after the airway has been established, and intraacinar vasculature develops after the alveoli are generated.
    - **III.** Alveolar development is complete when there is sufficient gas-exchange surface area to support extrauterine life.
    - **IV.** The esophageal lung bud arises from the embryonic mesoderm to form the tracheal bronchial tree.
    - **V.** Alveoli increase in number until 8 years of age and grow in size until chest wall growth is complete.
      - **A.** I and IV
      - **B.** I, II, and V
      - **C.** I, III, IV, and V
      - **D.** II and III
      - **E.** II, III, and V

REFERENCES

1. Burri P. Structural aspects of prenatal and post natal development and growth of the lung. In: McDonald J, ed. *Lung growth and development*. New York: Marcel Dekker; 1997:1-35.
2. Boyden E. Development and growth of the airways. In: Hodson W, ed. *Development of the lung*. New York: Marcel Dekker; 1977:3-35.
3. Reid L. The embryology of the lung. In: DeReuck A, Porter R, eds. *Development of the lung*. Boston: Little Brown; 1967: 109-130.
4. Sheffield M, Mabry S, Thibeault DW, et al. Pulmonary nitric oxide synthases and nitrotyrosine: findings during lung development and in chronic lung disease of prematurity. *Pediatrics*. 2006;118(3):1056.
5. Kreiger PA, Ruchelli ED, Mahboubi S, et al. Fetal pulmonary malformations: defining histopathology. *Am J Surg Pathol*. 2006;30(5):643.
6. Bourbon J, Boucherat O, Chailley-Heu B, et al. Control mechanisms of lung alveolar development and their disorders in bronchopulmonary dysplasia. *Pediatr Res*. 2005; 57(5 Pt 2):38R.
7. Langston C, Kida K, Reed M, et al. Human lung growth in late gestation and in the neonate. *Am Rev Respir Dis*. 1984;129(4):607.
8. Liggins GC. Growth of the fetal lung. *J Dev Physiol*. 1984;6(3):237.
9. Xu J, Tian J, Grumelli SM, et al. Stage-specific effects of cAMP signaling during distal lung epithelial development. *J Biol Chem*. 2006;281(50):38894.
10. Loosli CG, Potter EL. Pre- and postnatal development of the respiratory portion of the human lung with special reference to the elastic fibers. *Am Rev Respir Dis*. 1959; 80(1, Part 2):5.
11. Spooner BS, Wessells NK. Mammalian lung development: interactions in primordium formation and bronchial morphogenesis. *J Exp Zool*. 1970;175(4):445.
12. Hislop A, Reid L. Growth and development of the respiratory system: anatomical development. In: Davies J, Dobbing J, eds. *Scientific foundation of paediatrics*. London: Medical Books; 1974:214-254.
13. Itoh K, Itoh H. A study of cartilage development in pulmonary hypoplasia. *Pediatr Pathol*. 1988;8(1):65.
14. Thurlbeck WM. Prematurity and the developing lung. *Clin Perinatol*. 1992;19(3):497.
15. Hilslop A, Reid L. Formation of the pulmonary vasculature. In: Hodson W, ed. *Development of the lung*. New York: Marcel Dekker; 1979:37-86.
16. Boyden EA. The time lag in the development of bronchial arteries. *Anat Rec*. 1970;166(4):611.
17. Cooney TP, Thurlbeck WM. The radial alveolar count method of Emery and Mithal: a reappraisal 2—intrauterine and early postnatal lung growth. *Thorax*. 1982;37(8): 580.

18. Bruce MC, Honaker CE, Cross RJ. Lung fibroblasts undergo apoptosis following alveolarization. *Am J Respir Cell Mol Biol*. 1999;20(2):228.
19. Hislop AA, Wigglesworth JS, Desai R. Alveolar development in the human fetus and infant. *Early Hum Dev*. 1986;13(1):1.
20. Reid L. 1976 Edward B.D. Neuhauser lecture: the lung: growth and remodeling in health and disease. *AJR Am J Roentgenol*. 1977;129(5):777.
21. Thurlbeck WM. Postnatal growth and development of the lung. *Am Rev Respir Dis*. 1975;111(6):803.
22. Dunnill M. Postnatal growth of the lung. *Thorax*. 1962;17(4): 329.
23. Zeltner TB, Burri PH. The postnatal development and growth of the human lung. II. Morphology. *Respir Physiol*. 1987;67(3):269.
24. Zeltner TB, Caduff JH, Gehr P, et al. The postnatal development and growth of the human lung. I. Morphometry. *Respir Physiol*. 1987;67(3):247.
25. Boyden EA, Tompsett DH. The changing patterns in the developing lungs of infants. *Acta Anat (Basel)*. 1965; 61(2):164.
26. Berrocal T, Madrid C, Novo S, et al. Congenital anomalies of the tracheobronchial tree, lung, and mediastinum: embryology, radiology, and pathology. *Radiographics*. 2004;24(1):e17.
27. Kotecha S. Lung growth: implications for the newborn infant. *Arch Dis Child Fetal Neonatal Ed*. 2000;82(1):F69.
28. Wirbelauer J, Speer CP. The role of surfactant treatment in preterm infants and term newborns with acute respiratory distress syndrome. *J Perinatol*. 2009;29(suppl 2):S18.
29. Fraga JR, Mirza AM, Reichelderfer TE. Association of pulmonary hypoplasia, renal anomalies, and Potter's facies. *Clin Pediatr (Phila)*. 1973;12(3):150.
30. Swischuk LE, Richardson CJ, Nichols MM, et al. Bilateral pulmonary hypoplasia in the neonate. *AJR Am J Roentgenol*. 1979;133(6):1057.
31. Nogee LM, de Mello DE, Dehner LP, et al. Brief report: deficiency of pulmonary surfactant protein B in congenital alveolar proteinosis. *N Engl J Med*. 1993;328(6):406.
32. Karamanoukian HL, O'Toole SJ, Holm BA, Glick PL. Making the most out of the least: new insights into congenital diaphragmatic hernia. *Thorax*. 1997;52(3):209.
33. Potter EL. Bilateral renal agenesis. *J Pediatr*. 1946;29:68.
34. King JC, Mitzner W, Butterfield AB, et al. Effect of induced oligohydramnios on fetal lung development. *Am J Obstet Gynecol*. 1986;154(4):823.
35. Perlman M, Williams J, Hirsch M. Neonatal pulmonary hypoplasia after prolonged leakage of amniotic fluid. *Arch Dis Child*. 1976;51(5):349.
36. Nagai A, Thurlbeck WM, Deboeck C, et al. The effect of maternal CO_2 breathing on lung development of fetuses in the rabbit. Morphologic and morphometric studies. *Am Rev Respir Dis*. 1987;135(1):130.
37. Thurlbeck WM, Cooney TP. Dysmorphic lungs in a case of leprechaunism: case report and review of literature. *Pediatr Pulmonol*. 1988;5(2):100.
38. Ofulue AF, Kida K, Thurlbeck WM. Experimental diabetes and the lung. I. Changes in growth, morphometry, and biochemistry. *Am Rev Respir Dis*. 1988;137(1):162.
39. Ofulue AF, Thurlbeck WM. Experimental diabetes and the lung. II. In vivo connective tissue metabolism. *Am Rev Respir Dis*. 1988;138(2):284.
40. Cooney TP, Wentworth PJ, Thurlbeck WM. Diminished radial count is found only postnatally in Down's syndrome. *Pediatr Pulmonol*. 1988;5(4):204.
41. Lipsett J, Tamblyn M, Madigan K, et al. Restricted fetal growth and lung development: a morphometric analysis of pulmonary structure. *Pediatr Pulmonol*. 2006;41(12): 1138.
42. Reale FR, Esterly JR. Pulmonary hypoplasia: a morphometric study of the lungs of infants with diaphragmatic hernia, anencephaly, and renal malformations. *Pediatrics*. 1973;51(1):91.
43. Moessinger AC, Abbey-Mensah M, Driscoll JM, et al. Pulmonary hypoplasia, a disorder on the rise? [abstract]. *Pediatr Res*. 1983;17:327A.
44. Moessinger AC, Collins MH, Blanc WA, et al. Oligohydramnios-induced lung hypoplasia: the influence of timing and duration in gestation. *Pediatr Res*. 1986;20(10):951.
45. Page DV, Stocker JT. Anomalies associated with pulmonary hypoplasia. *Am Rev Respir Dis*. 1982;125(2):216.
46. George DK, Cooney TP, Chiu BK, et al. Hypoplasia and immaturity of the terminal lung unit (acinus) in congenital diaphragmatic hernia. *Am Rev Respir Dis*. 1987;136(4):947.
47. Silver MM, Vilos GA, Milne KJ. Pulmonary hypoplasia in neonatal hypophosphatasia. *Pediatr Pathol*. 1988;8(5):483.
48. Alcorn D, Adamson TM, Lambert TF, et al. Morphological effects of chronic tracheal ligation and drainage in the fetal lamb lung. *J Anat*. 1977;123(Pt 3):649.
49. Blachford KG, Thurlbeck WM. Lung growth and maturation in experimental oligohydramnios in the rat. *Pediatr Pulmonol*. 1987;3(5):328.
50. Crone RK, Davies P, Liggins GC, et al. The effects of hypophysectomy, thyroidectomy, and postoperative infusion of cortisol or adrenocorticotrophin on the structure of the ovine fetal lung. *J Dev Physiol*. 1983;5(5):281.
51. Erenberg A, Rhodes ML, Weinstein MM, et al. The effect of fetal thyroidectomy on ovine fetal lung maturation. *Pediatr Res*. 1979;13(4 Pt 1):230.
52. Liggins GC, Kitterman JA, Campos GA, et al. Pulmonary maturation in the hypophysectomised ovine fetus. Differential responses to adrenocorticotrophin and cortisol. *J Dev Physiol*. 1981;3(1):1.
53. Morishige WK, Joun NS. Influence of glucocorticoids on postnatal lung development in the rat: possible modulation by thyroid hormone. *Endocrinology*. 1982;111(5):1587.
54. Pinkerton KE, Kendall JZ, Randall GC, et al. Hypophysectomy and porcine fetal lung development. *Am J Respir Cell Mol Biol*. 1989;1(4):319.
55. Sosenko IR, Frantz ID 3rd, Roberts RJ, et al. Morphologic disturbance of lung maturation in fetuses of alloxan diabetic rabbits. *Am Rev Respir Dis*. 1980;122(5):687.
56. Schneeberger EE. Alveolar type I cells. In: Crystal RG, West JB, eds. *The lung: scientific foundations*. New York: Raven Press; 1991:1677-1685.
57. Notter RH, Shapiro DL. Lung surfactants for replacement therapy: biochemical, biophysical, and clinical aspects. *Clin Perinatol*. 1987;14(3):433.
58. Adamson IY, Bowden DH. The type 2 cell as progenitor of alveolar epithelial regeneration. A cytodynamic study in mice after exposure to oxygen. *Lab Invest*. 1974;30(1):35.
59. Kresch MJ, Gross I. The biochemistry of fetal lung development. *Clin Perinatol*. 1987;14(3):481.
60. Mescher EJ, Platzker AC, Ballard PL, et al. Ontogeny of tracheal fluid, pulmonary surfactant, and plasma corticoids in the fetal lamb. *J Appl Physiol*. 1975;39(6):1017.
61. Adams FH, Fujiwara T, Rowshan G. The nature and origin of the fluid in the fetal lamb lung. *J Pediatr*. 1963;63:881.
62. Olver RE, Strang LB. Ion fluxes across the pulmonary epithelium and the secretion of lung liquid in the foetal lamb. *J Physiol*. 1974;241(2):327.
63. Harding R, Sigger JN, Wickham PJ, et al. The regulation of flow of pulmonary fluid in fetal sheep. *Respir Physiol*. 1984;57(1):47.
64. Carmel JA, Friedman F, Adams FH. Fetal tracheal ligation and lung development. *Am J Dis Child*. 1965;109:452.
65. Kitterman JA, Ballard PL, Clements JA, et al. Tracheal fluid in fetal lambs: spontaneous decrease prior to birth. *J Appl Physiol*. 1979;47(5):985.

66. Dickson KA, Maloney JE, Berger PJ. Decline in lung liquid volume before labor in fetal lambs. *J Appl Physiol*. 1986;61(6):2266.
67. Brown MJ, Olver RE, Ramsden CA, et al. Effects of adrenaline and of spontaneous labour on the secretion and absorption of lung liquid in the fetal lamb. *J Physiol*. 1983;344:137.
68. Enhorning G, Chamberlain D, Contreras C, et al. Isoxsuprine-induced release of pulmonary surfactant in the rabbit fetus. *Am J Obstet Gynecol*. 1977;129(2):197.
69. Lawson EE, Brown ER, Torday JS, et al. The effect of epinephrine on tracheal fluid flow and surfactant efflux in fetal sheep. *Am Rev Respir Dis*. 1978;118(6):1023.
70. Bland RD, Fike CD, Teague WG, et al. Vasopressin decreases lung water in fetal lambs [abstract]. *Pediatr Res*. 1985;19(4):399A.
71. Kitterman JA. Fetal lung development. *J Dev Physiol*. 1984;6(1):67.
72. Bland RD, Hansen TN, Haberkern CM, et al. Lung fluid balance in lambs before and after birth. *J Appl Physiol*. 1982;53(4):992.
73. Bland RD, McMillan DD, Bressack MA, et al. Clearance of liquid from lungs of newborn rabbits. *J Appl Physiol*. 1980;49(2):171.

Fetal Gas Exchange and Circulation

2

Robert L. Joyner, Jr.

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. Discuss the identifiable stages of heart development and explain the development of the heart chambers.
2. Name the three fetal shunts and discuss their role during fetal circulation.
3. Explain the direction of blood flow and relative vascular pressures in the placenta, umbilical vein, three fetal shunts, right-side heart chambers, left-side heart chambers, pulmonary artery, lungs, aorta, and umbilical arteries.
4. Describe the cardiac and pulmonary sequences of events that occur when transitioning from fetal to extrauterine life, including the changes in fetal shunts.

Key Terms

angiogenic clusters
aorticopulmonary septum
atrial bulge
blastocyst
bulboventricular loop
bulbus cordis
chorion
chorionic membrane
chorionic villi
dextral looping
ectoderm
embryonic disk
endocardial cushions
endoderm
foramen ovale
intimal mounds
mesoderm
placenta
septum primum
septum secundum
trophoblast
ventricular bulge
Wharton's jelly
zygote

What initially may seem like a remote concept for respiratory care practitioners—a basic understanding of embryology—is essential to understanding the care of the newborn. Whether care is being provided to a premature newborn with respiratory distress syndrome as a result of insufficient or poorly functioning surfactant or to a newborn afflicted with persistent pulmonary hypertension resulting from severe meconium staining, all respiratory care practitioners working with infants must have a breadth of knowledge of embryology and fetal development that provides them with an understanding of normal development and what to expect when something goes awry.

EMBRYOLOGICAL OVERVIEW

The rapidly growing embryo and fetus must develop a vascular network to circulate nutrients and provide gas exchange. The fetus depends on the mother's circulation for nutrient and gas exchange; however, the maternal and fetal vascular networks are separate systems, and no blood is shared between the two. By day 22 of gestation the primitive fetal heart begins to beat, with myocardial pump function supporting circulation by day 27 to day 29.[1]

FERTILIZATION TO IMPLANTATION

As the fertilized egg, or **zygote,** travels to the uterus, it undergoes numerous iterations of cell division but has no nutrient source, as in a bird egg. The ball of developing cells, at this point termed the **blastocyst,** must attach itself and implant in the uterine lining for nourishment. The outer surrounding layer of the blastocyst is the **trophoblast,** which combines with tissues from the endometrium to form the **chorionic membrane** around the blastocyst.[2] Inside the blastocyst, a group of

Box 2-1 Origin of the Various Tissue Systems From the Three Embryonic Germ Layers

ECTODERM
- Central nervous system: brain and spinal cord
- Peripheral nervous system: cranial nerves and spinal nerves
- Sensory epithelia of the eyes, inner ears, and nose
- Glandular tissues: posterior pituitary gland, adrenal medulla
- Skin: epidermal layer
- Specializations of the skin: sweat and sebaceous glands, hair follicles, nails, mammary glands
- Teeth: enamel

MESODERM
- Cardiovascular system: heart and blood vessels
- Lymphatic system vessels
- All connective tissue: general connective tissue and cartilage, bone, bone marrow, and blood cells
- All muscle tissue: skeletal, cardiac, and smooth
- Skin: dermis and hypodermis
- Kidneys and ureters, spleen
- Reproductive tissues (not including the germ cells)
- The three major body cavities: pericardium, left and right pleura, and peritoneum
- Serous linings of organs within the body cavities
- Teeth: dentine, cementum, and pulp

ENDODERM
- Digestive system: stomach, small and large intestines, epithelial lining of the entire digestive system except parts of the mouth and pharynx, and anus (which are supplied by the ectoderm)
- Respiratory system: pharynx, lungs, and epithelial lining of the trachea and lungs
- Urinary system: bladder and lining of the urethra
- Liver and pancreas and epithelial lining of all glands that open into the digestive system
- Tonsils, thymus, thyroid, parathyroid
- Epithelial lining of auditory tube and tympanic cavity

Adapted from Moore KL, Persaud TVN, editors: *The developing human: clinically oriented embryology,* ed 6, Philadelphia: WB Saunders, 1998, pp 63-82.

cells arrange on one side in the shape of a figure eight. The central portion is the **embryonic disk,** which forms the three embryonic germ layers: the **ectoderm** and the **endoderm,** followed by the **mesoderm.**[3] Box 2-1 lists the tissue systems that arise from the three germ layers.

The outer or top loop of the figure eight envelops the embryonic structure and forms the amniotic sac, whereas the inner or bottom loop forms the yolk sac. The yolk sac soon degenerates and incorporates into the embryo, giving way for the amniotic sac to grow. Suspended in the cavity of the blastocyst, the amniotic sac then surrounds the entire embryo. The embryo attaches to the outer layer through the umbilical stalk, which later becomes the umbilical cord.

MATERNAL–FETAL GAS EXCHANGE

As the umbilical cord matures, finger-like projections extend into the outer lining of the **chorion,** or **chorionic villi** (Figure 2-1). Within the chorionic villi a capillary network forms and connects to the umbilical stalk. The villi intertwine into the blood-filled lacunar cavities of the endometrium of the maternal uterus.[2] Oxygen, carbon dioxide, and nutrients diffuse through the vast capillary surface area of this indirect connection between mother and fetus. As fetal development continues, the region of this interface becomes limited to the discus-shaped **placenta,** because the amniotic sac completely fills the chorionic cavity. The umbilical cord connects the placenta to the fetus with one large vein and two smaller arteries. As the cord grows, the vessels tend to spiral.[4] **Wharton's jelly,** a gelatinous substance inside the umbilical cord, helps protect the vessels and may prevent the cord from kinking.

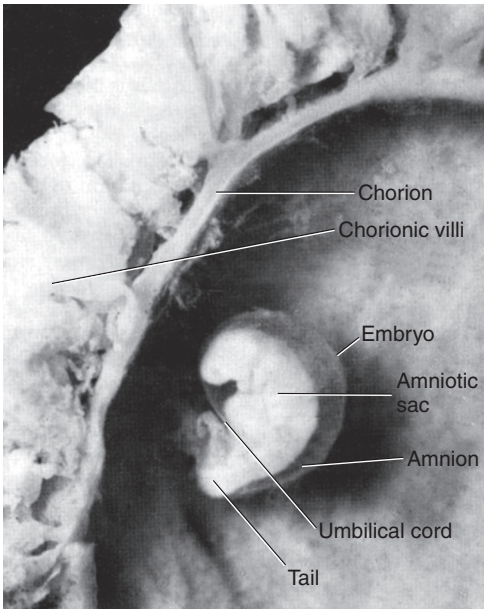


FIGURE 2-1 Implanted human embryo, approximately day 28, showing the relationship of the chorion, amnion, and chorionic villi. The umbilical cord and tail are difficult to differentiate in this view. (From Blechschmidt E, editor: *The stages of human development before birth.* Philadelphia, 1961, WB Saunders.)

CARDIOVASCULAR DEVELOPMENT

During the third week of gestation, the heart is fully formed. The heart is considered to be the first complete organ formed. By 8 weeks of gestation, the fetal heart is fully functional, complete with all chambers, valves, and major vessels. In addition, the fetal heart must accommodate the circulatory configuration required to support a fetus that is residing, growing, and maturing enclosed within a fluid-filled environment. The anatomic solutions to circulate oxygenated blood cannot be the same in the placenta-respiring fetus as it is in the air-breathing newborn. As the embryonic heart changes are described, note which of them may result in the cardiac anomalies discussed in Chapter 24. Table 2-1 lists the timing of the key cardiac developments.

Table 2-1 Timetable of Significant Events During Fetal Heart Development

TIME OF GESTATION	EVENT
Early Development	
Week 3	
Day 16	Angiogenic clusters (blood islands) appear
Day 18	Heart tubes form
Day 21	Heart tubes fuse
Chamber Development	
Week 4	
Day 22	Fusion of heart tubes complete Heart begins to beat Bidirectional blood flow begins
Day 23	Folding, looping, ballooning begin
Day 25	Atrial septation begins with growth of septum primum
Day 28	Ventricular septation starts Endocardial cushions form Unidirectional blood flow begins
Week 5	
Day 32	Septum secundum starts
Week 6	
Day 37	Foramen ovale complete
Maturation	
Day 46	Ventricle formation complete
Day 49	Four chambers complete
	Valve formation matures
Week 8	
Day 52	Aorta/pulmonary artery complete separation
Day 56	Valve formation complete

EARLY DEVELOPMENT

During early embryonic development, small cellular pools, referred to as **angiogenic clusters** or blood islands, supply nutrition to the growing embryo. These clusters coalesce to form two heart tubes lined with specialized myocardial tissue.[5] On approximately day 18 the heart tubes fold into what will become the thoracic cavity. At this point they become close enough to fuse, and they grow into a complete single-chamber tubular structure by day 21. The cardiovascular system forms primarily from the mesoderm layer, but myocardial tissue has a diverse origin related to the recruitment of myocytes from surrounding tissue types during embryogenesis.[6] By day 22 cardiac contractions are detectable and bidirectional tidal blood flow begins.[4]

CHAMBER DEVELOPMENT

Dramatic changes begin to occur during the fourth week of gestation. The heart tubes continue to merge into three identifiable structures called the **bulbus cordis,** the **ventricular bulge,** and the **atrial bulge.** These structures empty into the sinus venosus, which also receives blood from three additional sources: the vitelline veins (arising from the yolk sac), the common cardinal veins (from the embryo), and the umbilical veins (from the primitive placenta) (Figure 2-2).[7] These structures continue to bend, fold, and dilate by

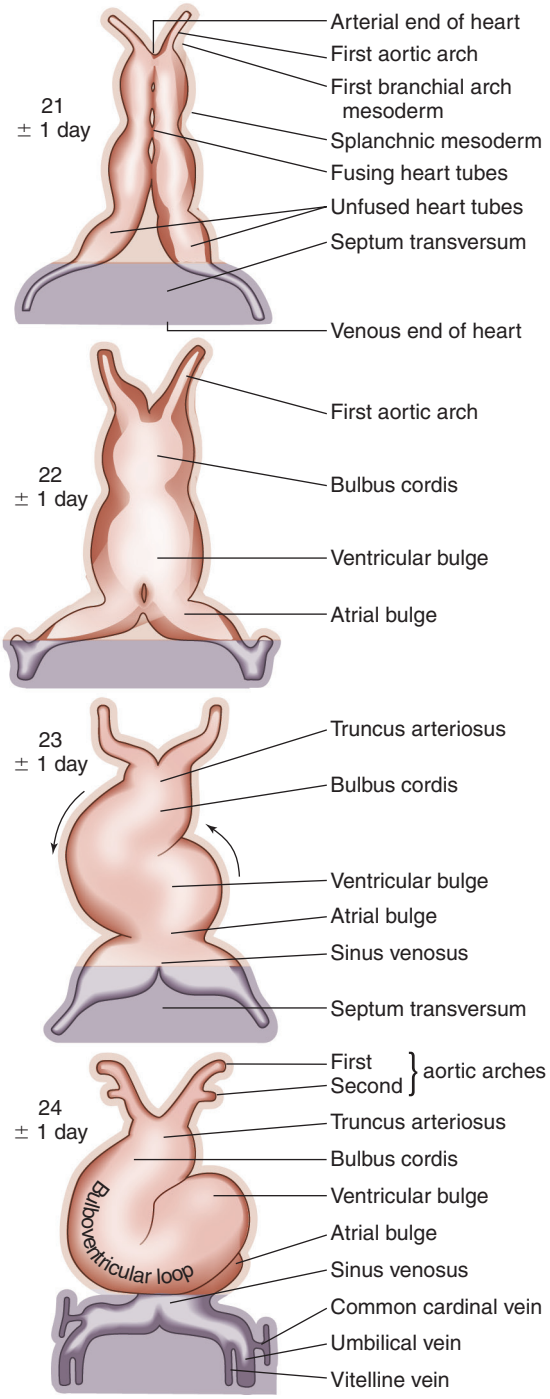


FIGURE 2-2 Formation of the primordial heart chambers after fusion of the heart tubes at a gestational age of 3 weeks. (From Moore KL, editor: *The developing human: clinically oriented embryology,* ed 3. Philadelphia, 1982, WB Saunders.)

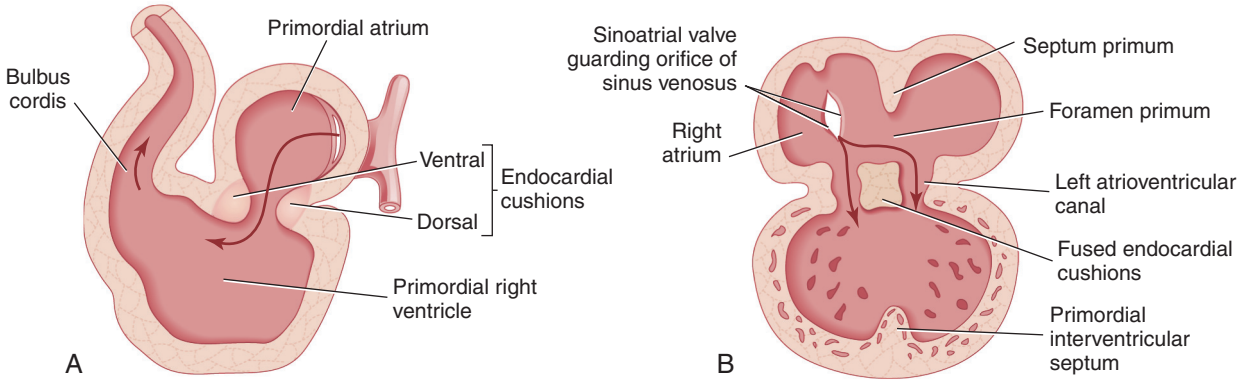


FIGURE 2-3 **A,** Sagittal view of the developing heart during week 4, showing the position of the atrium, bulbus cordis, ventricles, and endocardial cushions merging from the ventral and dorsal sides. **B,** Traditional view of the developing heart during weeks 4 to 5, showing budding interventricular septum, fused endocardial cushions, septum primum, and the left and right atria. The ventricular septum continues to fold and grow upward between the ventricles. (Modified from Moore KL, editor: *The developing human: clinically oriented embryology,* ed 3. Philadelphia, 1982, WB Saunders.)

incorporating components from surrounding tissue structures as the truncus arteriosus (which connects the heart to the future arterial system) becomes recognizable.[8] Note that initially the atrial bulge is inferior to the ventricular bulge. Between days 23 and 28 a process referred to as **dextral looping** occurs, whereby the ventricular bulge balloons into a C-shaped loop that pushes the atrial bulge in a superior direction (see Figure 2-2). Subsequently the embryonic heart appears as a twisted S-shape, and the ventricular structure merges with the bulbus cordis to form a one-ventricle structure known as the **bulboventricular loop,** which continues to dilate.[9]

Simultaneous with the external changes, the **septum primum** begins the separation of the primitive atrium, followed shortly by growth of the **endocardial cushions,** which will separate the atria from the ventricles. During this time the left atrium incorporates the primordial pulmonary veins as four pulmonary veins empty into the primordial left atrium. The right horn of the sinus venosus grows in dominance and merges into the future right atrium from the inferior and superior vena cavae. By the end of the fourth week the dilating ventricular spaces fold into each other and force the ventricular septal bud upward at the base of the bulboventricular loop (Figure 2-3).[4] By this time blood flow matures into a unidirectional path as the myocardium continues to strengthen by recruiting myocytes from the surrounding mesenchymal tissue.[3,6]

During weeks 5 and 6 the internal and external structures continue to mature rapidly. Between the atria the **septum secundum** begins to appear. By week 6 the septum secundum and a flap from the septum primum form the **foramen ovale,** one of the fetal shunts discussed later in this chapter (Figures 2-4 and 2-5). The atrioventricular canal continues to mature, and the endocardial cushions separate the ventricular spaces from the atrium. The muscular portion of the

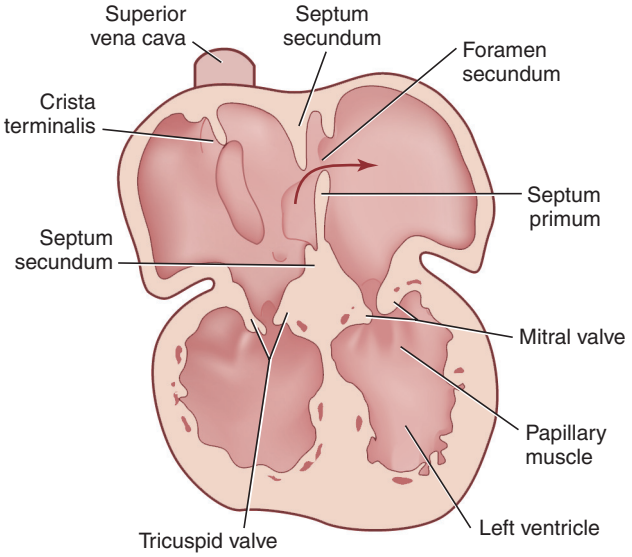


FIGURE 2-4 Frontal view of the fetal heart between weeks 5 and 6, showing the development of the four chambers nearing completion. The *arrow* shows the one-way path through the foramen ovale. (Modified from Moore KL, editor: *The developing human: clinically oriented embryology,* ed 3. Philadelphia, 1982, WB Saunders.)

ventricular septum continues to grow into the ventricular space as the two ventricles dilate. Ridges also appear opposite each other in the bulbus cordis and truncus. They grow toward each other and fuse into a spiraling **aorticopulmonary septum,** which ultimately separates into the aorta and pulmonary arteries.[3] A fetal heart rate of about 95 beats per minute becomes discernible during this period and increases by approximately 4 beats per day until heart development is complete.[10]

MATURATION

Continuing maturation of the internal and external structures characterizes weeks 7 and 8. The ventricles finish forcing the ventricular septum up from its base.

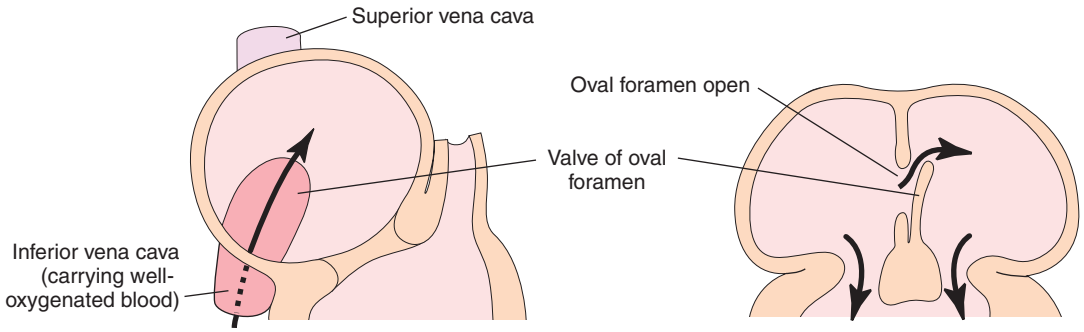


FIGURE 2-5 Frontal view *(right)* and side view *(left)* schematics of the foramen ovale. The septum primum forms the flap, and the septum secundum remains open to form the foramen ovale. The arrows show the one-way path through the foramen ovale. (From Moore KL, editor: *The developing human: clinically oriented embryology,* ed 3. Philadelphia, 1982, WB Saunders.)

A small intraventricular foramen remains, and blood flows between the two ventricles until the endocardial cushions fuse with the ventricular septum (see Figure 2-4). At the end of the seventh week, tissue from remnants of the bulbus cordis and tissue from the endocardial cushions grow into the ventricular foramen, closing it as they merge with the muscular ventricular septum. The tricuspid and mitral valves form from specialized tissue surrounding the two atrioventricular openings. The aorticopulmonary septum divides the bulbus cordis and truncus into an aortic and pulmonary trunk. As these outflow tracts continue to mature, the semilunar valves form at the base of each structure.[8] Early in the eighth week the outflow tracts and valves are completely developed. At this stage, development of the cardiac structures is complete, and blood flows through the fetal circulation pathway. The heart continues to develop, increasing proportionately more in length than width, paralleling embryonic growth.[11,12]

FETAL CIRCULATION AND FETAL SHUNTS

Fetal circulation necessarily differs from circulation after the infant is born, because external respiration by the fetus does not occur within the lungs. Figure 2-6 illustrates fetal circulation and the three shunts present in the fetus that close soon after birth. The mother's lungs and liver perform most of the metabolic functions required by the same organs of the fetus. The fetal circulation pathway allows blood flow to be shunted around the fetal liver and lungs. Shunting most of the blood volume through the fetal heart, bypassing the lungs, facilitates pumping the required large quantities of fetal blood to the placenta, which is the gas, nutrient, and waste exchange interface between the maternal and fetal organ systems.[11]

Oxygenated blood travels from the placenta to the fetus through the umbilical vein. The ductus venosus, the first fetal shunt, appears continuous with the umbilical vein, shunting approximately 30% to 50% of the oxygen-rich blood directly to the inferior vena cava, effectively bypassing the fetal liver. The amount of shunting through the ductus venosus appears to decrease with gestational age.[13] The oxygen-rich blood within the umbilical vein empties into the inferior vena cava and mixes with oxygen-depleted systemic venous blood as it flows to the right atrium. Even though some admixture occurs, the blood entering the right atrium contains the highest oxygen saturations available to the fetus.

In the right atrium most of the blood flow from the inferior vena cava crosses through a hole within the atrial septum, called the *foramen ovale,* into the left atrium. The foramen ovale, the second fetal shunt, is formed during septation of the atria, as described previously. The septum primum acts as a one-way valve over the ostium secundum (see Figure 2-5). The remainder of the blood in the right atrium mixes with desaturated blood from the superior vena cava and drains into the right ventricle. Blood in the right ventricle contains slightly higher oxygen content than blood from the superior vena cava and is pumped into the pulmonary artery to the developing lungs.

The pulmonary vascular resistance (PVR) in utero is high. Likely mechanisms include physical compression of the vessels resulting from relatively low lung volumes and hypoxic pulmonary vasoconstriction resulting from the low partial pressure of oxygen within the alveolus of the fetus. Both mechanisms help induce chemical mediators that maintain a high resistive tone in the pulmonary vascular bed.[14] Up to 13% to 25% of the fetal blood flow presented to the right atrium reaches the lungs.[11,15]

Blood from the pulmonary veins empties into the left atrium and then flows into the left ventricle, out the aortic valve, and into the ascending aorta, where it supplies blood with the highest oxygen content to the head, right arm, and coronary circulation. The high PVR causes most of the blood flowing through the pulmonary artery from the right ventricle to pass through the less resistant ductus arteriosus, the third fetal shunt, directly into the aorta. This allows blood within the pulmonary artery to bypass the lungs

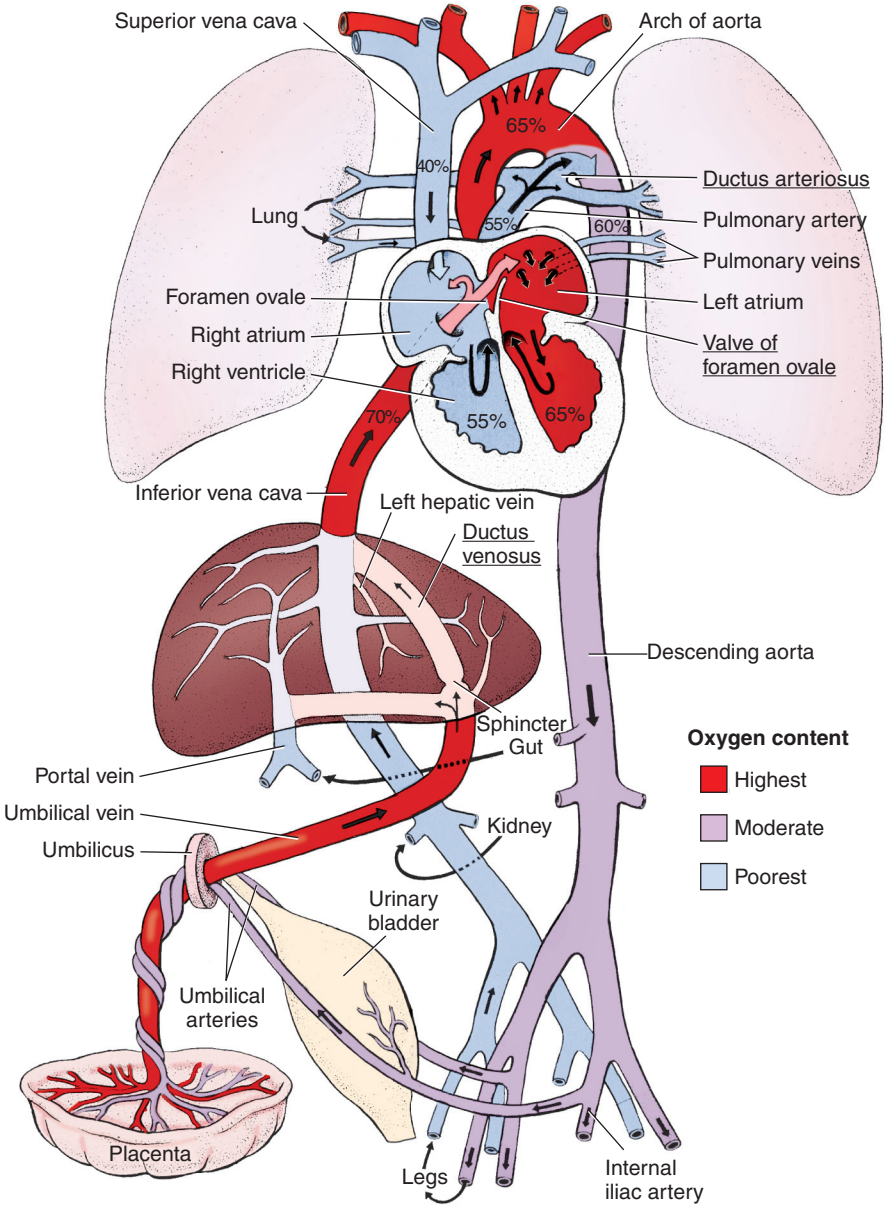


FIGURE 2-6 A diagram of the fetal circulation showing blood containing oxygen and nourishment moving from the placenta to the fetal heart and through the three fetal shunts: the ductus venosus, the foramen ovale, and the ductus arteriosus. (Modified from Moore KL, editor: *The developing human: clinically oriented embryology,* ed 3. Philadelphia, 1982, WB Saunders.)

and left heart. Because large quantities of blood are required to flow to the placenta, this permits the right ventricle and left ventricle to pump almost in parallel. The path of fetal circulation and percentage of oxygen saturation in various locations are illustrated in Figure 2-6.[16]

The deoxygenated blood from the upper torso returns to the right atrium via the superior vena cava. Finally, blood in the descending and abdominal aorta flows through common iliac arteries to two umbilical arteries and back to the placenta for oxygenation.[17] Initially 17% to 20% of the fetal cardiac output flows through the umbilical arteries, but as the fetus matures, this rises to 33%.[18] At any point, the placenta contains as much as half of the fetal blood volume. Because of the large vascular surface area of the placenta, impedance to blood flow is extremely low, allowing blood flow through the placenta to remain consistent and stable.[11]

TRANSITION TO EXTRAUTERINE LIFE

Clamping the umbilical vessels removes the low-pressure system of the placenta from fetal circulation. During the first breath, several factors drastically reduce the PVR and increase pulmonary blood flow.[19] Inflation of the lungs initiates gas exchange, which in turn dilates the pulmonary arterioles. Rising systemic

arterial oxygen pressure (Pao_2) also stimulates the release of endogenous pulmonary vasodilating cytokines that act locally to increase the diameter of the pulmonary arterial vasculature.[20] Stretching of the pulmonary parenchyma also physically expands the vasculature. Besides vasodilation, lung inflation results in the inhibition of vasoconstricting agents produced by the lung to facilitate fetal circulation.[19]

Once the cord is clamped and the PVR decreases, pressures in the right side of the heart decrease and pressures in the left side increase. Because the foramen ovale flap allows blood to flow only from right to left, it closes when the pressures in the left atrium become greater than those in the right atrium. Closing the foramen ovale further facilitates the increase of blood flow to the lungs during the transitional period and is necessary to maintain normal extrauterine circulation.

Because the pressure in the aorta also increases and becomes greater than the pressure in the pulmonary artery, the amount of shunting through the ductus arteriosus decreases. The functional closure of the ductus arteriosus occurs as a result of being exposed to an increase in Pao_2, a decrease in PVR leading to the reduction in blood pressure within the ductal lumen, a decrease in the local production of prostaglandins, and a reduction in the number of prostaglandin receptors within the tissue of the ductus arteriosus.[21,22] Normally, constriction of the ductus arteriosus starts to occur at birth, and 20% of the ductus closes within 24 hours, with 80% closed in 48 hours and 100% by 96 hours after birth.[23] Anatomic closure of the ductus arteriosus begins in the last trimester as endothelial tissue begins to proliferate into the lumen of the ductus, forming bulges known as **intimal mounds.** Initially assisted by vasoconstriction, the ductal lumen closes completely as gestational and postgestational age advances.[24] By 2 to 4 weeks of age, the anatomic closure is complete and blood flow normalizes to the adult pattern of circulation.[23] The structure that was once the ductus arteriosus is referred to as the *ligamentum arteriosum* in adults.

Case Study *Dystocia-Associated Respiratory Distress*

A 32-year-old woman has just given birth to a 38-week newborn after prolonged labor as a result of shoulder dystocia. The baby was born apneic, with minimal muscle tone and a heart rate of 80 beats per minute. The newborn was attended to immediately by the neonatal resuscitation team, who provided positive pressure ventilation for approximately 30 seconds. The newborn began breathing spontaneously and was transferred to the intensive care nursery on supplemental oxygen. Three hours later, despite the supplemental oxygen, the baby was still cyanotic. The physician ordered pulse oximetry of the right hand and left foot, which revealed saturations of 96% and 75%, respectively.

1. What two anatomic shunts normally present in the fetus can result in persistent cyanosis in the newborn?
2. Why would the newborn in this case be at risk for refractory hypoxemia?
3. Why are the two oximetry readings necessary, and why are the probes placed at the sites specified by the physician?

See Evolve Resources for answers.

Key Points

- The heart is the first complete organ formed. Identifying the stages of development of the heart is important in understanding congenital problems that can occur when development does not proceed as expected.
- The ductus venosus, foramen ovale, and ductus arteriosus are the anatomic shunts present in the fetus that allow fetal circulation. These shunts are essential to proper nutrient and gas exchange in the fetus.
- The three anatomic shunts and the pressure gradients induced by the circulatory systems (e.g., placental, pulmonary, and systemic) are all necessary to ensure proper directional blood flow through the fetus. This provides for gas and nutrient exchange and appropriate distribution of blood through the fetus.
- Transition from fetal circulation to adult circulation during the birthing process is a complex event that takes place flawlessly in nearly every birth. Recognizing the signs and symptoms of inappropriate transition is important to ensure that the right care is quickly delivered.

Assessment Questions

Select the best answer. See Evolve Resources for answers.

1. Which of the following are true statements concerning the development of the circulatory system?

I. Heart development is completed by about 32 weeks of gestation.
II. Heart development, other than growth, is complete when valve formation is complete.
III. Angiogenic clusters supply nutrition in the earliest stages of the growing embryo.
IV. The right-side myocardial fibers begin contracting before the left side to provide blood flow to the lungs.
V. At about 3 weeks, two heart tubes fuse into what will become the basic structure of the four-chamber heart.

A. I, III, and V
B. II and III
C. II, III, and IV
D. II, III, and V
E. III and IV

2. Which of the following are recognizable structures during development of the heart after the heart tubes fuse?
   - I. Sinus venosus
   - II. Bulbus cordis
   - III. Atrial bulge
   - IV. Ventricular bulge
   - V. Truncus arteriosus

   A. I and III
   B. I, II, IV, and V
   C. II, III, and IV
   D. II, III, IV, and V
   E. III, IV, and V

3. The oxygenated blood leaves the placenta and travels to the fetus through the _____.
   A. Aortic artery
   B. Umbilical vein
   C. Umbilical artery
   D. Spiral artery
   E. Ductus arteriosus

4. Most of the fetal blood entering the main pulmonary artery is shunted to the aorta through the _____.
   A. Foramen ovale
   B. Ductus venosus
   C. Ductus arteriosus
   D. Superior vena cava
   E. Iliac arteries

5. Most of the fetal blood entering via the umbilical vein is shunted to the inferior vena cava through the _____.
   A. Foramen ovale
   B. Ductus venosus
   C. Ductus arteriosus
   D. Superior vena cava
   E. Iliac arteries

6. Normal circulatory changes occurring within the transitional stage at birth include which of the following?
   - I. A decrease in pulmonary vascular resistance
   - II. A decrease in systemic vascular resistance
   - III. A decrease in pulmonary artery pressure
   - IV. An increase in left ventricular pressure
   - V. An increase in pulmonary blood

   A. I and IV
   B. I, II, IV, and V
   C. I, III, IV, and V
   D. II, III, and V
   E. III, IV, and V

7. Most of the fetal blood entering via the right atrium is shunted to the left atrium through the _____.
   A. Foramen ovale
   B. Ductus venosus
   C. Ductus arteriosus
   D. Superior vena cava
   E. Aortoiliac shunt

8. When discussing fetal circulation, which of the following is true?
   A. Fetal shunts help shunt the best-oxygenated blood to the head.
   B. Pressure gradients related to blood flow are the opposite of those in an adult.
   C. Fetal shunts help bypass the lungs.
   D. The placenta has low vascular resistance.
   E. All of the above.

9. What *one* set of actions causes the systemic circulation to transition from a low-resistance system to a high-resistance system?
   A. Clamping the umbilical cord and creating a short period of hypoxia
   B. Getting a higher concentration of oxygen into the lungs with the first breath
   C. Clamping the umbilical cord, thus preventing blood flow to the placenta
   D. Pulmonary hypertension from a change in blood flow direction
   E. Expulsion of the placenta at birth

10. Anatomic narrowing of the ductus arteriosus begins in the last trimester by which process?
    A. The formation of bulges known as *intimal mounds*
    B. The release of tolazoline compounds
    C. Ductal termination
    D. The formation of the aortic valve
    E. Activating thrombokinins

REFERENCES

1. Pensky B. *Review of medical embryology*. New York: McMillan; 1982:291-335.
2. Kingdom JC, Kaufmann P. Oxygen and placental vascular development. *Adv Exp Med Biol*. 1999;474:259.
3. Moore KL, Persaud TVN, eds. *The developing human: clinical oriented embryology*. Philadelphia: WB Saunders; 1998:63-82.
4. England MA, ed. *Color atlas of life before birth: normal fetal development*. Chicago: Year Book Medical; 1996:102.
5. Gourdie RG, Kubalak S, Mikawa T. Conducting the embryonic heart: orchestrating development of specialized cardiac tissues. *Trends Cardiovasc Med*. 1999;9(1–2):18.
6. Eisenberg LM, Markwald RR. Cellular recruitment and the development of the myocardium. *Dev Biol*. 2004;274(2):225.
7. Abdulla R, Blew GA, Holterman MJ. Cardiovascular embryology. *Pediatr Cardiol*. 2004;25(3):191.
8. Moorman A, Webb S, Brown NA, et al. Development of the heart: (1) formation of the cardiac chambers and arterial trunks. *Heart*. 2003;89(7):806.

9. Bartman T, Hove J. Mechanics and function in heart morphogenesis. *Dev Dyn*. 2005;233(2):373.
10. Tezuka N, Sato S, Kanasugi H, et al. Embryonic heart rates: development in early first trimester and clinical evaluation. *Gynecol Obstet Invest*. 1991;32(4):210.
11. Kiserud T, Acharya G. The fetal circulation. *Prenat Diagn*. 2004;24(13):1049.
12. Marecki B. The formation of heart-proportion in fetal ontogenesis. *Z Morphol Anthropol*. 1992;79(2):197.
13. Kiserud T. Fetal venous circulation—an update on hemodynamics. *J Perinat Med*. 2000;28(2):90.
14. Heymann MA. Control of the pulmonary circulation in the fetus and during the transitional period to air breathing. *Eur J Obstet Gynecol Reprod Biol*. 1999;84(2):127.
15. Lakshminrusimha S, Steinhorn RH. Pulmonary vascular biology during neonatal transition. *Clin Perinatol*. 1999;26(3):601.
16. Rudolph AM. *Congenital diseases of the heart*. Chicago: Year Book Medical; 1974.
17. Sharma A, Ford S, Calvert J. Adaptation for life: a review of neonatal physiology. *Anaesth Intensive Care Med*. 2011;12(3):85.
18. Goldkrand JW, Moore DH, Lentz SU, et al. Volumetric flow in the umbilical artery: normative data. *J Matern Fetal Med*. 2000;9(4):224.
19. Rudolph AM. The development of concepts of the otogeny of the pulmonary circulation. In: Weir EK, Archer SL, Reeves JT, eds. *The fetal and neonatal pulmonary circulations*. Armonk, NY: Futura Publishing; 2000.
20. Hageman JR, Caplan MS. An introduction to the structure and function of inflammatory mediators for clinicians. *Clin Perinatol*. 1995;22(2):251.
21. Clyman RI. Mechanisms regulating the ductus arteriosus. *Biol Neonate*. 2006;89(4):330.
22. Hammerman C. Patent ductus arteriosus. Clinical relevance of prostaglandins and prostaglandin inhibitors in PDA pathophysiology and treatment. *Clin Perinatol*. 1995;22(2):457.
23. Lim MK, Hanretty K, Houston AB, et al. Intermittent ductal patency in healthy newborn infants: demonstration by colour Doppler flow mapping. *Arch Dis Child*. 1992;67(10 Spec No):1217.
24. Mirro R, Gray P. Aortic and pulmonary blood velocities during the first 3 days of life. *Am J Perinatol*. 1986;3(4):333.

3 Antenatal Assessment and High-Risk Delivery

Benjamin Hamar, Anne Hansen

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. Identify various high-risk conditions that may adversely affect pregnancy outcome.
2. Describe current methods used for antenatal and intrapartum assessment of fetal well-being.
3. Explain preterm labor and postterm pregnancy evaluation and management.
4. Describe the current recommendations for assisting the newborn from intrauterine to extrauterine life.

Key Terms

anencephaly
biophysical profile (BPP)
β-mimetic drugs
bronchopulmonary dysplasia (BPD)
cervical cerclage
cervical insufficiency
contraction stress test (CST)
Doppler ultrasonography
endomyometritis
esophageal atresia
fetal alcohol syndrome
fetal fibronectin
germinal matrix
gestational diabetes mellitus
group B *Streptococcus* (GBS)
growth restriction
hepatitis B virus (HBV)
herpes simplex virus (HSV)
human immunodeficiency virus (HIV)
hydrops fetalis
intrauterine growth restriction (IUGR)
intraventricular hemorrhage (IVH)
laminaria tent
Listeria monocytogenes
macrosomia
meconium aspiration
necrotizing enterocolitis (NEC)
nonstress test (NST)
oligohydramnios
oxytocin
placenta previa
placental abruption
polyhydramnios
Potter's sequence
preeclampsia
premature rupture of membranes (PROM)
preterm delivery
respiratory distress syndrome (RDS)
retinopathy of prematurity (ROP)
sepsis
sudden infant death syndrome (SIDS)
syphilis
teratogen
tocolytic
velamentous cord insertion

The transition from intrauterine to extrauterine life is a critical process that involves major physiological changes and may require medical attention for an optimal outcome. Cooperation and communication among all members of the health care team are essential to identify potential problems and to intervene in a timely manner. That team includes obstetricians, pediatricians, nurses skilled in obstetrics and neonatology, anesthesiologists, and respiratory therapists. Maternal history, antenatal assessment (as dictated by maternal–fetal risk factors), and intrapartum monitoring are all important in identifying the fetus or newborn at risk of decompensation during the perinatal period. This chapter outlines the essentials of antenatal assessment and touches

briefly on the management of some high-risk conditions: preterm delivery, postterm pregnancy, and extrauterine transition of the fetus. The following sections will also discuss some commonly encountered risk factors associated with pregnancy and delivery. Comorbidities of the mother and abnormalities of the pregnancy that contribute significantly to compromised fetal well-being and preterm delivery are described. The chapter concludes with a section on assisting the fetus to extrauterine life.

MATERNAL AND PERINATAL DISORDERS

At the initial prenatal visit the obstetric care provider obtains a comprehensive maternal history and performs a physical examination. Disorders that place a pregnancy at increased risk for an adverse pregnancy outcome are identified. Subsequent periodic visits serve the purpose of monitoring and treating these disorders and identifying new obstetric risks that may necessitate further care. The following sections discuss commonly encountered maternal–fetal risk factors and their impact on obstetric care and perinatal outcome.

DIABETES MELLITUS

Diabetes in pregnancy is classified broadly as pregestational or gestational.

Pregestational Diabetes Mellitus

Women whose diabetes was diagnosed before the onset of pregnancy (pregestational diabetes) are at significant risk for adverse maternal and fetal outcomes. Adverse maternal outcomes include an increased risk of developing diabetic ketoacidosis, proliferative retinopathy, and preeclampsia or eclampsia. Close maternal metabolic surveillance to achieve tight glycemic control throughout pregnancy has significantly decreased the frequency of these outcomes.

Adverse fetal outcomes include stillbirth and major fetal structural malformations. Tight glycemic control and antepartum testing have significantly decreased the risk of fetal death. The rate of fetal structural malformations in infants born to women with pregestational diabetes can be as high as 10% to 15% and is proportionate to prepregnancy glycemic control. This compares to a rate of 2% to 3% for infants in the general population. The most commonly encountered defects in pregestational diabetes are malformations of the cardiovascular system, including both the heart and great vessels, and the central nervous system, including the brain and spinal cord. Glycemic control during organogenesis in the first few weeks of pregnancy is critical in reducing the risk for congenital malformations. Therefore it is recommended strongly that women with pregestational diabetes receive counseling and treatment with the goal of achieving optimal glycemic control with a hemoglobin A1c of less than 6.5% before pregnancy.[1]

Poor blood sugar control during pregnancy in these women is associated with an increased risk of **macrosomia** (birth weight greater than 4000 g), shoulder dystocia, preterm delivery, and stillbirth. After delivery, the infants are at increased risk for metabolic disturbances in the neonatal period; these include hypoglycemia, hypocalcemia, hyperkalemia, hyperbilirubinemia, and relatively undermature pulmonary function.

With good maternal glycemic control, pregnancies complicated by diabetes can proceed to full term with a vaginal delivery. Cesarean delivery is reserved for traditional obstetric indications, though the threshold for the recommendation of cesarean for large infants is slightly lower because of the increased risk for shoulder dystocia.

Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) is abnormal glucose tolerance of variable degree that occurs during pregnancy. The frequency of this disorder varies according to body mass index, maternal age, and the ethnic background of the woman; it affects 5% to 6% of pregnancies in the United States. In the long term, women with GDM that is not controlled by diet alone are at risk of developing type 2 diabetes; nearly 50% will be diagnosed with type 2 diabetes within 10 to 15 years.[2]

Among pregnant women, selective screening based on risk factors only identify 50% of women with GDM. It is thus recommended that all pregnant women be screened for GDM. Traditionally patients have been screened with the 1-hour 50-g glucose challenge test, administered between 24 and 28 weeks of gestation. Screening should also be performed in the first trimester for women with significant risk factors for pregestational diabetes (e.g., obesity, prior GDM). For those with an abnormal screening result, the diagnosis of GDM is made when there are two abnormal values on a 3-hour, 100-g oral glucose tolerance test. Alternatively, a 1-step screening and diagnostic test can be performed with a 2-hour, 75-g oral glucose tolerance test.

Maternal glycemic control and fetal biophysical status are monitored in a manner similar to protocols for managing a pregnancy complicated by pregestational diabetes (Table 3-1). Diet and lifestyle modifications are initiated and are successful in achieving adequate glycemic control in 75% of women. For those who fail to achieve adequate control, oral hypoglycemics such as glyburide and metformin or subcutaneous insulin are initiated. Insulin resistance related to the placenta increases over the third trimester, so it is not uncommon for women to progressively struggle with glycemic control later in the pregnancy. GDM carries with it risks for macrosomia, shoulder dystocia, stillbirth, and neonatal metabolic disorders.

Table 3-1 Criteria for the Diagnosis of Diabetes Mellitus Using Oral Glucose Tolerance Testing

GLUCOSE LOAD TIME	100 g GLUCOSE		75 g GLUCOSE	
	Serum Glucose mg/dL (mmol/L)		*Serum Glucose* mg/dL (mmol/L)	
Fasting	95	5.3	92	5.1
1 hour	180	10.0	180	10.0
2 hours	155	8.6	153	8.5
3 hours	140	7.8		

The diagnosis of diabetes during pregnancy is based on the serum glucose after ingestion of an oral glucose load. The diagnosis is made when two serum glucoses are elevated after ingestion of the 100-g load or one elevated serum glucose after ingestion of the 75-g load.
Data from American Diabetes Association. Postpartum statement: diagnosis and classification of diabetes mellitus, *Diabetes Care* 2011;34:s562.

INFECTIOUS DISEASES

A number of infectious agents can affect pregnancy outcome. Among the most important in the United States are **group B *Streptococcus* (GBS), herpes simplex virus (HSV), human immunodeficiency virus (HIV),** and **hepatitis B virus (HBV).**

Group B *Streptococcus*

Approximately 10% to 40% of pregnant women are colonized with GBS. Their infants are at risk for death or severe morbidity from perinatal infection with GBS.

In the past, two approaches were adopted for the prevention of early-onset GBS disease: culture-based and risk-based approaches. More recently, and based on a large retrospective cohort study, the American College of Obstetricians and Gynecologists recommends the culture-based approach because of its superiority in prevention of GBS disease.[3]

Vaginal–rectal cultures are usually obtained at 35 to 37 weeks of gestation. Patients with positive cultures should be treated with antibiotics from the time of membrane rupture or from the onset of labor, with a goal of achieving at least 4 hours of therapy before delivery. Penicillin is the drug of choice, but ampicillin is a good alternative. In the case of allergy to penicillin, sensitivity studies for clindamycin and erythromycin should be performed. Vancomycin is indicated in the case of resistance to clindamycin or erythromycin or if sensitivity studies are not available. Patients who present in labor or with rupture of membranes with unknown GBS status should be given antibiotic prophylaxis in case of intrapartum fever, prolonged membrane rupture (more than 18 hours), or **preterm delivery** (before 37 weeks of gestation). Antibiotic prophylaxis for GBS disease should be given to all patients with GBS bacteriuria during the current pregnancy or with a previous infant with invasive GBS disease.[4]

Herpes Simplex Virus

Genital HSV infection is a common sexually transmitted disease characterized by primary infection and recurrent outbreaks. Women who have primary or recurrent genital HSV outbreaks associated with labor and delivery are at increased risk for vertical transmission to their infants. Neonatal herpes is associated with significant morbidity in the infant. If there are active maternal lesions on the cervix, vagina, or perineum that are likely to be in contact with the infant during delivery, cesarean delivery is recommended. In women with a history of genital herpes, suppression with acyclovir beginning at 36 weeks decreases the likelihood of an active lesion at term.[5] It should be noted that asymptomatic viral shedding can happen in the absence of active disease, but the viral burden is believed to be acceptable to allow for a vaginal delivery.

Human Immunodeficiency Virus and Hepatitis B Virus

At this time all pregnant women enrolled in prenatal care are screened for HIV and HBV infection. Both viruses can cause disease in the fetus.

Human Immunodeficiency virus. In the general obstetric population in the United States the frequency of HIV infection is about 1 per 1000. HIV can be transmitted to the fetus during delivery through exposure to maternal blood and vaginal secretions. Early studies showed that zidovudine used during pregnancy, labor, and as chemoprophylaxis in exposed infants for 6 weeks is associated with a decrease in perinatal HIV transmission from 22.6% to 7.6%.[6] With the advent of highly active antiretroviral treatment (HAART) and prophylactic cesarean delivery for significant viral loads, vertical transmission rates can be reduced to less than 0.5%. Optimal antenatal, intrapartum, and postnatal regimens continue to evolve. Breastfeeding should be discouraged in HIV-positive women, because the virus is secreted in breast milk.

Hepatitis B virus. Around the world approximately 2 billion individuals have been infected with HBV, and 240 million remain chronically infected. In the United States 0.5% of the population test positive for the hepatitis B surface antigen and are thus chronically infected.[7] Infants of women infected with HBV are at high risk of becoming infected at delivery. When these infants are treated with anti–hepatitis B immunoglobulin and begin vaccination within the first 12 hours of life, 90% of neonatal infections are prevented. Cesarean delivery of these newborns provides no protection at delivery.[8]

Cytomegalovirus, rubella, *Toxoplasma gondii*, ***Listeria monocytogenes,*** mycobacterial species, and *Treponema pallidum* (**syphilis**) can all significantly affect the mother, fetus, and fetoplacental unit. Antenatal diagnosis and consultation with maternal fetal medicine in suspected cases is critical in the management of these conditions.

TOXIC HABITS IN PREGNANCY

Maternal habits should be assessed early in the course of gestation. Smoking, alcohol use, and drug use in pregnancy can cause well-described adverse effects on the fetus. The American College of Obstetricians and Gynecologists estimates that the prevalence of substance abuse in pregnant women is about 10%.[9]

Alcohol

Alcohol is a potent **teratogen**, and **fetal alcohol syndrome** was first described in 1973 by Jones and colleagues.[10] Potential sequelae of fetal alcohol syndrome include mental retardation; prenatal and postnatal growth restriction; and brain, cardiac, spinal, and craniofacial abnormalities. It is usually seen among children of women who consume four to six drinks daily throughout pregnancy.[11] However, no safe range for drinking alcohol during pregnancy has been established.

Smoking

Smoking during pregnancy can cause several adverse effects. Carbon monoxide and nicotine, the main ingredients responsible, mediate their effects by decreasing the availability of oxygen to the fetus and placenta. A strong association occurs between cigarette smoking and lower birth weight.[12] The mean birth weight of infants of women who smoke during pregnancy is about 200 g less than that of infants of nonsmokers. Smoking is also associated with a higher incidence of preterm **premature rupture of membranes** (**PROM;** i.e., rupture of the membranes before the onset of labor before 37 weeks of gestation),[13] placental abruption (i.e., separation of the placenta before birth of the newborn), placenta previa (i.e., when the placenta partially or completely covers the cervix),[14] and risk of infant death from **sudden infant death syndrome (SIDS),** the unexplained death of an infant younger than 1 year of age.[15]

Cocaine

Cocaine has potent sympathomimetic action and is a potent constrictor of blood vessels. It can cause numerous maternal medical complications that include myocardial infarction, stroke, seizures, bowel ischemia, and death. Cocaine is also associated with adverse pregnancy sequelae including placental abruption, preterm delivery (delivery before 37 weeks), and **growth restriction** (estimated fetal weight less than the 10th percentile for gestational age).[16] It is also believed to cause congenital malformations of the limbs, heart, brain, and genitourinary tract.

Opiates

Infants born to women with chronic narcotic use (either prescription or illicitly obtained) are at risk for neonatal abstinence syndrome. The risk does not appear to be related to maternal dose or other antenatal factors. Women who are receiving prescription opiates should be maintained on a comfortable dose during pregnancy to avoid withdrawal. Weaning off narcotics is not recommended during pregnancy because of concerns for *in utero* withdrawal. Opiates do not appear to increase the risk for birth defects or adverse pregnancy outcomes.

Other Substances

Infants born to women who abuse other drugs during pregnancy can have significant withdrawal symptoms after birth and tend to be small for gestational age. The obstetric care provider can encourage prevention of substance abuse in pregnancy by identifying patients at risk, educating patients about the effects of drugs, and referring patients already abusing drugs.

HIGH-RISK CONDITIONS

HYPERTENSION AND PREECLAMPSIA

Hypertensive disease complicates 12% to 22% of pregnancies in the United States and is second only to pulmonary embolism as a cause of maternal mortality.[17] Perinatal morbidity and mortality are increased secondary to **intrauterine growth restriction (IUGR),** placental abruption, fetal demise, and preterm delivery. Additionally, preeclampsia can lead to maternal cerebrovascular complications and HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets), disseminated intravascular coagulation (DIC), and other complications. **Preeclampsia** is a pregnancy-specific multisystem disorder that is diagnosed with new-onset proteinuria and hypertension after 20 weeks of gestational age. It complicates approximately 5% to 8% of pregnancies. Predisposing factors for the development of preeclampsia are listed in Box 3-1.

Preeclampsia remains a poorly understood disease despite extensive research. A variety of underlying mechanisms have been proposed, but the current and most promising theory involves placentally mediated inhibitors of angiogenesis. Low-dose aspirin has been shown to reduce the risk for preeclampsia in women at high risk. Preeclampsia can be characterized as mild or

Box 3-1 Predisposing Factors for the Development of Preeclampsia

- Nulliparity (never having given birth to a child)
- Advanced maternal age
- Chronic hypertension
- Chronic renal disease
- Diabetes mellitus
- Twin gestation
- Molar pregnancy (gestational trophoblastic disease)
- Hydrops fetalis (total body edema [anasarca] with pleural and pericardial effusion)

Box 3-2 Criteria for the Diagnosis of Severe Preeclampsia

Clinical criteria for the diagnosis of severe preeclampsia is diagnosed in the presence of the following:

- Systolic blood pressure higher than 160 mm Hg
- Diastolic blood pressure higher than 110 mm Hg
- Proteinuria: more than 5 g per 24-hour urine collection
- Pulmonary edema
- Intrauterine growth restriction
- Oliguria: urine output less than 500 mL in 24 hours
- Thrombocytopenia: platelet count less than 100,000 per mL
- Headache
- Visual disturbances: scotomata, blindness
- Epigastric or right upper quadrant abdominal pain
- Hepatocellular dysfunction
- Grand mal seizure: definition of eclampsia

severe depending on presentation (Box 3-2). Delivery of the fetus and placenta is the definitive treatment of preeclampsia. Perinatal treatment may include administration of antihypertensives to reduce hypertensive complications and intravenous magnesium sulfate to reduce the incidence of eclamptic seizures. The management of preeclampsia depends on gestational age and other associated clinical factors. In general, preterm preeclampsia with severe features can be expectantly managed until 34 weeks unless exclusion criteria are met.[18] Preeclampsia without severe features can be managed until 37 weeks. Diagnosis of preeclampsia at term is an indication for delivery.

FETAL MEMBRANES, UMBILICAL CORD, AND PLACENTA

In utero the fetus is contained in the sterile, fluid-filled amniotic sac. If the membranes that compose the external lining of the amniotic sac rupture, the fetal environment is no longer sterile, increasing the risk of fetal infection. The causes of PROM are generally not known, but PROM is responsible for 35% to 40% of preterm births in the United States.[19] Preterm premature rupture of membranes (PPROM) may be managed expectantly with antibiotics (commonly ampicillin and erythromycin for 7 days) to prolong the latency period (time between rupture of membranes and labor).[20] If infection, abruption, or labor occurs, delivery is usually indicated. Otherwise, delivery is usually around 34 weeks gestational age. Previable PPROM is associated with higher risks for primary pulmonary hypoplasia and deformations such as Potter's sequence.

Abnormalities of the umbilical cord and placenta can have profound effects on fetal development and pregnancy outcome. The umbilical cord has a mean length of 55 cm and contains three vessels: two arteries and one vein. In 3% of pregnancies, the umbilical cord contains a single umbilical artery. A single umbilical artery is associated with fetal structural and chromosomal anomalies and fetal growth restriction.[21-22]

The length of the umbilical cord has long been recognized to be of clinical significance. A short cord predisposes to placental abruption and uterine inversion. A long cord is associated with cord prolapse (delivery of the cord before the infant, with compromise of blood flow from compression), cord knots, and nuchal cords (cord wrapped around the infant's neck). Marginal cord insertion (on the edge of the placenta) is of little clinical importance. **Velamentous cord insertion** (in which the umbilical vessels cross the fetal membranes unsupported by placenta or cord structure) may be associated with vasa previa and risk of rupture of a fetal vessel at the time of rupture of membranes, resulting in fetal exsanguination.

Placental abruption is separation of the placenta from its implantation any time before delivery of the fetus. Abruption complicates 1 in 180 deliveries.[23] Abruption results in varying degrees of impairment of nutrient and gas exchange between the mother and fetus. If the abruption is large enough, it can result in rapidly evolving fetal hypoxia, acidosis, and fetal death. In addition, the mother can suffer life-threatening hemorrhage and coagulopathy.

The risk for abruption increases with the following[22]:

- Prior abruption
- PPROM
- Hypertensive disease in pregnancy
- Increased age and parity
- Multiple gestation
- Trauma
- Cigarette smoking
- Thrombophilia
- Cocaine abuse
- Uterine leiomyomas behind the placental implantation site

Placenta previa occurs when the placenta implants over or close to the internal cervical os. Placenta previa complicates nearly 1 in 300 deliveries. Cesarean delivery is usually required. Placenta previa is associated with the following:

- Advanced maternal age
- Multiparity
- Prior cesarean delivery
- Multiple gestation

DISORDERS OF AMNIOTIC FLUID VOLUME

Early in pregnancy, amniotic fluid is derived from the fetal periderm (the as-yet noncornified fetal skin) and the fetal membranes that comprise the amniotic sac. Later, most amniotic fluid is the product of fetal urination, with little contribution from the now cornified fetal skin. Fetal swallowing is an important mechanism for absorption of amniotic fluid. The fetal lungs help circulate the amniotic fluid. The amniotic fluid index (AFI) is the sum of the sonographic

measurement of the depth of the largest vertical pocket of fluid in each uterine quadrant. Other measures of amniotic fluid include the single maximum vertical fluid pocket (MVP) by ultrasound.

Oligohydramnios, too little amniotic fluid or an AFI below 5 cm, may be associated with congenital anomalies (especially renal agenesis or urinary tract obstruction), placental insufficiency and fetal growth restriction, postterm pregnancy (pregnancy continuing beyond 42 weeks), or ruptured membranes. When oligohydramnios occurs early in gestation, it can cause primary lung hypoplasia and limb deformities. When renal agenesis occurs in association with oligohydramnios, it is called **Potter's sequence** and is always fatal. Later in gestation, oligohydramnios may lead to compression of the umbilical cord. In labor there is an increase in variable decelerations (as a result of cord compression) and an increase in cesarean delivery rate.[24]

Polyhydramnios, too much amniotic fluid or an AFI greater than 25 cm, may be associated with fetal malformations that might affect swallowing of amniotic fluid (e.g., **anencephaly;** congenital absence of the cranial vault; **esophageal atresia;** and tracheoesophageal fistula, a connection between the trachea and esophagus). Polyhydramnios can be caused by maternal diabetes or congenital infection. Polyhydramnios may be seen with **hydrops fetalis** (fluid within more than one fetal cavity), twin gestation (with twin–twin transfusion syndrome), poorly controlled maternal diabetes, and congenital infection (e.g., cytomegalovirus, parvovirus, or toxoplasmosis). Polyhydramnios overdistends the uterus and can lead to PROM, preterm labor, and cord prolapse.

PRETERM BIRTH

Preterm birth is the greatest cause of infant mortality in otherwise normal newborns. In the United States, 10% of neonates are born preterm and are at risk for significant morbidities, including **sepsis; respiratory distress syndrome (RDS); intraventricular hemorrhage (IVH),** bleeding into the ventricular system of the brain; **retinopathy of prematurity (ROP),** disorganized retinal vascular growth, which can lead to retina scarring and blindness; **bronchopulmonary dysplasia (BPD),** a chronic pulmonary disease associated with oxygen and positive pressure ventilation (PPV) and **necrotizing enterocolitis (NEC),** a bacterial infection of the intestinal wall; visual and hearing problems; and cerebral palsy. The more premature the infant, the greater are the risks for mortality and morbidity[25] (Table 3-2).

Box 3-3 lists some specific medical risk factors for preterm labor and delivery. Preterm birth can be seen as the final common pathway of a variety of underlying processes (Figure 3-1). A history of spontaneous preterm labor with delivery is one of the most important risk factors for subsequent preterm labor. With one prior preterm birth, a woman carries a 15% risk of subsequent preterm delivery; this risk increases to 32% with a history of two previous preterm births.[26] In women with prior preterm delivery, administration of weekly 17α-hydroxyprogesterone caproate has been shown to reduce the risk for recurrent preterm birth.[27]

Signs of preterm labor include back pain, menstrual-like pains, pelvic heaviness, vaginal discharge, and vaginal bleeding.[28] Labor is diagnosed with contractions

Table 3-2 Infant Mortality Rates in the United States, 2008

	LIVE BIRTHS NO. (%)	INFANT DEATHS NO. (%)	INFANT MORTALITY RATE*
Total Infants	4,247,726 (2)	28,075	6.61
<32 weeks	84,230 (1.6)	14,778 (53)	175.45
32-33 weeks	66,648 (2)	1172 (4)	17.58
34-36 weeks	372,162 (9)	2753 (10)	7.40
37-41 weeks	3,478,057 (82)	8470 (30)	2.44
≥42 weeks	240,795 (6)	648 (2)	2.69
Unknown	5834 (0.1)	255 (1)	

*Deaths of children up to 1 year of age per 1000 live births.
From Mathew TJ, Mac Dorman MF: Infant mortality statistics from the 2008 period: linked birth/infant death data set. *Natl Vital Stat Rep* 60(5):1-27, 2012.

Box 3-3 Medical Risk Factors Associated With Preterm Labor and Delivery

- Previous preterm delivery
- Premature rupture of membranes
- Genital infections: *Chlamydia trachomatis, Gardnerella vaginalis*
- Nongenital infections: pyelonephritis, pneumonia
- Chorioamnionitis: infection of fetal membranes and amniotic fluid
- Conditions that overdistend the uterus: multiple gestations, increased amount of amniotic fluid
- Bleeding in the first trimester of pregnancy
- Placental conditions: placental abruption or placenta previa
- Abnormalities of the uterine cavity: uterine septum or fibroids
- Fetal anomalies
- Cervical insufficiency
- Short interval between pregnancies
- Lifestyle factors
  - Smoking
  - Illicit drug use
  - Inadequate weight gain
  - Obesity
  - Young or advanced maternal age
  - Poverty
  - Short stature
- Occupational factors
  - Prolonged standing or walking
  - Strenuous work conditions
  - Long work hours

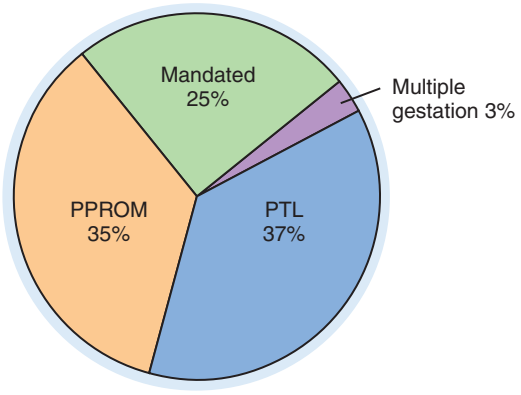


FIGURE 3-1 The four most common reasons for preterm birth. *PPROM*, Preterm premature rupture of membranes; *PTL*, preterm labor.

and cervical change. Several approaches to prevention of preterm labor have been studied. These include serial cervical examinations, home uterine activity monitoring, prophylactic use of oral **tocolytics** (an agent used to arrest uterine contractions), and bed rest. Efficacy data has been equivocal.

Fetal fibronectin (a glycoprotein produced in the chorion) is expressed in cervical and vaginal secretions in most cases of preterm labor. It has been studied as a marker of preterm labor in symptomatic patients. The absence of fetal fibronectin is a strong predictor that preterm delivery is unlikely to happen within 1 to 2 weeks, with a negative predictive value exceeding 95% in some studies.[29] It is particularly useful in the discrimination between preterm labor (contractions with cervical change) and preterm contractions (normal uterine activity).

Once preterm labor is diagnosed, prompt measures should be taken to try to stop labor and prevent an early delivery. Intravenous hydration is commonly the first approach used. It does not seem to be of clinical significance in a well-hydrated patient.[30] Excessive hydration should be avoided because it can potentiate the risk of pulmonary edema that is usually associated with tocolytic use. The following are commonly used tocolytics:

- Magnesium sulfate
- β-Mimetic agents
- Indomethacin (prostaglandin inhibitor)
- Nifedipine (calcium channel blocker)

Magnesium sulfate is usually given as an initial intravenous bolus of 4 to 6 g, followed by intravenous infusion at 2 to 4 g/hour. Its main mechanism of action is decreased free intracellular calcium ion concentration, resulting in decreased electrical potential of the cell. Magnesium sulfate infusion has the added benefit of reducing adverse neurologic sequelae associated with a premature birth.[31] Magnesium sulfate is contraindicated in patients with hypocalcemia, renal failure, and myasthenia gravis. Potential toxic effects of magnesium sulfate infusion include pulmonary edema, respiratory depression, cardiac arrest, muscular paralysis, and profound hypotension.[32] Loss of deep tendon reflexes usually precedes the previously mentioned complications. Deep tendon reflexes are checked frequently to monitor patients receiving therapy. Magnesium blood level can also be assessed. Toxic effects are rarely seen with levels less than 8 mg/dL or in patients with normal deep tendon reflexes.

β-Mimetic drugs (e.g., terbutaline and ritodrine), agents that mimic naturally occurring hormones that stimulate the β-adrenergic receptor, can also cause uterine relaxation. They decrease the electrical potential of the cell by increasing calcium binding to the intracellular sarcoplasmic reticulum, an effect mediated by cyclic adenosine monophosphate. They are contraindicated in patients with poorly controlled diabetes, thyrotoxicosis, or maternal cardiac disease. Potential side effects include hyperglycemia, hypokalemia, hypotension, pulmonary edema, arrhythmias, and myocardial ischemia. β-Mimetic drugs are most commonly administered subcutaneously.

Indomethacin (a prostaglandin inhibitor) reduces the synthesis of prostaglandins by inhibiting cyclooxygenase. It is contraindicated in patients with asthma, gastrointestinal bleeding, renal failure, coronary artery disease, and oligohydramnios. Its potential maternal complications include renal failure, gastrointestinal bleeding, and hepatitis (with chronic use). It can cause oligohydramnios, and when used after 32 weeks of gestation, it may induce closure of the ductus arteriosus in the fetus, leading to heart failure and hydrops. Indomethacin is administered either orally or rectally.

Tocolytics are widely used for the treatment of preterm labor. Studies have failed to show much success beyond delaying delivery for 48 hours.[33] They are generally used to achieve 48 hours of antenatal steroids.

All women between 24 and 34 weeks of gestation with a high likelihood of preterm delivery are candidates for antenatal corticosteroid therapy.[34] Betamethasone is the most commonly used agent and is administered in two doses of 12 mg, 24 hours apart. Maximal benefit occurs 48 hours after initiation of therapy, and the benefit lasts for 7 days. Corticosteroids reduce RDS and neonatal morbidity by 50%.[35] This effect is a result of induction of proteins that regulate the production of surfactant by type II cells in the fetal lungs. Corticosteroids also decrease the incidence of intracranial hemorrhage, probably by promoting maturation of the **germinal matrix,** a highly cellular and vascularized region of the brain that produces both neurons and glial cells that migrate to the cerebral cortex. Repeated corticosteroid courses should not be used routinely because of the possible risk of adverse neurodevelopmental outcome.[36] There is data that a second "rescue" course of steroids can be administered if more than a week has passed and there is additional risk for preterm delivery.[37] Steroids may also be given in the late preterm period (34 to 37 weeks), although it is not necessary to tocolyze or delay delivery to achieve a full course.[38]

Prevention of preterm delivery in patients with previous preterm deliveries is currently being studied. A study using weekly intramuscular injection of 17α-hydroxyprogesterone caproate showed promising results in decreasing the rate of recurrent preterm birth.[39] Other progesterone formulations and other routes of administration are being studied.[40,41]

CERVICAL INSUFFICIENCY

Cervical insufficiency is defined as painless dilation of the uterine cervix in the second trimester of pregnancy. This may lead to infection, rupture of membranes, or preterm labor and result in the delivery of a premature newborn. There is no consensus at this time concerning the causes of cervical insufficiency. Risk factors include cervical surgery (loop electrical excision procedure [LEEP] or cone biopsy), cervical trauma (from surgical injury or birth trauma), Müllerian anomalies, and collagen abnormalities (e.g., Ehlers-Danlos syndrome). A patient with risk factors for cervical insufficiency is generally evaluated by serial transvaginal ultrasound examination of the cervix beginning at 16 weeks to identify changes in cervical length and dilation (Figure 3-2). If cervical shortening or funneling of the cervix is diagnosed at any time into the late second trimester (22 to 24 weeks of gestation), a **cervical cerclage** may be considered.[42] Alternatively (or in conjunction with the cerclage), vaginal progesterone can be administered and has been shown to decrease the incidence of preterm delivery in the index pregnancy. For women with a history of pregnancy loss caused by cervical insufficiency, elective cerclage may be performed at 14 weeks of gestation.[43]

POSTTERM PREGNANCY

The most common reason for a diagnosis of postdate gestation is inaccurate dating because of either irregular ovulation or inaccurate recall of last menstrual period. Less common causes of postterm pregnancy are fetal anencephaly, placental sulfatase deficiency, and abdominal pregnancy. Most postterm pregnancies are of unknown cause; deficiency of prostaglandin production or refractoriness of the cervix to endogenous prostaglandins could be the cause.[44] An emerging modifiable risk factor associated with postterm pregnancy is obesity.[45]

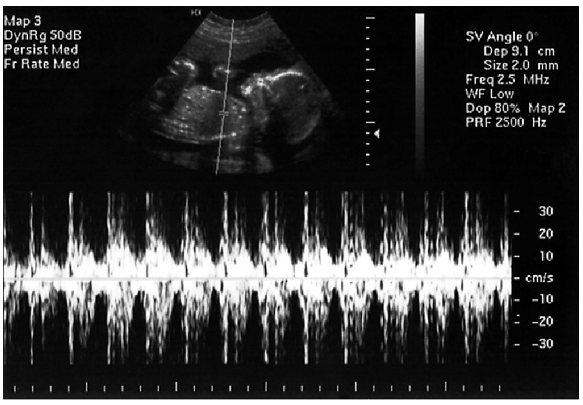


FIGURE 3-2 Ultrasound picture of a fetus at 23 weeks of gestation *(top)*, with a Doppler study of the fetal heart *(bottom)*. *Dop,* Doppler; *Fr,* frame; *Freq,* frequency; *PRF,* pulse-repetition frequency; *SV,* sample volume; *WF,* wall filter. (Courtesy Frank Fox, RDMS.)

Postterm pregnancy may be associated with maternal and neonatal problems. A woman may suffer from anxiety when she is past her due date and still undelivered. She is at higher risk of obstetric trauma (e.g., perineal laceration) from delivery of a large infant. Physically she is at increased risk of long-term sequelae such as incontinence and pelvic relaxation. The infant may experience oligohydramnios, macrosomia, **meconium aspiration** (inhalation of fetal fecal discharge into the fetal lungs), and placental insufficiency.

Fetal macrosomia increases the risk of cesarean delivery and increases the risk of birth trauma during vaginal delivery as a result of shoulder dystocia (when the anterior shoulder of the infant cannot pass below the mother's hip bone or requires significant manipulation to pass the pubic symphysis, resulting in brachial plexus palsy).

Meconium passage *in utero* is common after 40 weeks of gestation but may be a sign of fetal distress. Furthermore, aspiration of meconium may lead to obstruction of the respiratory passages and interference with surfactant function. For this reason, current recommendations include tracheal intubation of the limp, cyanotic newborn to remove meconium from below the vocal cords. A recent adequately powered randomized trial of amnioinfusion to prevent infant death or meconium aspiration failed to demonstrate any benefit to this intervention.[46] As a result, the American College of Obstetricians and Gynecologists recommends against routine amnioinfusion to prevent meconium aspiration syndrome.[47]

Placental insufficiency is another hazard to the fetus. When the placenta "ages," it fails to provide the fetus with substantial nutritional requirements. This may result in fetal IUGR.

To decrease the fetal risk of adverse outcomes, two strategies are widely used: antenatal testing and induction of labor. There are wide variations of practice regarding what method of testing to use (see Antenatal Assessment later in this chapter) and how often to perform testing. It is unclear whether labor induction results in improved outcomes compared with antenatal surveillance. The American College of Obstetricians and Gynecologists recommends labor induction for pregnancies at 41 weeks or more when the cervix is favorable. When the cervix is unfavorable, either cervical ripening followed by labor induction or fetal antenatal surveillance are acceptable options.[48]

Labor induction can be achieved with various medications when the cervix is favorable for induction. The Bishop score is commonly used to assess the cervix; when it is greater than 6, an induction is more likely to be successful.[49] Intravenous infusion of **oxytocin,** a hormone

secreted from the posterior pituitary that stimulates uterine contractions and milk letdown, is most commonly used in women with favorable cervical examinations. Oxytocin is started at a rate of 1 or 2 milliunits/minute and increased periodically until an adequate pattern of uterine contractions is achieved. Possible side effects include water retention with prolonged use of high doses (usually more than 20 milliunits/min). This can result in hyponatremia with maternal seizures and coma. Uterine rupture and amniotic fluid embolism have been cited with oxytocin use.

When the cervix is unfavorable for induction, its texture, dilation, and effacement can be improved by several modalities. Mechanical methods include placement of a Foley catheter balloon or osmotic dilator (**laminaria tent**) into the cervical canal. Laminaria are believed to act by absorbing water from the cervix, rendering it softer, resulting in dilation and effacement, a process referred to as *cervical ripening*. Pharmacologic agents have also been used for cervical ripening. Prostaglandin E_2 cervical gel (Prepidil) and vaginal insert (Cervidil) are widely used. They act by causing dissolution of collagen fibers in the cervix. The most common side effects include maternal fever, nausea, vomiting, and diarrhea. Misoprostol (Cytotec) is a prostaglandin E_1 analog that is approved by the US Food and Drug Administration for the prevention of gastric ulcers. Because of its uterotonic effect, it has been increasingly used for cervical ripening and labor induction. Its popularity stems from its effectiveness, low cost, and stability at room temperature; it can be administered orally or vaginally for cervical ripening.[50] Safety concerns have been raised in view of reports of uterine rupture occurring after misoprostol induction in patients with previous uterine scars.[51]

ANTENATAL ASSESSMENT

Assessing fetal well-being and identification of pregnancies at increased risk for adverse outcomes including stillbirth are the goals of antenatal assessment.

ULTRASOUND

One of the most widely used methods of noninvasive assessment of the fetus is ultrasonography (see Figure 3-2). Using ultra-high-frequency sound waves with either a transabdominal or transvaginal approach allows for detailed imaging and fetal assessment to be performed. Identifying multiple gestation and assessing chorionicity, evaluation of fetal anatomy, screening for markers for aneuploidy, serial assessment of fetal growth, measurement of amniotic fluid volume, evaluation of the placental location, and assessment of fetal status with the biophysical profile are all possible with two-dimensional grayscale ultrasound. In addition, Doppler flow studies measure blood flow to fetal organs. **Doppler ultrasonography** measures the shifts in frequency in the emitted ultrasound waves and their echoes, making it possible to measure the velocities of vascular structures. Umbilical artery Doppler allows for interpretation of placental function in the setting of growth restriction or twin–twin transfusion syndrome. Middle cerebral artery Doppler allows for screening for fetal anemia in cases of isoimmunization. Doppler of other vascular structures have been described for further fetal assessment. Ultrasonography is also invaluable for guiding the physician while performing chorionic villus sampling (CVS), amniocentesis, percutaneous umbilical blood sampling (PUBS), and other invasive procedures.

Three-dimensional ultrasound imaging is in use in obstetrics and has achieved a utility niche in certain centers for fetal assessment.

CHORIONIC VILLUS SAMPLING

CVS is performed between 10 and 14 weeks to obtain definitive genetic information about the fetus. Performance of a CVS earlier has been associated with fetal limb abnormalities. Using ultrasound guidance, either a needle is guided into the placenta transabdominally or a catheter is guided into the placenta transvaginally. Generally the placental location determines the approach used. A sample of the villi is obtained and adequacy of the specimen assessed by microscopy. Results can be confounded by confined placental mosaicism, which occurs in approximately 2% of specimens.[52]

AMNIOCENTESIS

After about 16 weeks, an amniocentesis can be used to obtain amniotic fluid for genetic, biochemical, or other analysis. Under ultrasound guidance, a needle is guided through the abdomen and into the amniotic sac (Figure 3-3). Fetal cells isolated from amniotic fluid can be used to assess for fetal chromosomal abnormalities (e.g., trisomy 21), fetal enzyme deficiencies (e.g., Tay-Sachs), and certain discrete genetic mutations (e.g., sickle cell disease). Cultures or polymerase chain reaction studies can be performed to evaluate for fetal infection. Near term, biochemical assays can be run to assess for fetal lung maturity.

NONSTRESS TEST AND CONTRACTION STRESS TEST

Fetal well-being is highly dependent on placental function. Placental function is commonly assessed by monitoring the fetal heart rate response when the fetus moves spontaneously **(nonstress test [NST])** or in reaction to induced uterine contractions **(contraction stress test [CST]).** For both tests, the fetal heart rate is monitored continuously. In the normally oxygenated fetus (as with a child or adult), cardiac output rises to support physical activity. This rise in cardiac output can be mediated by an increase in either heart rate or stroke volume. In the fetus, cardiac output rises by increasing the heart rate.

A reactive NST (Figure 3-4) requires at least two accelerations in fetal heart rate, each of at least 15 beats per minute and lasting at least 15 seconds. A reactive

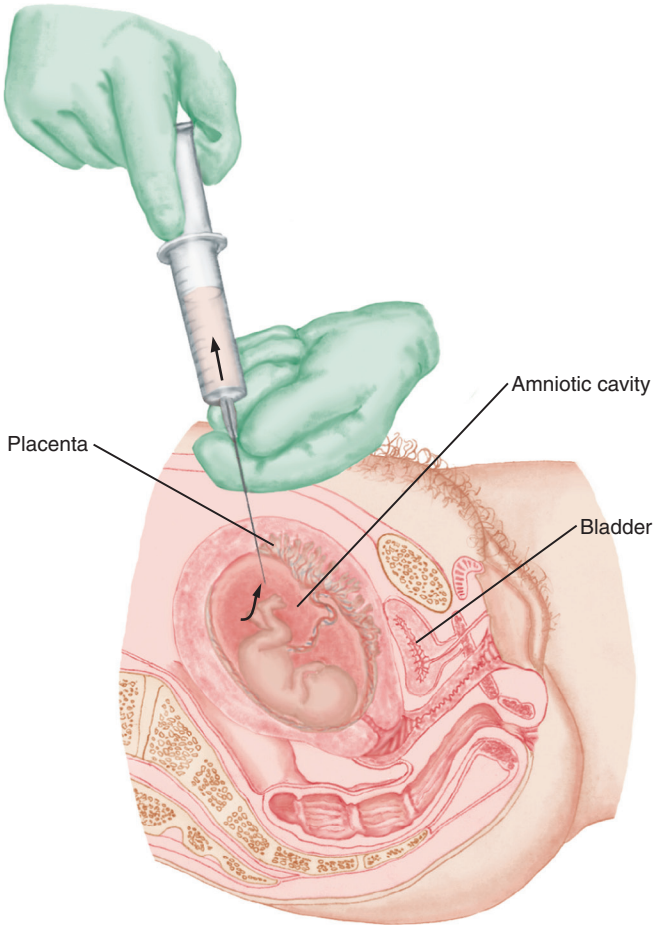


FIGURE 3-3 In amniocentesis, a needle is inserted through the expectant mother's abdomen to aspirate fluid from the amniotic sac. The fluid can then be tested to detect chromosomal abnormalities in fetal cells or other problems and to determine fetal lung maturity. (From McKinney E, James S, Murray S, Nelson K, Ashwill J: *Maternal-child nursing*, ed 5, St. Louis, 2018, Elsevier.)

NST is highly correlated with normal uteroplacental function. If no change in maternal clinical status transpires, this result predicts background stillbirth risk over the following week.[53] NST testing has been useful in the management of women with high-risk conditions (e.g., diabetes, hypertension, twins, advanced maternal age) to reduce the risk for stillbirth.

A CST is conducted by continuously monitoring the fetal heart rate while uterine contractions are stimulated by maternal intravenous infusion of a dilute solution of oxytocin. An adequate test involves three contractions within 10 minutes. In a normal pregnancy, fetal Po_2 (partial pressure of oxygen) decreases with each uterine contraction and then rapidly returns to normal. A fetal Po_2 drop below 12 mm Hg, resulting in slowing of the fetal heart rate, indicates uteroplacental insufficiency. This slowing of the fetal heart rate after a uterine contractions is called a *late deceleration.* A negative CST is one in which no late decelerations of the fetal heart rate develop with a frequency of three contractions, each lasting 40 to 60 seconds, per 10 minutes. A positive CST is diagnosed when late decelerations follow at least 50% of contractions. A suspicious CST is one in which late decelerations are inconsistent (follow less than 50% of contractions). Assuming no change in maternal clinical status, a negative CST predicts fetal survival if performed within 1 week of delivery. An abnormal CST prompts further evaluation or delivery.

FETAL BIOPHYSICAL PROFILE

The fetal **biophysical profile (BPP)** (Table 3-3) assesses placental function and fetal well-being.[54] In producing a BPP, five determinants of fetal status are assessed

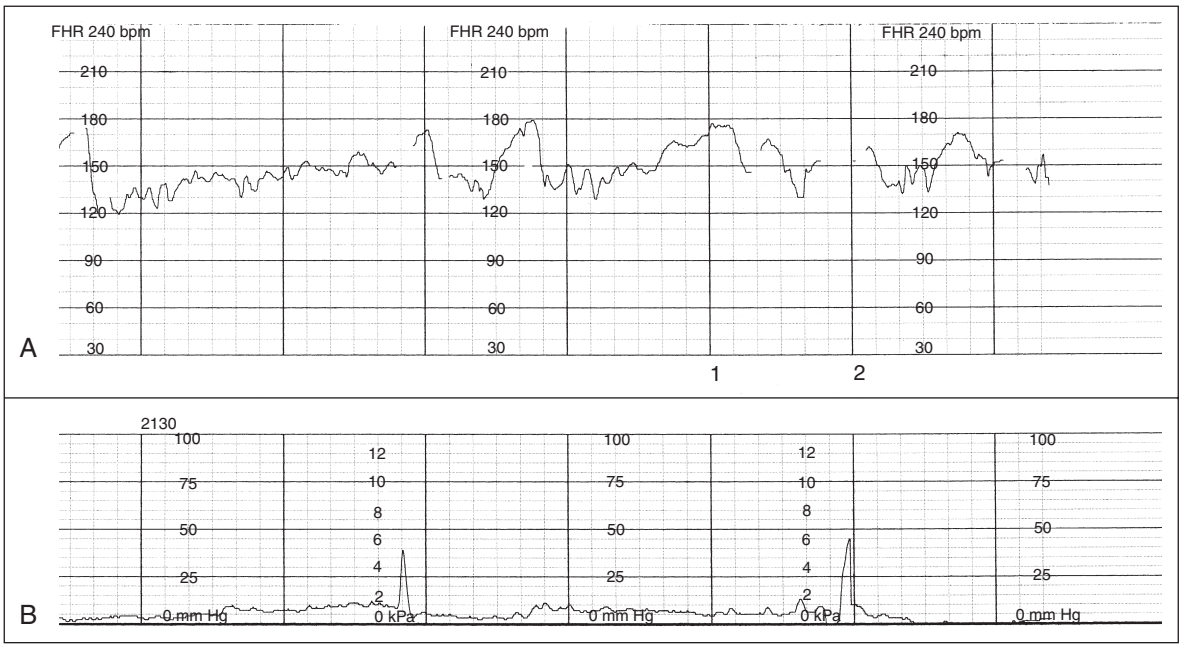


FIGURE 3-4 A nonstress test recording, produced with a cardiotocograph. **A,** The fetal heart rate *(FHR)* is recorded with an ultrasound probe as changes in beats per minute (bpm) over time. **B,** Uterine contractions are recorded with a pressure transducer as changes in pressure (mm Hg) over time. In this case the nonstress test is *reactive,* indicating normal uteroplacental function. (Courtesy Frank Fox, RDMS.)

Table 3-3 Biophysical Profile Scoring

BIOPHYSICAL VARIABLE	NORMAL (SCORE = 2)	ABNORMAL (SCORE = 0)
Fetal breathing movements	At least one episode of FBM, lasting at least 30 s, in 30 min	No FBM or no episode lasting >30 s in 30 min
Gross body movements	At least three discrete body/limb movements (episodes of active continuous movement, considered as a single movement) in 30 min	Two or fewer episodes of body/limb movements in 30 min
Fetal tone	At least one episode of active extension with return to flexion of fetal limb or trunk; opening and closing of hand considered normal tone	Either slow extension with return to partial flexion movement of limb in full extension or absent fetal movement
Reactive FHR	At least two episodes of FHR acceleration of >15 bpm and lasting at least 15 s associated with fetal movement in 20 min	Fewer than two episodes of acceleration of FHR or acceleration of <15 bpm in 40 min
Qualitative AFV	At least one pocket of AF that measures at least 1 cm in two perpendicular planes	Either no AF pockets or a pocket <1 cm in two perpendicular planes

AF, Amniotic fluid; *AFV,* amniotic fluid volume; *bpm,* beats per minute; *FBM,* fetal breathing movements; *FHR,* fetal heart rate.
Modified from Manning FA, et al: Fetal biophysical profile score and the nonstress test: a comparative trial. *Obstet Gynecol* 64:326, 1984.

and given a score of either 0 or 2. Four are assessed by ultrasonography. They include fetal breathing, fetal tone, fetal gross body movement, and amniotic fluid volume for a score out of a possible 8. If an NST is performed, it represents a fifth determinant and the score is out of a total of 10. A BPP score of 8 to 10 is considered normal and reassuring; a score of 6 is equivocal and is generally repeated within 24 hours; BPP scores of 0 to 4 are clearly abnormal, are associated with poor perinatal outcomes, and require close evaluation and usually prompt delivery.[55]

MODE OF DELIVERY

Most deliveries occur by the vaginal route. Typically, infants born vaginally are delivered head first (cephalic presentation). However, there are times when assisted vaginal delivery (with forceps or vacuum) or abdominal delivery (cesarean) is needed.

Breech Presentation

Breech presentation (legs or buttocks first) occurs in 3% to 4% of all births. The breech position creates a situation in which there is greater potential for complications at the time of delivery. Predisposing factors for breech presentation include multiparity, previous breech delivery, uterine anomalies, fetal anomalies, multiple gestation, and polyhydramnios. The Term Breech Trial Collaborative Group conducted a multicenter randomized controlled trial of planned cesarean versus planned vaginal delivery for breech presentation at term. It concluded that planned cesarean delivery is preferred because of lower risk for perinatal mortality or serious morbidity and no increase in serious maternal complications.[56] Two small randomized controlled trials published earlier did not find planned cesarean delivery of substantial benefit to the fetus.[57,58] At present, the American College of Obstetricians and Gynecologists recommends that patients with persistent breech presentation at term in a singleton gestation should have a planned cesarean delivery. This recommendation does not apply to patients who present with breech presentation in labor and with imminent delivery.[59] Transverse lie, in which the fetus is oriented transversely inside the uterus, is another malpresentation that requires cesarean delivery.

Assisted Vaginal Delivery

Obstetric forceps are an instrument used to cradle and guide the fetal head while applying traction to expedite delivery. The vacuum extractor is a suction device that holds the head tightly and allows traction to be applied. Indications for forceps or vacuum use include maternal cardiac, pulmonary, or neurologic disease (contraindicating the pushing process); maternal exhaustion in labor; and nonreassuring fetal status.

Cesarean Delivery

Cesarean delivery is the operative delivery of the fetus through the abdominal wall. It accounted for 33% of all births in the United States in 2010.[60]

Major indications for cesarean delivery include the following:

- Previous cesarean delivery
- Failure to progress in labor
- Malpresentation (breech or transverse)
- Placenta previa
- Nonreassuring fetal status

Although cesarean delivery might be the least traumatic method of delivery of the fetus, it is associated with the following:

- An increased risk of significant maternal blood loss
- Anesthesia complications
- Intraoperative bladder or bowel injuries
- Postoperative wound infection
- **Endomyometritis**
- Thromboembolic events

Transient Tachypnea of the Newborn and Type II Respiratory Distress Syndrome

The syndrome of transient tachypnea of the newborn (see Chapter 22), which includes the clinical features of cyanosis, grunting, and tachypnea during the first hours of life, is more commonly seen in infants delivered by cesarean, especially if performed before the onset of labor. The preferred explanation for the clinical features is delayed absorption of fetal lung fluid.[61]

INTRAPARTUM MONITORING

Despite controversy regarding the efficacy of intrapartum monitoring, its use has become ubiquitous in the United States. Its utility in high-risk patients is particularly valuable. The response of the fetal heart rate to uterine contractions provides information concerning the status of the fetus during labor. Fetal heart rate responses to uterine contractions and their likely etiologies are illustrated in Figures 3-5, 3-6, and 3-7. The

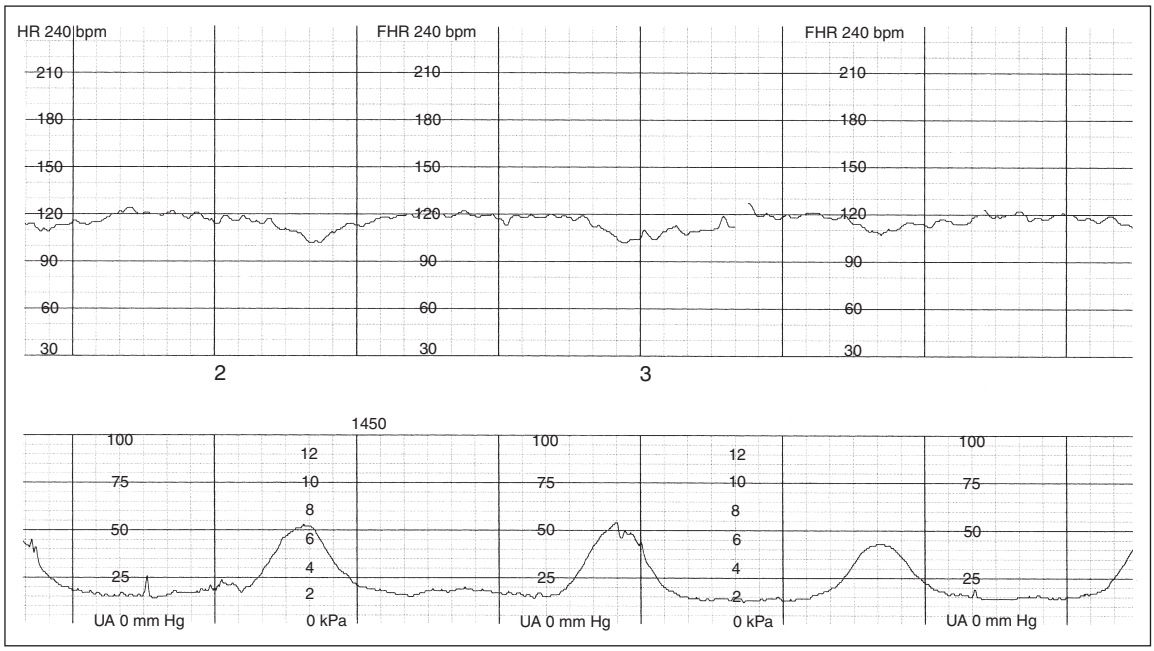


FIGURE 3-5 Early decelerations (coinciding with uterine contraction) usually are related to fetal head compression and pose little threat to the fetus.

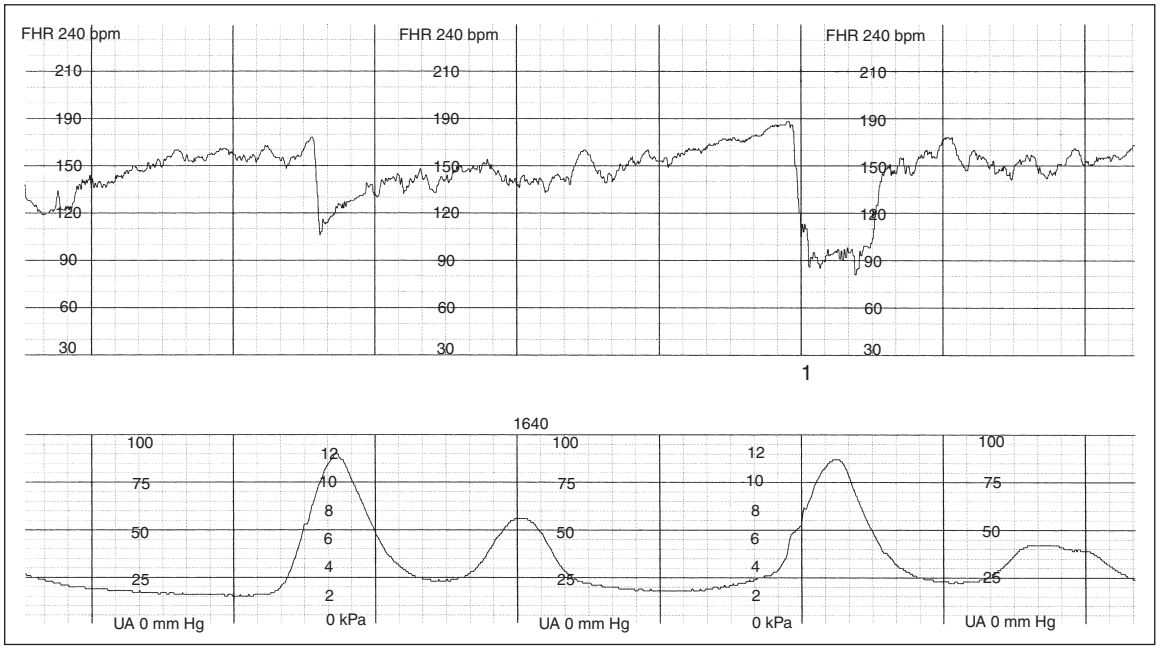


FIGURE 3-6 Variable decelerations are the most common. They are related to cord compression and have different configurations. Repetitive severe variable decelerations are associated with increased risk of fetal hypoxia.

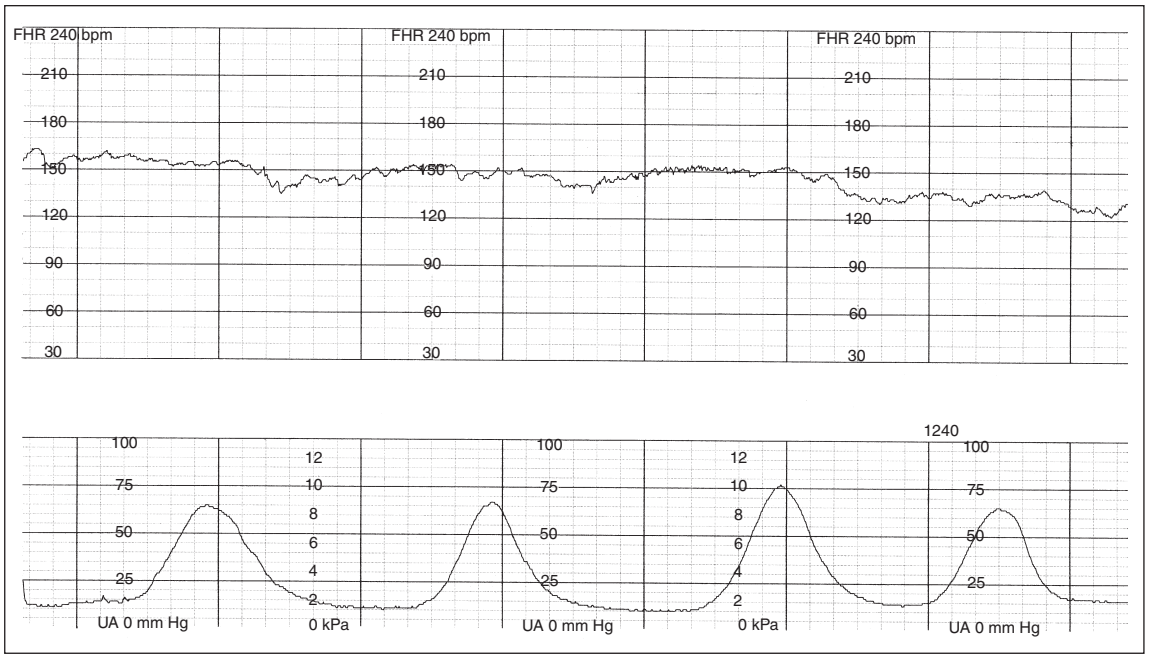


FIGURE 3-7 Late decelerations are related to uteroplacental insufficiency. They usually begin at the peak of the contraction and are associated with fetal distress.

nomenclature for fetal heart rate monitoring and classification of fetal heart rate tracings have undergone significant changes in recent years.[62] Fetal scalp sampling for pH and fetal pulse oximetry were used for fetal assessment but have largely fallen out of use because of lack of utility and efficacy.

FETAL TRANSITION TO EXTRAUTERINE LIFE

Appropriate evaluation and intervention at the time of delivery of a fetus/newborn are key to the successful transition from a pattern of fetal circulation to that of the newborn. The physiologic changes include increased Pao_2, decreased pulmonary vascular resistance, increased systemic vascular resistance, and closure of the foramen ovale and ductus arteriosus. These adaptations to extrauterine life usually occur in the first several hours after birth. Most newborns transition without intervention, but all newborns require a knowledgeable clinician to evaluate the success of the transition and intervene if the newborn displays maladaptation to the extrauterine environment.[63]

The environment where a baby is delivered can vary. The Guidelines for Perinatal Care delineate levels of hospital birthing services from level I through level III.[64] These levels have specific criteria that determine the type of pregnant women and newborns who should be cared for in a specific level of birthing hospital. Level I services provide basic maternity and newborn care to women with normal, term pregnancies. Level II services care for moderately ill pregnant women and newborns with a gestational age greater than 32 weeks. A level III service is defined as a birthing hospital that can care for the most complex of maternal, fetal, and newborn conditions. Depending on the level of perinatal service, resources for the care of pregnant women and newborns may vary.

All birth institutions should be prepared to offer antenatal counseling to parents if indicated and time permits. This counseling should be based on updated information regarding outcomes of the relevant condition. For impending premature deliveries, local morbidity and mortality data is critical to offering relevant counseling.[65]

In the event that a pregnant woman presents to a hospital with a perinatal designation that does not meet the needs of her pregnancy or the fetus, intrauterine transport to a higher level of perinatal service should be accomplished if at all possible. Sometimes, these transfers must occur after delivery. Many states have regionalized perinatal care systems that provide an organized approach to the transfer of pregnant women and newborns to higher levels of perinatal service as determined by level of illness and complexity as well as hospital resources.[64]

When a high-risk delivery occurs, whether planned or an emergency, key personnel, equipment, supplies, medications, and blood products need to be available. In most circumstances information from a woman's medical records can be obtained to provide baseline data regarding the patient. In trauma circumstances or when a pregnant patient is brought in unconscious or incapacitated, the situation can be very difficult. When a woman or fetus is deemed too unstable or labor has progressed too far to transfer the pregnant woman, preparation for delivery should occur. Maternal preparation should

include intravenous access, fetal and contraction monitoring, 100% oxygen via nonrebreather mask, and side-lying position to take pressure off the vena cava and maximize placental perfusion. Importantly, the team that will assess and provide newborn resuscitation must be alerted. If a cesarean delivery is planned, the goal is to begin surgery within 30 minutes of the decision to perform surgery—the so-called "decision to incision" time. Thus there should be a plan in place that ensures timely availability of surgical and anesthesia support staff.[66]

Preparations for the care of the newborn immediately after delivery need to be carefully planned regardless of the level of perinatal service in which a baby is delivered. Pregnant women are also brought to hospitals without delivery services, which requires that emergency departments be prepared to facilitate transition to extrauterine life and provide resuscitation for a newborn if necessary.

Systems should be in place for identifying newborns likely to require resuscitation and how to notify and gather a team if resuscitation is anticipated. The team members' roles should be clearly delineated before the delivery.

At a minimum, staff should be familiar with the recommendations for newborn resuscitation and have the equipment and medications necessary for the assessment and resuscitation of a newborn. The most recent edition of the American Heart Association and American Academy of Pediatrics *Textbook of Neonatal Resuscitation (NRP),* seventh edition, provides an excellent in-depth source for the most recent standards for newborn resuscitation in hospitals.[67]

The biggest changes to accepted resuscitation standards for newborns in the seventh edition of *NRP* pertain to delayed cord clamping and the management of newborns with meconium-stained amniotic fluid. There are also clarifications regarding oxygen delivery, use of PPV, approaches to thermoregulation, and communication.

Clamping of the umbilical cord should generally be delayed for 30 to 60 seconds for most term and preterm newborns. Circumstances when the placental circulation is not intact, such as abruption or cord avulsion, present clear exceptions to this recommendation. There are inadequate data regarding the risk-to-benefit ratio of delayed cord clamping when neonatal resuscitation is required.

In utero, a fetus may pass the first stool, called *meconium,* containing debris from amniotic fluid, vernix, and bowel exudate. Meconium aspiration can cause significant pulmonary complications; however, the timing of aspiration is now understood to primarily occur prenatally, not postnatally. Therefore the long-held practice of suctioning the trachea of newborns delivered through meconium-stained amniotic fluid is no longer recommended, not even for nonvigorous infants. The presence of meconium in the amniotic fluid is associated with *in utero* stress and therefore is a risk factor that prompts having present at the delivery a resuscitation team that includes a member with full resuscitation skills, including endotracheal intubation.

Most newborns make a successful transition to extrauterine life without intervention; however, 10% of newborns will require some intervention, and 1% will require extensive resuscitation.[68] The lower the gestational age of the newborn, the more likely he or she will require assistance. The transition needs to be observed by a skilled clinician. This can be done with the term infant placed skin to skin on the mother's chest. Interventions are necessary if the newborn is apneic or has gasping respirations, is bradycardic, or does not transition from cyanotic to pink within the expected time frame. These interventions are completed on a newborn resuscitation table, which may be present in the delivery room or located in an adjacent newborn stabilization room.

Thermal management is critically important to a successful extrauterine transition. Efforts should be made to reduce heat loss as much as possible. There is a marked increase in glucose and oxygen consumption when a newly born infant experiences cold stress. For an infant with a difficult transition, cold stress may precipitate the development of persistent pulmonary hypertension, a clinical situation in which pulmonary vascular resistance remains high, fetal shunts remain open, and blood flow to the newborn lung is minimal.[63] The temperature of the room in which the newborn will receive initial care should be 23 to 25° C (74-77° F). All newborns should immediately be dried, and a hat should be put on as soon as possible. Additionally, infants younger than 32 weeks of gestation should be placed on a conductive heat–gaining mattress and covered with a plastic wrap.[72]

After a newborn is dried, warmed, and stimulated, a skilled observer assesses the newborn's response and determines whether further interventions are indicated. Infants who are apneic may be in primary or secondary apnea. An apneic newborn needs to be immediately stimulated to breathe. The first maneuver is to clear the airway with either a bulb syringe or suction catheter. The response to stimulation will indicate primary or secondary apnea. The newborn will begin to breathe if the apnea was primary. Secondary apnea is only resolved with the implementation of PPV.

Provision of effective bag-mask ventilation, as evidence by adequate chest wall movement, is one of the most critical skills in neonatal resuscitation. This includes achieving an effective seal of the mask against the face and establishing patency of the airway. If PPV is necessary, infants who are at least 35 weeks of gestational age are initially ventilated with room air (21%), whereas infants younger than 35 weeks of gestational age can start with an Fio_2 between room air and 30%.[63]

Oxygen concentration is then adjusted using clinical assessment and preductal pulse oximetry. Specific guidelines for preductal pulse oximetry readings in the first 10 minutes of life in term babies are published and should be used to guide resuscitation maneuvers and administration of oxygen.[71]

There are three currently accepted methods of providing PPV: the self-inflating bag, the flow-inflating bag, and the T-piece resuscitator.[67] The self-inflating bag does not require a compressed gas source to fill but does not provide positive end-expiratory pressure (PEEP) without attaching a PEEP valve. The flow-inflating bag requires a gas source to distend it but can provide PEEP without an additional valve. The third device, the T-piece resuscitator, requires the operator to preset a peak inspiratory pressure and PEEP before providing PPV. Use of a device that can provide PEEP is preferable to ensure that the newborn's lungs remain inflated between breaths.[68]

The amount of pressure delivered by the self-inflating and flow-inflating bags is determined by the seal of the mask to the newborn's face and the squeeze the operator delivers when compressing the bag. The T-piece pressures are preset. The rate of ventilation recommended is 40 to 60 breaths per minute and is determined by how frequently the bag is squeezed, in the case of the self-inflating and flow-inflating bags. The rate when using the T-piece resuscitator is determined by depressing a valve on the tubing that attaches the T-piece device to the newborn mask. All devices used for newborn ventilation require safety features to avoid excessive pressure, which can result in lung injury and air leak. The T-piece resuscitator most reliably delivers ventilation at the prescribed pressures.[70]

Once ventilation is established, the newborn's response needs to be assessed. Chest rise and improvement in color should occur. A member of the team should attach a pulse oximeter to the preductal (right hand or wrist) limb and prepare to check a heart rate along the left side of the chest. An umbilical heart rate is no longer recommended, because this method is less accurate and may underestimate the actual heart rate.[69] Using these data the need for further resuscitation efforts can be determined. Decisions include the need to increase the Fio_2 and the need to perform chest compressions. Simultaneously another member of the team prepares an advanced airway for placement and prepares for the administration of medications.[71]

Chest compressions should be provided if the newborn's heart rate is less than 60 beats per minute after PPV. Chest compressions are administered with the two-thumb technique.[68] A skilled team member should place an endotracheal tube at this time if one has not already been placed.

Medications should be prepared for administration if the heart rate remains below 60 beats per minute after chest compressions. Placement of an umbilical catheter is ideal for epinephrine administration. However, the first dose of epinephrine may be given via the endotracheal tube if the placement of the umbilical line delays prompt administration of the medication. Doses of epinephrine will vary based on the route of administration.[71]

If the baby does not improve or remains asystolic, the effectiveness of each intervention must be assessed. The most common reason for lack of improvement is ineffective ventilation. After 10 minutes of complete and adequate resuscitation, if the baby shows no signs of life (remains asystolic without respiratory effort), it may be reasonable to discontinue resuscitative measures[70] because of the overwhelming likelihood of devastating neurologic injury or death.[72]

Infants who have had a difficult transition may have neonatal encephalopathy and could benefit from therapeutic hypothermia, a specialized therapy that slows metabolism to minimize brain injury after exposure to hypoxic or ischemic conditions.[73,74] This is a special circumstance in which a newborn is purposefully allowed to be cooled passively or actively until the core temperature drops to between 33° C and 34° C. Therapeutic hypothermia is generally provided to newborns at or near term within 6 hours of birth who have moderate to severe encephalopathy and a history and laboratory data supportive of a perinatal hypoxic ischemic event. Obtaining cord gases and placental pathology is useful. Therapeutic hypothermia is offered in level III perinatal centers and should not be undertaken without their guidance.[73,74]

Careful documentation is an important part of resuscitation. Ideally this should be written into a standard form that includes participating staff; time of initiation; frequent recording of respiratory rate, heart rate, and oxygen saturations; and interventions, including PPV, chest compressions, medications, and fluids.

Simulation of difficult deliveries and subsequent newborn resuscitations in a consequence-free environment are helpful in identifying the level of staff's competence and the strength of the systems that support their efforts in these challenging situations. Knowledge of the equipment, sequence of resuscitation, and teamwork need to be evaluated, as does the evidence of teamwork. Administrative support is necessary to ensure that the time and resources needed to complete a simulation are available and issues identified during the scenarios are rectified.[76]

When a delivery is imminent, preparation is critical. Necessary staff, equipment, and medications should be available and prepared. Resuscitation should proceed according to accepted sequences.[68] After the resuscitation, the staff should debrief the experience and use challenges to improve performance in the future.[78]

Case Study

Ms. S is a 28-year-old woman who is gravida 1, para 0 at 42 weeks and 1 day. Her pregnancy has been uncomplicated. She denies tobacco, alcohol, and drug use. Her blood type is O^+, antibody negative, and her prenatal labs are normal, including being GSB negative. She had a normal 1-hour glucose challenge test. She was seen in the obstetric clinic yesterday when a BPP was reported as within normal limits except for "slightly decreased volume of amniotic fluid."

She presents today to labor and delivery with regular, strong contractions. Her vaginal examination (VE) shows she is 4 cm dilated, 80% effaced, −2 station. The presenting fetal part is the head.

An epidural anesthetic is placed for pain control during labor. Two hours after admission her membranes spontaneously rupture and a small amount of green-tinged fluid appears. At this time her VE shows that she is 6 cm dilated, 90% effaced, 0 station. Dark green, thick meconium is present on the glove of the examiner. The fetal heart rate tracing shows that the heart rate is 160 beats per minute with variability of 25 to 30 beats per minute, no decelerations.

Two hours later Ms. S is fully dilated, with variable decelerations on the fetal heart rate monitor. She is now pushing. The neonatal team is called to attend the delivery of this postmature fetus with meconium-stained amniotic fluid.

The team arrives before the delivery and prepares the resuscitation table for the birth of a postterm infant with potential for meconium aspiration. The neonatologist prepares the laryngoscope and endotracheal tubes. The respiratory therapist prepares the blended gas source (air and oxygen), the T-piece resuscitator, and the self-inflating bag and mask. The nurse prepares the resuscitation table by turning on the heat and the pulse oximeter and prepares the pulse oximetry probe.

The baby is delivered limp, with decreased respiratory effort. The baby is placed on the warmer, dried, and stimulated by suctioning the mouth and nose. At 1 minute the baby is noted to have a heart rate greater than 100 beats per minute, gasping respirations, limited tone, and no reflexes and remains cyanotic, with an Apgar score of 4. The pulse oximetry probe is placed preductally, and SaO_2 reads 70%. The respiratory therapist notes the gasping respirations and begins to ventilate the baby with the T-piece resuscitator. The T-piece is set at 21% FiO_2, peak inspiratory pressure (PI) of 25 cm H_2O, and PEEP of 5 cm H_2O with a rate of approximately 40 breaths per minute. Chest excursion is observed to be inadequate. The mask is repositioned to create a better seal, and a mild jaw thrust is used to improve the patency of the airway with resulting improvement in chest wall movement. The nurse again checks the heart rate, and it is noted to be more than 100 beats per minute. Breath sounds are equal.

At three minutes after birth, the infant begins to breathe spontaneously and cry under the mask, begins to flex limbs, and becomes less blue. The SaO_2 now reads 80% at 5 minutes. The ventilation is discontinued. The neonatologist assigns a 5-minute Apgar of 8, 1 off for color and 1 off for tone. Two minutes later the infant is well flexed and has a lusty cry. The pulse oximeter reads 89%. The baby is then wrapped in a blanket and is placed on her mother's chest. The staff remains to ensure that the infant continues to transition successfully.

1. How often does gestation exceed 42 weeks?
2. What are some of the potential risk factors associated with a postterm pregnancy?
3. Why do you think amniotic fluid volume may be decreasing?
4. Did the neonatal team adequately prepare for the birth of the infant? Was their respiratory and airway management appropriate both in terms of the meconium-stained amniotic fluid and the poor chest wall movement with PPV?
5. What are your comments about their teamwork? How would you brief and debrief this clinical situation?
6. Are the newborn's recorded oxygen saturations as expected?

See Evolve Resources for answers.

Key Points

- Identification of prepregnancy chronic diseases and careful continuous assessment for disorders specific to pregnancy are important in maximizing maternal and fetal outcome.
- Fetal and cervical ultrasound, Doppler, and continuous electronic fetal monitoring are tools that can inform the progress of the pregnancy and maternal and fetal well-being. These tools often are used to determine maternal management, medications, bed rest, and indicated preterm delivery.
- Preterm labor can often be predicted. Strategies to lengthen gestation and improve the newborn outcome should be initiated as soon as preterm delivery is anticipated.
- Postterm pregnancy can be associated with maternal and fetal morbidity. Careful attention to fetal size and well-being should be implemented when a pregnancy becomes prolonged.
- Evidence-based strategies recently have been published regarding assisting newborns in the transition to extrauterine life. The use of titrated oxygen concentrations in response to the newborn's successful establishment of respiratory effort, vital signs, and preductal oxygen saturations are recommended.

Assessment Questions

See Evolve Resources for answers.

1. All of the following are criteria for a diagnosis of severe preeclampsia except _____.
- **A.** Headache
- **B.** Diastolic blood pressure higher than 110 mm Hg
- **C.** Generalized edema
- **D.** Intrauterine growth restriction

2. Cesarean delivery is indicated for which of the following maternal infections?
   - **A.** Group B *Streptococcus*
   - **B.** Hepatitis B
   - **C.** Hepatitis C
   - **D.** Anogenital herpes simplex virus
3. Polyhydramnios is associated with all of the following except _____.
   - **A.** Gestational diabetes
   - **B.** Anencephaly
   - **C.** Twin–twin transfusion syndrome
   - **D.** Use of prostaglandin synthase inhibitors
4. Late decelerations are usually caused by _____.
   - **A.** Uteroplacental insufficiency
   - **B.** Fetal anemia
   - **C.** Umbilical cord compression
   - **D.** Fetal head compression
5. The earliest sign of magnesium sulfate toxicity is _____.
   - **A.** Hypotension and tachycardia
   - **B.** Loss of deep tendon reflexes
   - **C.** Respiratory depression
   - **D.** Acute renal failure
6. When used for labor induction, misoprostol is contraindicated for patients with _____.
   - **A.** Postterm pregnancy
   - **B.** Preeclampsia
   - **C.** Previous cesarean section
   - **D.** Nulliparous pregnancy
7. All of the following are true about the use of induction of fetal lung maturity except _____.
   - **A.** Corticosteroids are contraindicated for patients with premature rupture of membranes.
   - **B.** Betamethasone and dexamethasone are the most commonly used corticosteroids.
   - **C.** Corticosteroid use is associated with a decreased risk of fetal intracranial hemorrhage.
   - **D.** Corticosteroid therapy reduces risk of respiratory distress syndrome and other morbidities by 50%.
8. In preparing the delivery or operating room for the delivery of an infant expected to require resuscitation, all of the following should be prepared except _____.
   - **A.** A warmed environment
   - **B.** A device that can only provide positive pressure ventilation at 100% oxygen
   - **C.** Staff skilled in assisting a newborn's transition to extrauterine life
   - **D.** A pulse oximeter for the newborn that is capable of accurate readings in low perfusion states
9. Full-term newborn infants initially resuscitated with 21% Fio_2 may require an increase in the concentration of inspired oxygen. This determination should be made based on _____.
   - **A.** The infant's skin color
   - **B.** The infant's respiratory effort
   - **C.** The postductal oxygen saturation (as measured by pulse oximeter)
   - **D.** The preductal oxygen saturation (as measured by pulse oximeter)
10. Preterm infants require additional strategies to prevent hypothermia in the delivery room. These include _____.
    - **A.** Polyethylene wrap for infants 28 weeks of gestation or less
    - **B.** Conductive heat–gaining mattress for infants 32 weeks of gestation or less
    - **C.** A and B
    - **D.** None of the above

REFERENCES

1. American Diabetes Association. Management of diabetes in pregnancy—2017. *Diabetes Care*. 2011;34:S15.
2. Landon MB, Gabbe SG. "Gestational diabetes mellitus." *Obstet Gynecol*. 2011;118:1379-1393.
3. American College of Obstetricians and Gynecologists. *Prevention of early-onset group B streptococcal disease in newborns*. Committee Opinion 485. Washington, DC: American College of Obstetricians and Gynecologists; 2011.
4. American College of Obstetricians and Gynecologists. *Prevention of early-onset group B streptococcal disease in newborns*. Committee Opinion 485. Washington, DC: American College of Obstetricians and Gynecologists; 2011.
5. Hollier LM, Wendel GD. Third trimester antiviral prophylaxis for preventing maternal genital herpes simplex (HSV) recurrences and neonatal infection. *Cochrane Database Syst Rev*. 2008;(1):CD004946.
6. Sperling RS, Shapiro DE, Coombs RW, et al. "Maternal viral load, zidovudine treatment, and the risk of transmisssion of human immunodeficiency virus type 1 from mother to infant." *N Engl J Med*. 1996;335:1621-1629.
7. World Health Organization. *Hepatitis B*. WHO Fact Sheet No. 204. http://www.who.int/mediacentre/factsheets/fs204/en. Published 2017, Geneva, Switzerland.
8. Dionne-Odom J, Tita ATN, Silverman NS. "Hepatitis B in pregnancy screening, treatment, and prevention of vertical transmission". *Am J Obstet Gynecol*. 2016;214:6-14.
9. Substance Abuse and Mental Health Service Administration. *Results from the 2015 National Survey on Drug Use and Health: Summary of national findings*. http://www.samhsa.gov/data/NSDUH/2k10MH_Findings/2k10MHResults.htm.

10. Jones KL, Smith DW, Ulleland CN, et al. Patterns of malformation in offspring of chronic alcoholic mothers. *Lancet*. 1973;1:1267.
11. Committee on Substance Abuse and Committee on Children with Disabilities. Fetal alcohol syndrome and fetal alcohol effects. *Pediatrics*. 1993;91:1004.
12. Hammoud AO, Bujold E, Sorokin Y, et al. Smoking in pregnancy revisited: findings from a large population-based study. *Am J Obstet Gynecol*. 2005;192:1856.
13. Harger JH, Hsing AW, Tuomala RE, et al. Risk factors for preterm premature rupture of membranes: a multicenter case control study. *Am J Obstet Gynecol*. 1990;163:130.
14. Ananth CV, Smulian JC, Vintzileos AM. Incidence of placental abruption in relationship to cigarette smoking and hypertensive disorders in pregnancy: a meta-analysis of observational studies. *Obstet Gynecol*. 1999;93:622.
15. Taylor JA, Sanderson M. A reexamination of the risk factors for sudden infant death syndrome. *J Pediatr*. 1995;126:887.
16. Shiono PH, Klebanoff MA, Nugent RP, et al. The impact of cocaine and marijuana use on low birth weight and preterm birth: a multicenter study. *Am J Obstet Gynecol*. 1995;172:19.
17. American College of Obstetricians and Gynecologists. Hypertension in pregnancy. *Obstet Gynecol*. 2013;122:1122-1131.
18. Sibai BM. Evaluation and management of severe preeclampsia before 34 weeks' gestation. *Am J Obstet Gynecol*. 2011; 205:191-198.
19. American College of Obstetricians and Gynecologists. Premature rupture of membranes—Practice Bulletin 139. *Obstet Gynecol*. 2013;122(4):918-930.
20. Mercer BM. Preterm premature rupture of the membranes. *Obstet Gynecol*. 2003;101:178-193.
21. Rinehart BK, Terrone DA, Taylor CW, et al. Single umbilical artery is associated with an increased incidence of structural and chromosomal anomalies and growth restriction. *Am. J Perinatol*. 2000;17:229.
22. Cunningham FG, Leveno KJ, Bloom SL, et al, eds. *Williams obstetrics*. 24th ed. New York: McGraw-Hill; 2014.
23. Oyelese Y, Ananth CV. Placental abruption. *Obstet Gynecol*. 2006;108:1005-1016.
24. Baron C, Morgan MA, Garite TJ. The impact of amniotic fluid volume assessed intrapartum on perinatal outcome. *Am J Obstet Gynecol*. 1995;173:167.
25. Mathews TJ, Mac Dorman MF. Infant mortality statistics from the 2008 period linked birth/infant death data set. *Natl Vital Stat Rep*. 2012;60(5):1-27.
26. Carr-Hill RA, Hall MH. The repetition of spontaneous preterm labor. *Br J Obstet Gynaecol*. 1985;92:921.
27. Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17α-hydroxyprogesterone caproate. *N Engl J Med*. 2003;348:2379-2385.
28. Iams JD. Prediction and early detection of preterm labor. *Obstet Gynecol*. 2003;101:402-412.
29. Lockwood CJ, Senyei AE, Dische MR, et al. Fetal fibronectin in cervical and vaginal secretions as a predictor of preterm delivery. *N Engl J Med*. 1991;325:669.
30. Pircon RA, Strassner HT, Kirz DS, et al. Controlled trial of hydration and bed rest versus bed rest alone in the evaluation of preterm uterine contractions. *Am J Obstet Gynecol*. 1989;161:775.
31. American College of Obstetricians and Gynecologists. Magnesium sulfate before anticipated preterm birth for neuroprotection—Committee Opinion Number 455. *Obstet Gynecol*. 2010;115:669-671.
32. American College of Obstetricians and Gynecologists. *Management of preterm labor*. Practice Bulletin 171. Washington, DC: American College of Obstetricians and Gynecologists; 2016.
33. Haas DM, Caldwell DM, Kirkpatrick P, et al. Tocolytic therapy for preterm delivery: systematic review and network meta-analytics. *BMJ*. 2012;345:E6226.
34. American College of Obstetricians and Gynecologists. *Antenatal corticosteroid therapy for fetal maturation*. Committee Opinion 402. Washington, DC: American College of Obstetricians and Gynecologists; 2008.
35. NIH Consensus Development Panel on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes. Effect of corticosteroids for fetal maturation on perinatal outcomes. *JAMA*. 1995;273:413.
36. American College of Obstetricians and Gynecologists. *Antenatal corticosteroid therapy for fetal maturation*. Committee Opinion 402. Washington, DC: American College of Obstetricians and Gynecologists; 2008.
37. Garite TJ, Kurtzman J, Maurel K, et al. Impact of a 'rescue course' of antenatal corticosteroids: a multicenter randomized placebo-controlled trial. *Am J Obstet Gynecol*. 2009; 200:248.e1-e9.
38. Society for Maternal-Fetal Medicine. Implementation of the use of antenatal corticosteroids in the late preterm birth period in women at risk for preterm delivery. *Am J Obstet Gynecol*. 2016;215:B13-15.
39. Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17α-hydroxyprogesterone caproate. *N Engl J Med*. 2003;348:2379-2385.
40. Spong CY. Prediction and prevention of recurrent spontaneous preterm birth. *Obstet Gynecol*. 2007;110:405-415.
41. Berghella V. Progesterone and preterm birth prevention: translating clinical trials data into clinical practice. *Am J Obstet Gynecol*. 2012;206:376-386.
42. Drakeley AJ, Roberts D, Alfirevic Z. Cervical stitch (cerclage) for preventing pregnancy loss in women. *Cochrane Database Syst Rev*. 2003;1:CD003253.
43. American College of Obstetricians and Gynecologists. *Cervical cerclage for the management of cervical insufficiency*. Practice Bulletin 142. Washington, DC: American College of Obstetricians and Gynecologists; 2014.
44. Caughey AB, Stotland NE, Washington AE, et al. Who is at risk for prolonged and post term pregnancy? *Am J Obstet Gynecol*. 2009;200:683.
45. Leddy MA, Powers ML, Schulkin J. The impact of maternal obesity on maternal and fetal health. *Rev Obstet Gynecol*. 2008;1(4):170.
46. Fraser WD, Hofmeyr J, Lede R, et al. Amnioinfusion for the prevention of meconium aspiration syndrome. Amnioinfusion Trial Group. *N Engl J Med*. 2005;353:909.
47. American College of Obstetricians and Gynecologists. *Amnioinfusion does not prevent meconium aspiration syndrome*. Committee Opinion. Washington, DC: American College of Obstetricians and Gynecologists; 2006:346.
48. American College of Obstetricians and Gynecologists. *Management of late-term and postterm pregnancies*. Practice Bulletin 146. Washington, DC: American College of Obstetricians and Gynecologists; 2014.
49. American College of Obstetricians and Gynecologists. Induction of labor—Practice Bulletin 107, 2016.
50. Wing DA, Rahall A, Jones MM, et al. Misoprostol: an effective agent for cervical ripening and labor induction. *Am J Obstet Gynecol*. 1995;172:1811.
51. Wing DA, Lovett K, Paul RH. Disruption of prior uterine incision following misoprostol for labor induction in women with previous cesarean delivery. *Obstet Gynecol*. 1998;91:828.
52. Kalousek DK, Vekemans M. "Confined placental mosaicism." *J Med Genet*. 1996;33:529-533.
53. American College of Obstetricians and Gynecologists. Antepartum fetal surveillance—Practice Bulletin 145. *Obstet Gynecol*. 2014;124(1):182-192.
54. Manning FA, Lange IR, Morrison I, et al. Fetal biophysical profile score and the non-stress test: a comparative trial. *Obstet Gynecol*. 1984;64:326.

55. Vintzileos AM, Campbell WA, Rodis JF. Fetal biophysical scoring: current status. *Clin Perinatol*. 1989;16:661.
56. Hannah ME, Hannah WJ, Hewson SA, et al. Planned caesarean section versus planned vaginal birth for breech presentation at term: a randomized multicentre trial. *Lancet*. 2000;356:1375.
57. Collea JV, Chein C, Quilligan EJ. The randomized management of term frank breech presentation: a study of 208 cases. *Am J Obstet Gynecol*. 1990;137:235.
58. Gimovsky ML, Wallace RL, Schifrin BS, et al. Randomized management of the non-frank breech presentation at term: a preliminary report. *Am J Obstet Gynecol*. 1983;146:34.
59. American College of Obstetricians and Gynecologists. *Mode of term singleton breech delivery*. Committee Opinion 265. Washington, DC: American College of Obstetricians and Gynecologists; 2001.
60. Martin JA, Hamilton BE, Ventura SJ, et al. Births: final data for 2010. *Natl Vital Stat Rep*. 2012;61:1.
61. Rozance PJ, Rosenberg AA. The neonate. In: Gabbe SB, Niebyl JR, Simpson JL, et al, eds. *Obstetrics: normal and problem pregnancies*. 6th ed. New York: Churchill Livingstone; 2012:485.
62. American College of Obstetricians and Gynecologists. *Intrapartum fetal heart rate monitoring: nomenclature, interpretation and general management principles*. Practice Bulletin 106. Washington, DC: American College of Obstetricians and Gynecologists; 2015.
63. Blackburn ST, Loper, DL. The respiratory system. In: Blackburn ST, Loper DL, eds. *Maternal, fetal and neonatal physiology: a clinical perspective*. 4th ed. Philadelphia: Saunders; 2013:297.
64. American Academy of Pediatrics, American College of Obstetricians and Gynecologists. Organization of perinatal healthcare. In: Lockwood C, Lemons J, eds. *Guidelines for perinatal care*. Elk Grove Village, IL: AAP; 2012:6.
65. Batton DG, Committee on Fetus and Newborn. Clinical report–Antenatal counseling regarding resuscitation at an extremely low gestational age. *Pediatrics*. 2009;124:422.
66. Crosby WM, Cook LJ. Unit 1: Is the mother sick? Is the fetus sick? In: Kattwinkel J, Cook LJ, Hurt H, Nowacek GA, Short JG, eds. *Maternal and fetal evaluation and immediate newborn care*. Elk Grove Village, IL: AAP; 2007-2012:1623.
67. American Heart Association/American Academy of Pediatrics. Overview and principles of resuscitation. In: Kattwinkel J, ed. *Neonatal resuscitation textbook plus*. Elk Grove Village, IL: AAP; 2016:1.
68. Kattwinkel J, Perlman JM, Aziz K, et al. Part 15: neonatal resuscitation: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122:S909.
69. Mariani G, Dik PB, Ezquer A, et al. Pre-ductal and post-ductal O_2 saturations in healthy term neonates after birth. *J Pediatr*. 2007;150:418.
70. Bennett S, Finer NN, Rich W, et al. A comparison of three neonatal resuscitation devices. *Resuscitation*. 2005;67:113.
71. Barber CA, Wyckoff MH. Use and efficacy of endotracheal versus intravenous epinephrine during neonatal cardiopulmonary resuscitation in the delivery room. *Pediatrics*. 2006;118:1028.
72. Singh A, Duckett J, Newton T, et al. Improving neonatal unit admission temperatures in preterm babies: exothermic mattresses, polythene bags, or a traditional approach? *J Perinatol*. 2010;30:45.
73. Gluckman PD, Wyatt JS, Azzopardi D, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. *Lancet*. 2005;365:663.
74. Shankaran S, Laptook AR, Ehrenkranz RA, et al. Whole body hypothermia for neonates with hypoxic ischemic encephalopathy. *N Engl J Med*. 2005;353:1574.
75. Laptook AR, Shankaran S, Ambalavanan N, et al. Outcomes of term infants using apgar score at 10 minutes following hypoxic ischemic encephalopathy. *Pediatrics*. 2009;124:1619.
76. Reed DJ, Hermelin RL, Kennedy CS, et al. Interdisciplinary onsite team-based simulation training in the neonatal intensive care unit: a pilot report. *J Perinatol*. 2017;37(4):461-464. doi:10.1038/jp.2016.238.
77. Batton DG, Committee on Fetus and Newborn. Clinical report–Antenatal counseling regarding resuscitation at an extremely low gestational age. *Pediatrics*. 2009;124:422.
78. Harrington DJ, Redman CW, Moulden M, et al. The long-term outcome in surviving infants with Apgar zero at 10 minutes: a systematic review of the literature and hospital-based cohort. *Am J Obstet Gynecol*. 2007;196:463.e1.

Examination and Assessment of the Neonatal and Pediatric Patient

4

Brian K. Walsh

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. List steps for initial stabilization of the newborn
2. Describe care to be given to infants born with meconium staining
3. Describe the Apgar scoring system and how and when it is performed on the newborn
4. List criteria for determining whether an infant is large for gestational age, appropriate for gestational age, or small for gestational age
5. List critical vital signs to be evaluated as part of the newborn's initial physical examination
6. Describe criteria for determining whether an infant is displaying apneic spells
7. Identify signs and symptoms of respiratory distress in the newborn
8. Describe the technique for rapid identification of a pneumothorax in a newborn
9. List the elements of a basic neurological examination in the newborn
10. Identify and use historical and physical findings to develop a differential diagnosis of a child's respiratory condition
11. Determine the severity of a child's respiratory condition
12. Communicate important historical and physical findings concerning a child's respiratory condition to the health care team in a timely manner

Key Terms

acrocyanosis
Apgar score
apnea
Ballard score
bilateral choanal atresia
bronchial fremitus
chief complaint
encephaloceles
fontanels
gastroschisis
grunting
head bobbing
hygromas
lanugo
leukocytosis
leukopenia
kyphosis
micrognathia
microstomia
mottling
myelomeningoceles
nasal flaring
omphalocele
pectus carinatum
pectus excavatum
periodic breathing
prune-belly syndrome
scoliosis
sternocleidomastoids
stertor
stridor
subgaleal hemorrhage
tactile fremitus
transillumination
vernix caseosa

Box 4-1 Perinatal Factors Associated With Increased Risk of Neonatal Depression

ANTEPARTUM (FETOMATERNAL)
- Maternal diabetes
- Postterm status (born at greater than 42 weeks of gestation)
- Maternal infection (especially group B *Streptococcus* or herpes)
- Hemorrhage
- Substance abuse
- No prenatal care
- Age older than 35 years
- Multifetal gestation
- Diminished fetal activity
- Maternal anemia or Rh isoimmunization
- Oligohydramnios or polyhydramnios
- Small fetus for maternal dates
- Previous fetal or neonatal death
- Immature pulmonary maturity studies
- Chronic or pregnancy-induced hypertension
- Preterm labor or premature rupture of membranes
- Other maternal illness (e.g., cardiovascular, thyroid, neurologic)
- Drug therapy (e.g., magnesium, adrenergic blockers, lithium)
- Congenital abnormalities

INTRAPARTUM
- Maternal or fetal infection
- Prolapsed cord
- Prolonged labor
- Maternal sedation
- Operative or device-assisted delivery
- Meconium-stained delivery
- Prolonged rupture of membranes
- Breech or other abnormal presentation
- Indices of fetal distress (e.g., abnormal heart rate)

See Chapter 3.

The first few moments of an infant's life are the most critical. At this time the newborn must make the transition from intrauterine to extrauterine life. Most infants enter extrauterine life with crying and vigorous activity. However, approximately 1 out of 10 babies (10%) born in the United States each year are premature, resulting in the death of approximately 36% of those born before 37 weeks of gestation.[1] Adverse maternal and fetal conditions contribute to the need to initiate resuscitative efforts in approximately 6% to 10% of all deliveries, with extensive resuscitation required in less than 1%.[2]

Ideally, a detailed history of perinatal problems associated with an infant who may require resuscitation (Box 4-1) should be available.

STABILIZING THE NEONATE

Stabilizing the newborn starts with proper positioning followed by drying and warming. Immediately after delivery, place the infant on a preheated radiant warmer (Figure 4-1), and position the infant with the neck slightly flexed. Placing a small roll under the shoulders often attains the correct position.

DRYING AND WARMING

Preventing heat loss is critical when caring for a newborn, because cold stress increases oxygen consumption and impedes effective resuscitation. If possible, the infant should be delivered in a warm, draft-free area.[3] Heat loss can be greatly reduced by rapidly drying the infant's skin, immediately removing wet linens, and wrapping the infant in prewarmed blankets.[4]

CLEARING THE AIRWAY

Airway obstruction should be suspected if the newborn's respiratory efforts are not effective. The head should be immediately repositioned and suction should be used to clear the airway of potential obstruction. Either a bulb syringe or a suction catheter should be used to clear the mouth first and then the nose. To avert injury and atelectasis, as well as interference with the infant's ability to establish adequate ventilation, excessive suctioning of clear fluid from the nasopharynx should be avoided.[2]

Attempts to suction meconium from the pharynx or trachea before birth, during birth, or after birth increase the likelihood of severe aspiration pneumonia.[4] Some obstetricians orally and nasally suction meconium-stained infants after delivery of the head but before delivery of the shoulders. However, a large, multicenter, randomized trial showed no benefit from this practice.[5] Therefore current recommendations for infants with meconium staining include the following:
- No intrapartum suctioning should occur.
- Infants who are vigorous at birth (i.e., strong respiratory effort, heart rate greater than 100 beats per minute, good muscle tone) should not receive tracheal suctioning.

FIGURE 4-1 Radiant warmer. (From Price D, Gwin J: *Pediatric nursing: an introductory text*, ed 11. Philadelphia, 2012, Saunders.)

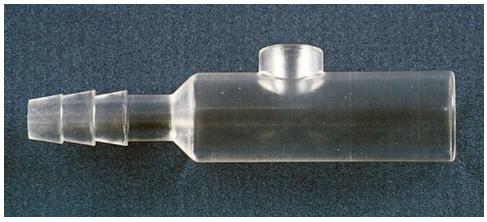


FIGURE 4-2 Meconium aspirator. (From Pfenninger JL, Fowler GC: *Pfenninger and Fowler's procedures for primary care,* ed 3, Philadelphia, 2011, Saunders.)

- Infants who are not vigorous (i.e., no or poor respiratory effort, heart rate less than 100 beats per minute, poor muscle tone) may receive direct laryngotracheal suctioning.[4]

For direct laryngotracheal suctioning, the infant should be intubated and suction applied directly to the endotracheal tube with the help of a meconium aspirator (Figure 4-2). The practitioner should constantly apply suction while removing the tube from the airway, repeating the intubation and suctioning procedure until meconium is no longer visible in the airway or until resuscitation is required.

PROVIDING STIMULATION

If the newborn does not respond to the extrauterine environment with a strong cry, good respiratory effort, and the movement of all extremities, the infant requires stimulation. Flicking the bottoms of the feet, gently rubbing the back, and drying with a towel are all acceptable methods of stimulation. Slapping, shaking, spanking, and holding the newborn upside down are contraindicated and potentially dangerous to the infant.[6] In the delivery room the initial steps of warming, clearing the airway, and stimulation of the non–meconium-stained infant should occur within 30 seconds after birth.[4]

APGAR SCORE

Introduced in 1952 by Virginia Apgar, the **Apgar score** (Table 4-1) is an evaluation of newborns based on five factors: heart rate, respiratory effort, muscle tone, reflex irritability, and skin color.[7] Historically, proponents of the Apgar score have encouraged evaluation of newborns immediately after birth. It has also been used as a predictive index of neonatal mortality and neurologic or developmental outcome and continues to be used as the best-established index of immediate postnatal health.[8] The Apgar score obtained 1 minute after delivery provides an immediate evaluation of the infant and an objective measure for evaluating future interventions. However, in the delivery room resuscitation may be well underway at the 1-minute mark and should not be interrupted for Apgar scoring.

Scoring again at 5 minutes of age gives information about the infant's ability to recover from the stress of birth and adapt to extrauterine life. When the 5-minute Apgar score is less than 7, additional scores are usually obtained at 5-minute intervals until the score is greater than 7. Survival of the infant is unlikely if the score remains 0 after 10 minutes of resuscitation.[9]

The most important of the signs is heart rate, which indicates life or death. Failure of the heart rate to respond to resuscitation is an ominous prognostic sign.[8] Heart rate appears to be least affected by developmental maturity but may still be inadequate because of developmental difficulties in establishing cardiorespiratory function at birth.

In the immediate newborn period, skin color has the weakest correlation with the other four components of the Apgar score. Also, color does not reliably correlate with umbilical arterial pH, carbon dioxide pressure, and base excess.[10]

GESTATIONAL AGE AND SIZE ASSESSMENT

Ideally, gestational age assessment is performed before the neonate is 12 hours old, to allow the greatest reliability for infants less than 26 weeks of gestational age.[11-13] Evaluating gestational age requires consideration of several factors. The three main factors are as follows:

- Gestational duration based on the last menstrual cycle
- Prenatal ultrasound evaluation
- Postnatal findings based on physical and neurologic examinations

Postnatal examinations for determining gestational age include the **Ballard score,** which is based on external physical findings, and neurologic criteria. Often a gray-white cheeselike substance, called **vernix caseosa,**

Table 4-1 Apgar Scoring

	APGAR SCORE		
PARAMETER	**0**	**1**	**2**
Heart rate	None	<100 beats/min	>100 beats/min
Respiratory rate	None	Weak, irregular	Strong cry
Skin color	Pale blue	Body pink, extremities blue	Completely pink
Reflex irritability (response to stimulation)	No response	Grimace	Cry, cough, or sneeze
Muscle tone	Limp tone	Some flexion	Wmoell flexed

Neuromuscular maturity

	−1	0	1	2	3	4	5
Posture							
Square window (wrist)	>90°	90°	60°	45°	30°	0°	
Arm recoil		180°	140°–180°	110°–140°	90°–110°	<90°	
Popliteal angle	180°	160°	140°	120°	100°	90°	<90°
Scarf sign							
Heel to ear							

Physical maturity

Skin	Sticky Friable Transparent	Gelatinous red, translucent	Smooth pink, visible veins	Superficial peeling &/or rash, few veins	Cracking pale areas, rare veins	Parchment, deep cracking, no vessels	Leathery, cracked, wrinkled
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald	
Plantar surface	Heel-toe 40-50 mm: −1 <40 mm: −2	>50 mm no crease	Faint red marks	Anterior transverse crease only	Creases anterior 2/3	Creases over entire sole	
Breast	Imperceptible	Barely perceptible	Flat areola, no bud	Stippled areola, 1-2 mm bud	Raised areola, 3-4 mm bud	Full areola, 5-10 mm bud	
Eye/ear	Lids fused loosely: −1 tightly: −2	Lids open; pinna flat, stays folded	Sl. curved pinna; soft, slow recoil	Well-curved pinna; soft but ready recoil	Formed & firm; instant recoil	Thick cartilage; ear stiff	
Genitals (male)	Scrotum flat, smooth	Scrotum empty, faint rugae	Testes in upper canal, rare rugae	Testes descending, few rugae	Testes down, good rugae	Testes pendulous, deep rugae	
Genitals (female)	Clitoris prominent, labia flat	Prominent clitoris, small labia minora	Prominent clitoris, enlarging minora	Majora & minora equally prominent	Majora large, minora small	Majora cover clitoris & minora	

Maturity rating

score	weeks
−10	20
−5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

FIGURE 4-3 New Ballard score. (From Ballard JL: New Ballard score, expanded to include extremely premature infants. *J Pediatr* 119:417–423, 1991.)

is present in the skin folds of a term infant. However, vernix is even more abundant on a preterm infant and suggests an earlier gestational age. The presence of **lanugo,** the fine hair that covers premature infants mostly over the shoulders, back, forehead, and cheeks, indicates an even younger gestational age (Figure 4-3).

Once gestational age is determined, weight, length, and head circumference are plotted on a standard newborn grid. Any infant whose birth weight is less than the 10th percentile for gestational age is small for gestational age; similarly, an infant whose birth weight is more than the 90th percentile is large for gestational age. When using intrauterine growth curves, it may be necessary to consider charts that are race and gender specific.[14] Along with prematurity, abnormal gestational age and size for gestational age are associated with many neonatal disease processes (Figure 4-4).

PHYSICAL EXAMINATION OF THE NEONATE

The physical examination of an adult is generally conducted in a rigid head-to-toe format. When examining an infant, however, the order of the examination is modified to establish critical information; for example, auscultation of the heart and lungs is done before the infant becomes agitated and begins to cry. However, the examiner must still completely examine the baby in an orderly and prioritized manner. As a general rule, the following order works best, although this approach may require modification based on the clinical situation.

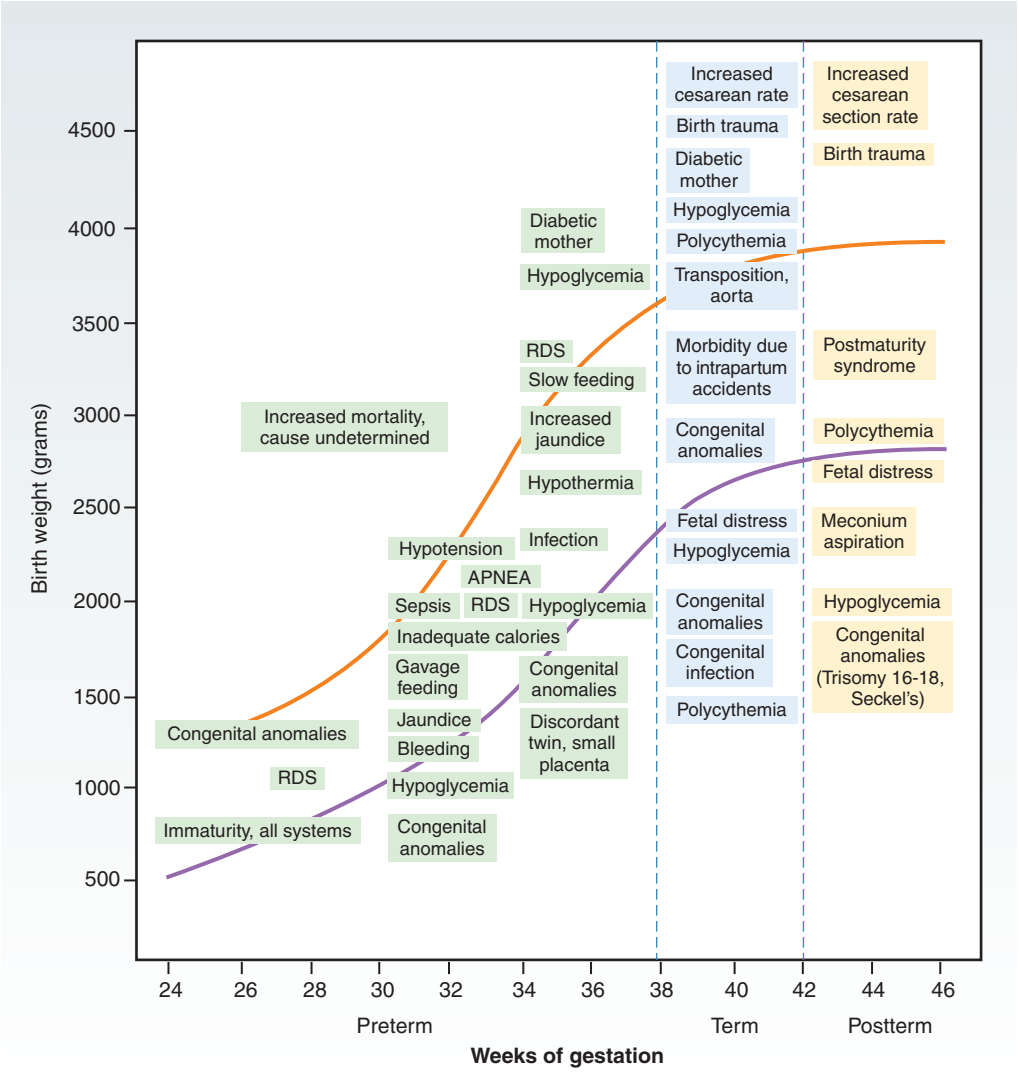


FIGURE 4-4 Weeks of gestation. *RDS,* Respiratory distress syndrome. (Adapted from Lubchenco L: *The high risk infant,* Philadelphia, 1976, WB Saunders.)

VITAL SIGNS

The team must quickly assess the infant's vital signs. Table 4-2 lists normal ranges for neonatal blood pressure. Absolute numbers are not as important as the relative ranges when considering the clinical situation. Heart rate of a neonate is often best assessed by listening with a stethoscope for the apical beat over the precordium. In the delivery room, lightly grasping the base of the umbilical cord and feeling the pulse can quickly estimate heart rate. As an example, the heart rate is normally 120 to 170 beats per minute. The heart rate of a term infant in deep sleep may decrease to 80 or 90 beats per minute. An infant undergoing a painful procedure or who is hungry may have a transient heart rate greater than 200 beats per minute. In comparison, a neonate older than 35 weeks of gestation has greater variability in heart rate than an infant born at 27 to 35 weeks of gestation. Presumably, in the younger infant, parasympathetic–sympathetic interaction and function are less developed.[15]

Table 4-2 Normal Values for Vital Signs in the Neonatal Patient

BIRTH WEIGHT (g)	SYSTOLIC/DIASTOLIC BLOOD PRESSURE (mm Hg)*	MEAN BLOOD PRESSURE (mm Hg)
>600	45/20	25
>1000	48/25	35
>2000	50/30	40
>3000	50/35	45
>4000	65/40	50
Newborn older than 12 h	75/50	60
Respiratory rate (30-60 breaths/min)		
Heart rate (120-170 beats/min)		

*From Versmold HT, et al: Aortic blood pressure ranges during the first 12 hours of life in infants with birth weight 610 to 4220 grams. *Pediatrics* 67:607, 1981.

Normal values for temperature are 97.6 ± 1° F (axillary) and 99.6 ± 1° F (rectal); however, temperature on arrival in the nursery may be lower if the delivery room was cold or may be higher if the radiant warmer was operating at a higher temperature because of incorrect probe position or warmer malfunction.

The health care provider should record the respiratory rate and blood pressure when determining vital signs.

GENERAL INSPECTION

Observing the infant's overall appearance is an important aspect of the physical examination. Ideally, the infant should be examined as he or she lies quietly and unclothed in a neutral thermal environment. Body position and symmetry, both at rest and during muscular activity, provide valuable information regarding possible birth trauma. For example, an infant who does not move his or her arms symmetrically could have a broken clavicle or an injury to the brachial plexus (Figure 4-5).

The infant's skin is an indicator of intravascular volume, perfusion status, or both. Both perfusion and underlying skin color affect the appearance of the skin. Capillary refill time should be less than 3 seconds. Refill should be assessed by pressing the sole of the infant's foot or the palm of its hand with a finger. Perfusion should be good and skin color pink. Some infants have blue hands and feet with decreased perfusion, or **acrocyanosis,** in the immediate postnatal period. True cyanosis is associated with blue or dusky mucous membranes and circumoral area.

Observing skin and color often provides diagnostic clues. **Mottling** refers to irregular areas of dusky skin alternating with areas of pale skin. An extremely pale or mottled infant suggests hypotension or anemia. A ruddy, reddish-blue appearance is often associated with a high hematocrit value or polycythemia and neonatal hyperviscosity syndrome (hematocrit >65%).[16] The yellow color associated with mild to moderate jaundice is common among newborns after the first day of life. Jaundice on the first day of life, however, is always an indication for immediate evaluation.[17]

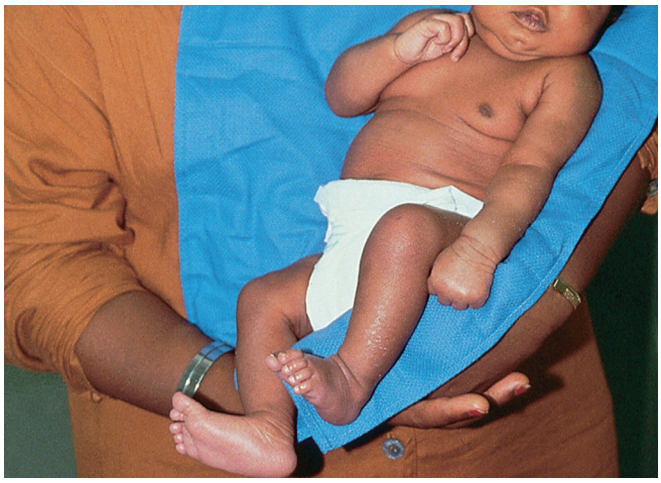


FIGURE 4-5 Left-sided brachial plexus. (From Hockenberry M, Wilson D, Rodgers C: *Wong's essentials of pediatric nursing,* ed 10, St. Louis, 2017, Elsevier.)

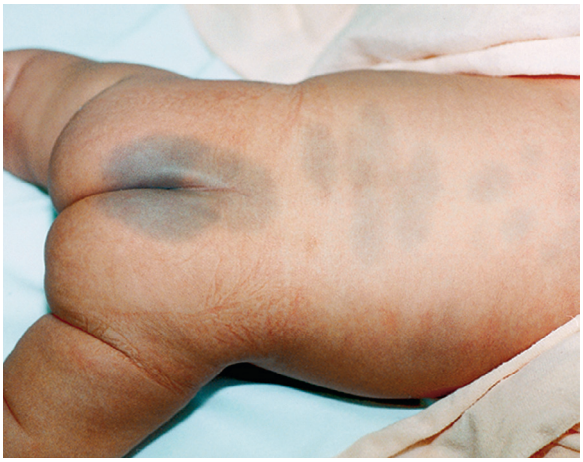


FIGURE 4-6 Mongolian spot. (From Price D, Gwin J: *Pediatric nursing: an introductory text,* ed 11, Philadelphia, 2012, Saunders.)

An infant exposed to meconium-stained amniotic fluid in utero for more than a few hours often presents with yellow-green staining of the skin, nails, and umbilical cord. Irregular areas of pale blue-black pigmentation over the sacrum and buttocks (Mongolian spots; Figure 4-6) are commonly seen on black (African, African-American or African-Caribbean) and Asian infants. These spots are often confused with bruising (Table 4-3).

RESPIRATORY FUNCTION

The normal newborn respiratory rate is 40 to 60 breaths per minute but may vary depending on multiple factors. The team should watch the infant's respiratory effort closely and note irregular respirations. Respiratory rates that exceed 60 breaths per minute but normalize over the next several hours may indicate transient tachypnea of the newborn. All newborns display an irregular breathing pattern. The neonate normally breathes in the range of 70 to 80 breaths per minute for 10 to 20 seconds, slows to a rate of 20 or 30 breaths per minute for a short time, and then breathes at a faster rate again. The average respiratory rate over several minutes is 40 to 60 breaths per minute. **Periodic breathing,** a common finding among premature infants, is characterized by an irregular pattern of intermittent respiratory pauses longer than 5 seconds.

Apnea is a pathologic condition in which breathing ceases for longer than 20 seconds. Apnea may be associated with cyanosis, bradycardia, pallor, and hypotonia (abnormally low muscle tone). Often apnea is associated with nonspecific symptoms of diseases seen with many neonatal conditions. All

Table 4-3 Common Dermal Findings in the Neonatal Patient

FINDING	DESCRIPTION	CONDITION
Jaundice	Yellowish skin	Hyperbilirubinemia
True cyanosis	Centrally blue or dusky skin	Hypoxia
Acrocyanosis	Bluish hands and feet	Cold stress, ↓ circulation; normal for first few hours
Petechiae	Pinpoint hemorrhagic areas	Birth trauma, thrombocytopenia
Telangiectatic nevi	"Stork bites": red, flat areas	Capillary dilation, benign
Subcutaneous fat necrosis	Discrete firm masses in subcutaneous tissue	Trauma
Lanugo	Fine hair	More noticeable in preterm infants, benign
Sclerema	Hardening of skin	Septicemia, shock, cold stress
Ruddy complexion	Deep reddish skin	Polycythemia or high hematocrit value
Ecchymoses	Bruising of various sizes	Birth trauma, disseminated intravascular coagulation
Mongolian spots	Irregular areas of pale blue over sacrum and buttocks	Benign, common in black and Asian infants
Strawberry hemangiomas	Bright red, flat spots 1-3 mm in diameter	Benign, usually resolve spontaneously
Milia	White papules <1 mm on forehead, chin, and nose	Distended sebaceous glands that disappear later
Erythema toxicum	Whitish pink papular rash	Cause unknown
Pallor	Pale or white skin	Blood loss or hypovolemia
Vernix caseosa	Whitish gray, cheeselike substance	More abundant on preterm infants
Mottled skin	Uneven color, blotchy	Decreased perfusion

episodes of apnea must be investigated to establish the cause.[18]

It is important to note signs of respiratory distress (Table 4-4). The Silverman scoring system considers multiple factors to quantify an infant's distress (Figure 4-7). Although not always used as a measure of respiratory distress, the Silverman system highlights important respiratory observations during a physical examination. Signs of distress include nasal flaring, expiratory grunting, tachypnea, and retractions. **Nasal flaring** occurs during inspiration when the muscles of the nasal passages contract, resulting in flaring of the alae nasi, widening of the nostrils, and reduction in airway resistance. **Grunting** is an audible expiratory noise caused by closure of the glottis during expiration in an attempt to provide increased positive end-expiratory pressure and to maintain lung volume. Retractions of the chest wall during inspiration may occur in the suprasternal, substernal, subcostal, and intercostal regions. Retractions usually indicate reduced lung compliance but are also associated with obstructive airway processes with normal lung compliance. Chest wall retractions are more prominent and easily observed in the neonate than in an older child or adult. The newborn musculature is relatively thin and weak, and the thoracic cage is very compliant. The flexible chest wall and thoracic cage of the newborn exhibit noticeable retractions as lung compliance worsens. Abdominal and thoracic respiratory muscles normally move in parallel. Paradoxical respirations represent thoracic and abdominal respiratory efforts that are not synchronous. This "see-saw" effect often indicates severe respiratory distress.

Auscultation of the newborn can sometimes prove difficult. The newborn chest is small, and sounds easily transmit from one lung region to another. Abdominal sounds may even transmit to the lungs, although bowel sounds heard from the chest in place of absent breath sounds may indicate a diaphragmatic hernia (see Chapter 23). Localizing auscultation findings in a preterm infant is often difficult or impossible with single-head stethoscopes. Auscultation with a double-head stethoscope has proved useful in some situations.[19] Comparison of the breath sounds from the right and left sides helps distinguish asymmetries. Asymmetrical sounds may indicate unilateral disease such as pneumothorax or a malpositioned endotracheal tube. Diminished breath sounds, wheezes, and stridor can occur in neonates. See Auscultation later in this chapter for a detailed discussion of pediatric breath sounds.

CHEST AND CARDIOVASCULAR SYSTEM

The circumference of a newborn's chest is equivalent to the head circumference. Inspection of the chest may reveal malformations such as **pectus carinatum** (protruding xiphisternum or xiphoid process, also called *pigeon chest*) or **pectus excavatum**

Table 4-4 Signs of Respiratory Distress in the Neonatal Patient

	APNEA	TACHYPNEA	REFRACTIONS	GRUNTING	NASAL FLARING	STRIDOR	CYANOSIS	BREATH SOUNDS	OTHER FINDINGS
Respiratory distress syndrome		++	++	++	++		+	Decreased, rales	Premature infants, infants of diabetic mothers
Pneumothorax		++	+	+	+		+	Decreased, asymmetrical	Asymmetry of the chest, PMI shifted
Pneumonia	+	++	++	++	++		+	Rales and rhonchi	
Upper airway obstruction	+	±		++		++			Gasping or labored breathing
Diaphragmatic hernia		++		+	++		++	Bowel sounds in chest	Scaphoid abdomen, often associated with pneumothorax
Meconium aspiration	+	++	++	+	+		+	Decreased	Hyperexpansion of chest, atelectasis, pneumothorax
Transient tachypnea		++	+	+	+			Fine rales	Resolves in <24 hr
Apnea of prematurity	+++		±				±	Normal	Bradycardia

PMI, Point of maximal cardiac impulse.

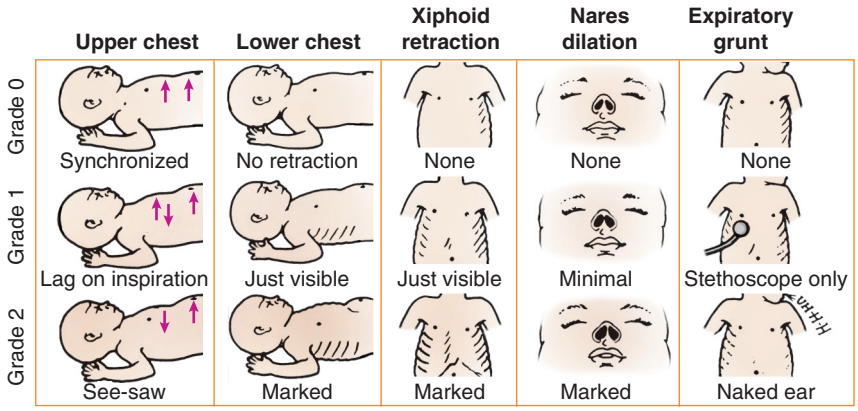


FIGURE 4-7 Silverman score. (Modified from Silverman WA, Anderson DH: A controlled clinical trial of effects of water mist on obstructive respiratory signs, death rate and necropsy findings among premature infants. *Pediatrics* 17:1–6, 1956.)

(funnel chest). Bulging or asymmetry of the chest wall usually indicates important pathologic conditions.

The point of maximal cardiac impulse (PMI) is the position on the chest wall at which the cardiac impulse can be maximally seen. The PMI is usually seen in newborns because of the relatively thin and flexible chest wall. Typically, the PMI is relatively close to the sternal border because of the predominance of the right ventricle in the fetal period. A mediastinal shift caused by a pneumothorax will move the PMI away from the affected side of the chest.

With suspected pneumothorax, **transillumination** of the chest wall should be performed, using a high-energy flashlight or fiberoptic device in a darkened room. The light source should be placed on the chest wall of the suspected side. A large pneumothorax will reveal an excessively pink and illuminated, usually irregular, area of light, or "glowing" area, through the chest wall when compared with the contralateral side.

Heart rate variations from 120 to 170 beats per minute may be normal depending on gestational age, as discussed earlier. The rapid rate and rhythm of heart sounds make them difficult to determine. Neonates have a high incidence of arrhythmias in the first few days of life. Between 1% and 5% of all newborns exhibit some disturbance in heart rate or rhythm.[20] Many demonstrate "dropped beats," which on evaluation are premature atrial contractions. These episodes are usually benign, but any newborn with an irregular rhythm should have an electrocardiogram performed to assess the arrhythmia.

Cardiac murmurs are described as a soft to loud, harsh sound similar to a forcible exhalation with the mouth open. Many heart murmurs are transient and not associated with anomalies.

The heart size, shape, and thoracic positioning on chest radiography are often helpful in assessing infants with congenital heart disease.

Palpating the pulses of a quiet infant often provides important diagnostic information. Weak pulses suggest low cardiac output states such as shock and hypoplastic left-sided heart syndrome. Bounding pulses are seen in infants with patent ductus arteriosus and left-to-right shunt. The bounding characteristic of the pulse results from rapid runoff of the blood into the low-resistance pulmonary circulation. This lowers the systolic blood pressure and produces a wider pulse pressure. Brachial and femoral pulses should be equal in intensity and felt simultaneously. A delayed or weak femoral pulse can indicate coarctation of the aorta.

The range of normal blood pressures at various weights has been well established (see Table 4-2). In the absence of data, an adequate mean blood pressure (MBP) is calculated as follows:

$$\text{Adequate MBP} = \text{Gestational age (weeks)} + 5$$

For example, an infant of 24 weeks of gestation should have an MBP of approximately 29 mm Hg, and a term newborn, 40 weeks of gestation, should have an MBP of approximately 45 mm Hg.

A pulse oximeter can provide valuable information in the evaluation of the cardiovascular system. Because the sensor of the pulse oximeter is applied to a distal extremity, the oximeter will display a low pulse rate and perfusion signal as peripheral pulses and perfusion decrease. The cause of this poor perfusion must be determined. However, if the oximeter suggests decreased perfusion while central blood pressure remains normal, the cause may be volume depletion with compensatory peripheral vasoconstriction. In addition, placing pulse oximeters on preductal and postductal sites allows for assessing right-to-left ductal-level shunting, as seen with persistent pulmonary hypertension of the newborn. In this case the right arm, or preductal site, will have a higher saturation, and the postductal site, or left arm and lower extremities, will have a lower saturation because of venous admixture occurring postductally.

ABDOMEN

Successful abdominal examination requires a calm and quiet infant. The examiner should observe the contour of the abdomen and determine whether it is scaphoid (sunken anterior wall), flat, or distended. Distention is a significant finding characterized by tightly drawn skin through which engorged subcutaneous vessels can easily be seen. More noticeable abnormalities of the abdomen include **prune-belly syndrome,** which is a congenital lack of abdominal musculature; **omphalocele,** a protrusion of the membranous sac that encloses abdominal contents through an opening in the abdominal wall into the umbilical cord; and **gastroschisis,** a defect in the abdominal wall lateral to the midline with protrusion of the intestines (Figure 4-8).[21]

When examining the abdomen, the examiner should auscultate and palpate over all four quadrants. Bowel sounds are usually heard over the entire abdomen, generally described as a "tinkling" or "rumbling." Because bowel sounds are not continuous, it may take several seconds to hear them. Decreases or increases in the amount or changes in the characteristics of bowel sounds may indicate a pathologic abdominal condition.

The umbilical cord is yellowish white with three blood vessels. The two small and thick-walled arteries and one large and thin-walled vein are easily visible at the end of a freshly cut cord. Wharton's jelly surrounds the vessels. A single umbilical artery suggests congenital anomalies, especially those of the urinary tract. The presence of meconium in the amniotic fluid causes a greenish yellow staining of the umbilical cord. The umbilical cord of an infant who is large for gestational age and born to a mother with diabetes is often large and fat. Conversely, infants with intrauterine growth retardation often have thin cords with little Wharton's jelly. With an umbilical hernia the intestinal muscles do not close around the umbilicus, and the intestines protrude into this weakened tissue. Such a defect may require surgery or may resolve without intervention as the muscles become stronger.

HEAD AND NECK

The head is usually the presenting part and often shows evidence of bruising and molding as a result of pressures exerted during the birth process. Molding of the skull with overlapping cranial bones is common. In term infants the molding should resolve within a few days. The **fontanels** are the nonossified areas between the cranial bones that make up the skull. The fontanels and suture lines should be soft and should not bulge. Craniotabes are soft skull areas that can be compressed like a ping-pong ball and may be a normal finding, especially in premature infants.

Any evidence of edema under the scalp should be examined carefully, especially in infants who had vacuum- or forceps-assisted delivery. Rarely edema is attributed to a **subgaleal hemorrhage,** tearing of the emissary veins, where edema from blood loss can extend from the eyes to the nape of the neck. Blood loss may occur fairly rapidly after delivery and be sufficient to cause hypovolemic shock.[22,23]

More than 150,000 children are born with notable birth defects and syndromes in the United States each year.[24] Congenital anomalies are the leading cause of infant mortality in the postneonatal period. Unusual facies may suggest a number of distinct dysmorphic genetic syndromes. *Smith's Recognizable Patterns of Human Malformation* is an invaluable resource in the evaluation of infants with unusual facies.[25] It also provides standard measurements for the newborn. Facial paralysis or asymmetrical facies

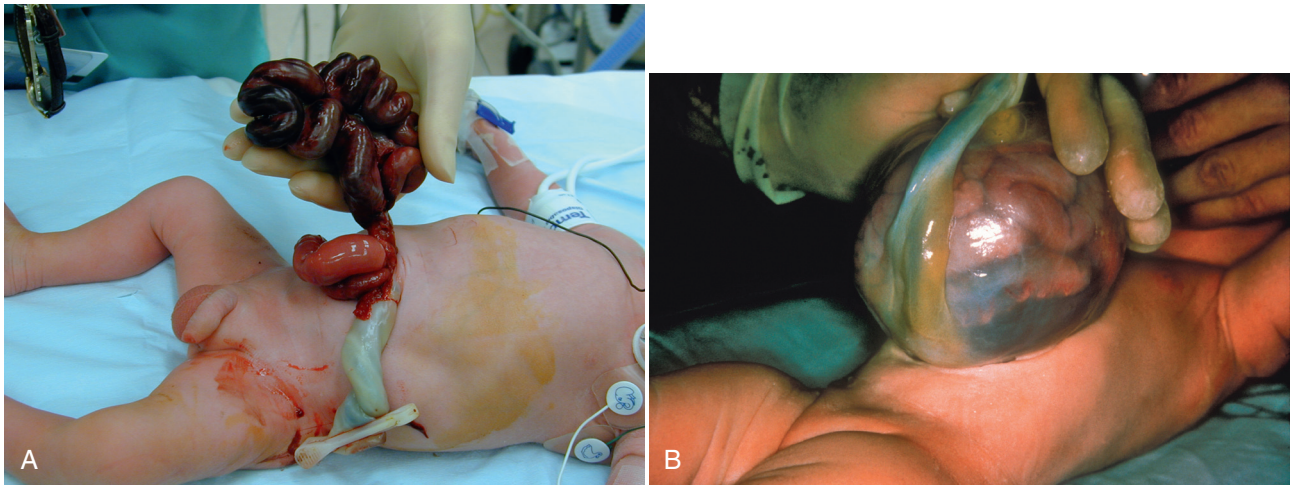


FIGURE 4-8 **A,** Gastroschisis. **B,** Omphalocele. (From Price D, Gwin J: *Pediatric nursing: an introductory text,* ed 11, Philadelphia, 2012, Saunders.)

is often noticed in an otherwise normal-appearing infant. Facial paralysis may be readily apparent only when the infant cries.

The eyes are often swollen and edematous from the birth process. After resolution of the swelling, the eyes should be assessed for excessive spacing and any unusual slant. Antibiotic ointment or silver nitrate is applied to the eyes after delivery to prevent infection. In infants older than 28 weeks of gestation, the pupils should be round and regular and should react to light. The examiner should assess the ears for placement and deformation. Deformed, posteriorly rotated, or low-set ears are associated with various genetic anomalies. Ears are considered low set when the upper insertion of the ear is below the level of a line drawn through the corner of the orbits of the eyes.

Newborns breathe preferentially through the nose; therefore the examiner should alternately occlude each side and listen to breath sounds to assess the patency of each nostril. If the infant appears to be breathing comfortably, many nurseries no longer attempt to pass catheters, because nasal trauma, obstruction, and edema are serious risks. An oral airway or endotracheal tube is often required if **bilateral choanal atresia,** the incomplete opening into the nasopharynx as a result of membranous or bony structures, is present. Abnormalities of the mouth, lips, and oral cavity are seen in many infants. **Microstomia,** small mouth, is common in infants with the chromosomal defect trisomy 18, whereas midfacial clefts, cleft lip and palate, are common with trisomy 13. Pierre Robin syndrome is characterized by a cleft palate, posteriorly displaced tongue, and **micrognathia,** a small lower jaw.[26]

Examination of the oral cavity and pharynx for less obvious palatal clefts, mucous cysts, Epstein's pearls, or natal teeth can be performed with a flashlight or laryngoscope blade light. The neck is examined for obvious shortening, vertebral anomalies, or limitations in movement. A variety of cysts, **hygromas** (sacs of fluid resulting from a blockage in the lymphatic system), sinuses, and masses may be present laterally or at the midline. Large neck lesions may apply pressure to the trachea and impair breathing.

The clavicles are often broken during the delivery of large infants with shoulder dystocia (difficult delivery because the anterior shoulder of the infant cannot pass below the mother's hip bone) or in breech deliveries. Commonly the injury is noted when the infant refuses to move the affected shoulder. The break is usually easily palpable as an area of crepitus overlying the bone. Therapy is usually not necessary for fractured clavicles in the newborn, because they heal without intervention.

MUSCULOSKELETAL SYSTEM, SPINE, AND EXTREMITIES

The intrauterine environment often affects the extremities and musculoskeletal system. Many limb and other deformations in the fetus result from intrinsic (fetal) or extrinsic (uterine) factors.

Extra digits may be familial or may be associated with a number of syndromes. They can be present on hands or feet or both. The digits can vary from fully formed and articulated to simple skin tags.

Joint contractures or abnormal positioning of one or more limbs may result from a fetal problem or intrauterine compression. Clubfoot, talipes equinovarus, is a common example.[27,28] An isolated joint–extremity malformation suggests extrinsic factors, whereas multiple deformations are more common with primary fetal neurologic or muscular diseases.

The symmetry and bony structure of the spine are easily examined in newborns. The infant is suspended in a prone position with one hand, then the examiner visually and digitally evaluates the structures. Many infants have a small indentation (sacral dimple) near the end of the spine. If the bottom of the dimple is easily seen without associated bony defects, no further evaluation is required. However, if the defect cannot be fully visualized or if there are bony defects, associated tufts of hair, or drainage of clear fluid, further evaluation is necessary. A few infants have the congenital malformations collectively called *spina bifida* (Figure 4-9). These defects result from failure of the embryonic neural tube to form correctly in the third to fifth week of gestation. The defects usually involve bone, skin, the covering of the central nervous system (meninges), and nerve tissue. Defects that occur over the spine are called **myelomeningoceles** (Figure 4-10), and those involving the brain are called **encephaloceles.**

It is important to evaluate the hips of all infants even if there is no evidence of asymmetry or other bone, joint, or muscular problems. The pelvis is stabilized on a flat surface while the joint is flexed and abducted to the surface. A telescoping feeling or the presence of a "clunk" suggests congenital laxity or dislocation of the hip.[28] Often, several days must pass before the hips of infants born in the breech position can be appropriately evaluated.

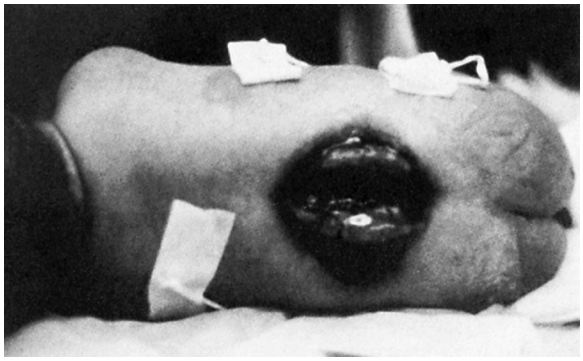


FIGURE 4-9 Infant with spina bifida.

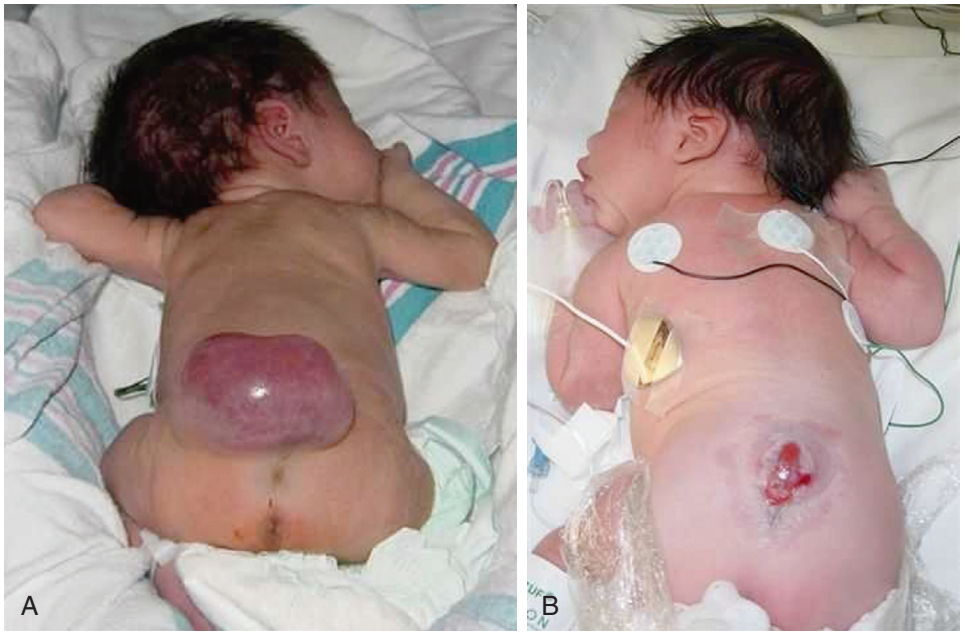


FIGURE 4-10 **A,** Myelomeningocele with intact sac. **B,** Myelomeningocele with ruptured sac. (Courtesy Dr. Robert C. Dauser, Neurosurgery, Baylor College of Medicine, Houston, TX. From Hockenberry M, Wilson D, Rodgers C: *Wong's essentials of pediatric nursing,* ed 10, St. Louis, 2017, Elsevier.)

CRY

After the examiner has obtained some newborn experience, it is impressive how much information something as simple as a baby's cry can provide. A loud and vigorous cry is usually a sign of a healthy infant. A moaning, weak, or faint cry suggests illness. Often, an infant with respiratory distress syndrome strains with a grunting cry. An infant with a piercing, high-pitched cry often has a neurologic injury, drug withdrawal, or increased intracranial pressure. Hoarse crying can be associated with laryngeal edema, as in recently extubated infants. However, a hoarse cry may also be heard with congenital hypothyroidism, cretinism, or hypocalcemia with laryngospasm. Perhaps the most distinctive cry is associated with a deletion of the short arm of the fifth chromosome. The catlike cry of these infants gives the syndrome the name *cri du chat,* French for "cry of the cat."

NEUROLOGIC ASSESSMENT

The general neurologic state of the infant is assessed during much of the physical examination. The examiner should note whether the infant responds appropriately to his or her surroundings or is lethargic or overly irritable. It is also important to determine whether the infant moves all extremities and whether the movements are symmetrical and smooth or jittery and jerky. Infants with evidence of difficult delivery may manifest signs of extremity weakness associated with trauma to the brachial plexus.

Muscle tone is assessed in a term infant by picking the neonate up under the arms. A normal infant will suspend well. An infant with decreased tone will noodle through the hands. Infants with normal tone will maintain their extremities in a flexed position at rest.

A number of reflexes are present in newborns. The most well-known is the grasp reflex, in which the newborn infant grasps a finger placed in the palm of the hand. A similar downward curving of the toes occurs if a finger is pressed against the sole of the foot; this is referred to as the *plantar grasp reflex*. The startle reaction to sound or touch is similar to the Moro reflex (Figure 4-11), which occurs when

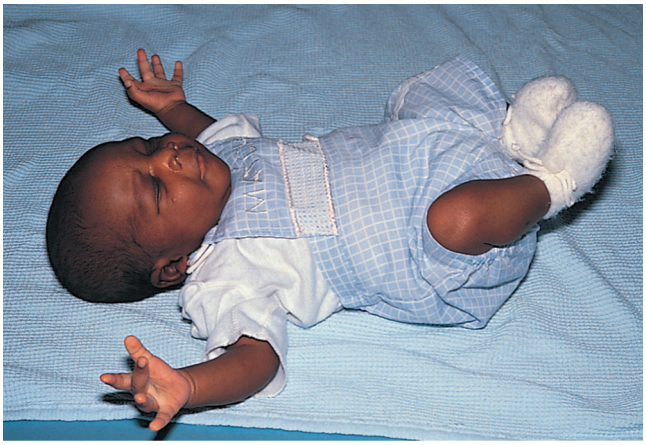


FIGURE 4-11 Moro reflex. (From Price D, Gwin J: *Pediatric nursing: an introductory text,* ed 11, Philadelphia, 2012, Saunders.)

the head is allowed to fall back slightly. A normal term infant's extremities will extend rapidly with open hands. The neonate will then slowly flex them back toward the body. Infants will respond to a bright light by shutting their eyelids tight. They will often turn toward unique sounds or sights and may focus on objects, especially faces. Suspending the infant and touching the top of the foot against a surface can demonstrate the stepping reflex: The infant should lift the leg and then place it flat on the surface.[29]

PEDIATRIC PATIENT HISTORY

Unlike neonatal patients, children present with previous history, and despite numerous advances in laboratory testing, the ability to obtain a pediatric history remains essential to the practice of pediatric respiratory care. In most encounters of children with respiratory conditions, the history provides the necessary information to formulate a differential diagnosis and suggest additional evaluation and management. Thus the clinician should spend considerable effort enhancing history-taking skills.

The history for a new patient can be divided into the following categories:

- Chief complaint or primary concern
- History of the present illness (HPI)
- Medical history (MH)
- Review of symptoms (ROS)
- Family history
- Social and environmental histories

CHIEF COMPLAINT

The chief complaint consists of the reason the child presents for health care. The chief complaint may simply be a symptom or sign observed by the child or caregivers and in need of further evaluation, as in the case of a new patient who presents for the evaluation of cough or chest pain. The chief complaint may also be a specific established diagnosis, as in the case of a child admitted to the hospital for treatment of acute asthma or a pulmonary exacerbation of cystic fibrosis (CF). For a new patient, the initial step is to establish the chief complaint or primary concern. Additional information in the form of a medical history is then sought to further elucidate and clarify historical findings that point to either a specific diagnosis or set of diagnoses (differential diagnosis) that then leads to further evaluation (e.g., physical examination, laboratory testing).

NEW PATIENT HISTORY

For a new patient, the medical history consists of specific components including the HPI, MH, ROS, family history, and social and environmental histories (Box 4-2). Important components of the HPI include duration, intensity or severity, and improvement or deterioration of symptoms. Knowledge of the following may help point to a specific disease or narrow the differential diagnosis:

- Triggers of symptoms
- Aggravating or alleviating factors
- Medications that have previously or are currently being used and whether these medications have been helpful
- Chronicity
- Recurrence or seasonality of symptoms

Review of current medications, including nonprescription and alternative medications, dosing, and when and how taken, as well as what the medications are taken for, may provide useful information.

Where the child lives, adult visitors from areas of endemic tuberculosis, and recent travel history may also suggest unsuspected exposures or diseases.

FOLLOW-UP OR ESTABLISHED PATIENT HISTORY

For a follow-up or established patient, the medical history is not usually focused on developing differential diagnoses or establishing a specific diagnosis but rather on determining current lung health and whether there have been any changes since the last visit. In this situation, the medical history consists of an interim history and review of key components of the MH, ROS, and social and environmental histories (Box 4-3). Questions are directed toward determining whether there were any interim respiratory infections or exposures and whether these triggered exacerbation of the primary disease.[30] Exposure to environmental tobacco smoke should be asked about specifically.[31] If an exacerbation of the primary disease occurs, it is important to determine whether this exacerbation led to a clinic visit, emergency room visit, or hospitalization or whether the caregivers were able to manage the exacerbation at home. Information concerning the presence or absence of allergic, nasal, respiratory, or gastrointestinal symptoms is sought. If symptoms are present, the examiner should determine whether they are better or worse than at the previous visit and whether new symptoms are presenting and are these related to the primary disease. Quality-of-life issues should be explored. Missing school, an inability to participate in normal daily and physical activities, or the caregiver(s) missing work because of an increase in the child's respiratory symptoms suggests that disease management is less than optimal. Review of current medications, including nonprescription and alternative medications; dosing; when and how taken; what the medications are taken for; and whether there have been changes in medications, dosing, or both since the previous visit also yields important information. Adherence with and understanding of the treatment plan should be explored. Changes in school and family

Box 4-2 New Patient History

CHIEF COMPLAINT OR PRIMARY REASON FOR VISIT

- History of present illness
- Duration
- Intensity or severity
- Improvement or deterioration
- Triggers
- Aggravating or alleviating factors
- Medications (past and current)
- Chronicity
- Seasonality

MEDICAL HISTORY

- Perinatal history
- Acute care and emergency room visits
- Hospitalizations and surgeries
- Immunizations
- Previous evaluations

REVIEW OF SYMPTOMS

- Family history
- Social and environmental histories

Important components of the medical history that may contribute to establishing a diagnosis include the following:

- History of prematurity
- Birth weight
- Need for and duration of oxygen therapy, assisted ventilation, or both in the neonatal period
- Previous emergency room visits, hospitalizations, or both for respiratory disturbances (including intensive care unit admissions and any need for assisted ventilation)
- Previous surgeries
- Immunization history

Results of previous evaluations may also provide important diagnostic clues.

The review of symptoms attempts to identify symptoms that were not identified in the history of present illness and that may be related or contribute to the child's underlying respiratory condition. A systematic review of symptoms in the following categories may suggest contributions of atopic diseases, gastroesophageal reflux, and immunodeficiency, as well as thoracic cage, neurologic, and neuromuscular disorders, to the presenting pulmonary complaint:

- Allergic
- Dermatologic
- Developmental
- Gastrointestinal
- Immunologic
- Otolaryngologic
- Musculoskeletal
- Neurologic
- Neuromuscular

The family history may also provide valuable information. Important conditions in the biological parents, siblings, and other close relatives to ask about include the following:

- Presence or absence of asthma
- Chronic or seasonal bronchitis
- Atopic diseases
- Recurrent pneumonia
- Cystic fibrosis
- Immunodeficiency
- Infertile males (may suggest cystic fibrosis)
- Tuberculosis
- Hemoptysis
- Early childhood serious illnesses or deaths
- Congenital heart disease
- Dextrocardia (heart situated on the right side of the body)
- α_1-Antiprotease deficiency

Important components of the social and environmental histories include the following:

- Who the child lives with
- Who assists the child with medications and therapies
- Level of adherence to medications and therapies
- Occupations of the caregivers
- Housing conditions
- Environmental tobacco smoke exposure
- Personal smoking
- Presence of visible mold
- Pets in the home
- Other significant exposures
- Use of day care
- School grades and performance
- Participation in and any difficulties with extracurricular activities

Box 4-3 Follow-up or Established Patient History

CHIEF COMPLAINT OR PREVIOUS DIAGNOSIS OR PROBLEM

Interim History

- Respiratory infections
- Exacerbations of primary disease
- Triggers and/or exposures
- Quality of life
- Medications

REVIEW OF KEY COMPONENTS

- Medical history
- Review of symptoms
- Social and environmental histories

situations; exposure to environmental tobacco smoke, allergens, and airway irritants; and recent travel or exposure to sick adults may also yield clues to changes in status of the primary disease. If an explanation of worsening or less than optimal control of the primary disease is not forthcoming, then a more detailed history similar to the initial medical history may be necessary.

PULMONARY EXAMINATION

The setting in which an examination occurs determines the pace of the examination and the information

Box 4-4 Pulmonary Examination

- Inspection
- Vital signs
- Heart rate
- Respiratory rate
- Temperature
- Blood pressure
- Oxygen saturation
- Respiratory distress
- Tachypnea
- Breathlessness
- Head bobbing
- Grunting
- Nasal flaring
- Retractions
- Chest wall
- Shape
- Muscle mass and strength
- Adipose tissue
- Palpation
- Neck
- Masses or adenopathy
- Trachea
- Chest
- Fremitus
- Motion with deep breathing
- Percussion
- Hyperresonance
- Dullness
- Auscultation
- Grunting
- Stridor
- Stertor
- Breath sounds
- Symmetry
- Intensity
- Location: lobes and segments
- Phases: inspiration, expiration, or both
- Adventitious sounds
- Crackles: fine or coarse
- Wheezes: low or high pitched
- Monophonic or polyphonic

gained. A child with respiratory distress may require rapid physical assessment and immediate institution of therapy. A crying child is almost impossible to examine. Efforts should be made to perform an examination in a calm, expeditious, and professional manner and in such a manner as not to upset the child. Examining a small child in the caregiver's lap may be particularly helpful in allaying the child's fears and keeping the child calm. In general, the pulmonary examination includes inspection, palpation, percussion, and auscultation (Box 4-4) and begins at the initiation of contact with the child. All components of the pulmonary examination yield valuable information, and the impulse to primarily or only use one's stethoscope should be avoided. Establishing a specific examination routine is helpful in completing all the evaluation components and in increasing one's comfort and expertise in physical assessment of a child with respiratory disease.

INSPECTION

Inspection begins at the bedside with review of the child's vital signs and first contact with the child and caregiver. Vital signs of importance include heart rate, respiratory rate, temperature, blood pressure, and, if available, pulse oximetry. Initial inspection is directed at determining whether the child is in respiratory distress. A child in respiratory distress may display both nonpulmonary and pulmonary signs. Nonpulmonary signs of respiratory distress include anxiety, fussiness, irritability, depressed level of consciousness or responsiveness, and tachycardia. Pulmonary signs include tachypnea, breathlessness, head bobbing, grunting, nasal flaring, retractions, oxygen saturation less than 90%, and cyanosis. A child in severe respiratory distress requires rapid assessment and immediate institution of appropriate therapy. The chest wall is inspected to evaluate for chronic obstructive lung, neuromuscular, and musculoskeletal diseases. Inspection for respiratory distress and of the chest wall is best done with the child's upper torso unclothed.

The respiratory rate can be a sensitive indicator of the severity of underlying lung disease.[30-32] Normal respiratory rates vary on the basis of age and activity level (Table 4-5). In general, the respiratory rate is best determined when the child is asleep or resting quietly.[33,34] In an ill-appearing child, the presence of fever may be a confounding factor that results in tachypnea proportional to the degree of fever and the appearance of respiratory distress. In a child with no underlying lung disease, relief of fever should result in resolution of tachypnea and apparent respiratory distress.

Head bobbing, nasal flaring, and grunting are common signs of respiratory distress in infants and young children and are compensatory mechanisms to decrease the work of breathing. **Head bobbing** occurs when the **sternocleidomastoids** (neck muscles that serve to flex and rotate the head), in an attempt to overcome decreased lung compliance, increased airway resistance, or both, contract during inspiration, pulling the head down and the clavicles and rib cage up (Figure 4-12). This results in the head bobbing forward in synchrony with each inspiration. Nasal flaring and grunting can be present in the pediatric patient as well. The presence of one or more of these signs typically indicates significant airway obstruction or lung disease.

Table 4-5 Normal Respiratory Rates in Sleeping and Awake Pediatric Patients

	SLEEPING BREATHS PER MINUTE			AWAKE BREATHS PER MINUTE		
AGE	NUMBER STUDIED	MEAN	RANGE	NUMBER STUDIED	MEAN	RANGE
6-12 months	6	27	22-31	3	64	58-75
1-2 years	6	19	17-23	4	35	30-40
2-4 years	16	19	16-25	15	31	23-42
4-6 years	23	18	14-23	22	26	19-36
6-8 years	27	17	13-23	28	23	15-30
8-10 years	19	18	14-23	19	21	15-31
10-12 years	11	16	13-19	17	21	15-28
12-14 years	6	16	15-18	7	22	18-26

From Iliff A, Lee VA: Pulse rate, respiratory rate, and body temperature of children between two months and eighteen years of age. *Child Dev* 23:237, 1952. Rusconi F, Castagneto M, Porta N, et al. Reference values for respiratory rate in the first three years of life. *Pediatrics* 94:350, 1994.

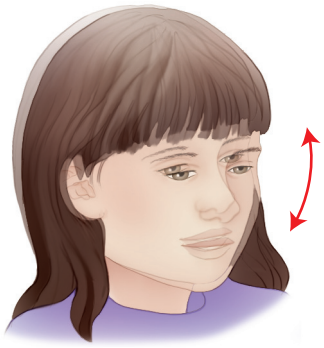


FIGURE 4-12 Head bobbing.

Suprasternal, intercostal, and subcostal or substernal retractions and asynchronous chest and abdominal wall motion are common signs of respiratory distress in both younger and older children and may be related to significant airway obstruction, lung disease, or both. Retractions result from the pulling in of the skin between and below the ribs, above the sternum in the suprasternal notch, or both, because of significant airway obstruction and lung disease (Figures 4-13, 4-14, and 4-15). Suprasternal retractions are also referred to as *tracheal tugging*. In most circumstances, a direct correlation exists between the degree of retractions and the severity of respiratory distress. Infants, young children, and children with muscle weakness may develop paradoxical inward motion of the chest wall and concomitant outward movement of the abdominal wall (i.e., asynchrony of chest and abdominal wall, or "see-sawing" motion) with increasing degrees of respiratory distress. As discussed earlier, in neonates, infants, and young children this see-sawing motion occurs because of their compliant rib cage, whereas in older children with muscle disease it occurs because of weakness of the abdominal wall musculature.

Inspection of the chest wall may reveal increased anteroposterior diameter, abnormal shape, muscular weakness, or obesity. Chest wall inspection should include anterior, posterior, and lateral examination. Chronic obstructive lung diseases such as severe asthma, advanced CF, and severe bronchopulmonary dysplasia may be associated with increased anteroposterior diameter of the chest as a result of

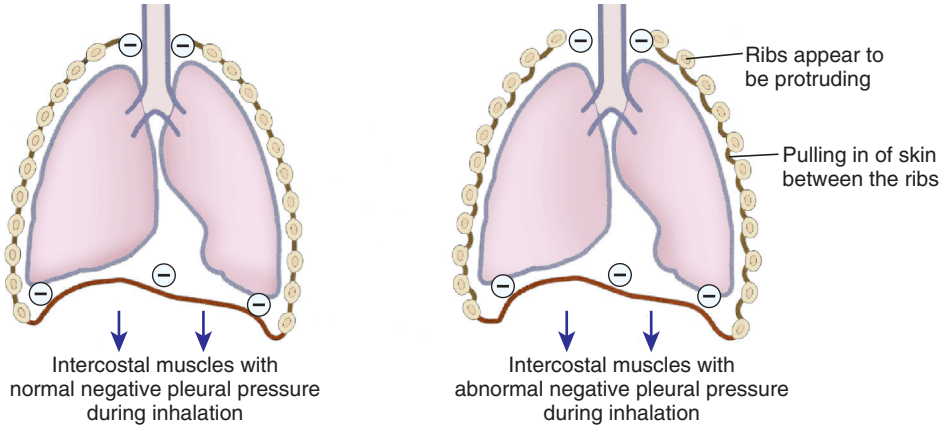


FIGURE 4-13 Intercostal retractions. Soft tissue between the ribs is pulled inward (retracted) because of the extremely high negative pleural pressure.

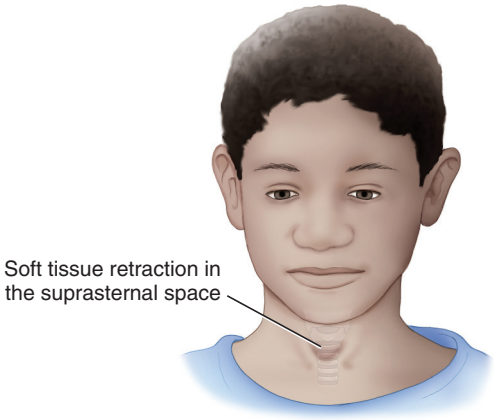


FIGURE 4-14 Suprasternal retractions. Soft tissue in the suprasternal space is retracted because of high negative pressure, most often caused by the patient's attempt to breathe against an airway obstruction.

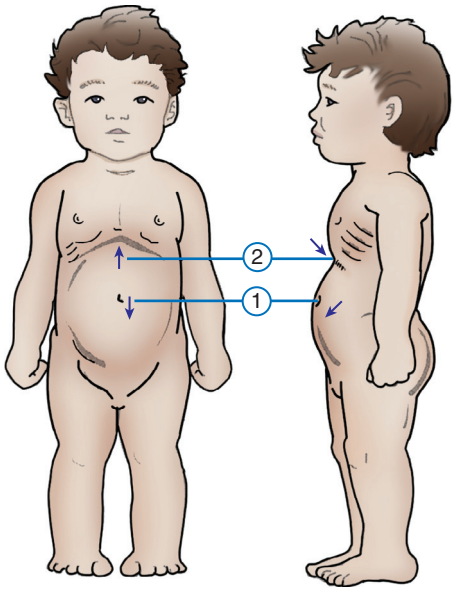


FIGURE 4-15 Subcostal and substernal retractions. Airway obstruction results in a pulling inward of the lower costal margins. The abdomen is protruding *(1)*, and there is a sunken substernal notch *(2)*. See-saw movement of the chest and stomach is also present.

increased air trapping. The chest wall may be abnormally shaped, such as in pectus carinatum ("pigeon breast"), pectus excavatum ("sunken chest"), **kyphosis** ("hunchback" appearance), and **scoliosis** (abnormal "sideways" spinal curvature). The chest wall may also be bell-shaped or have obvious rib abnormalities. Muscular weakness may result in decreased chest wall muscle mass; poor head control; or obvious weakness of the trunk, extremities, or both. Obesity may cause excessive deposition of adipose tissue around the neck, chest, and abdomen. Abnormal chest wall shape, muscular weakness, and obesity can result in significant restrictive lung dysfunction.

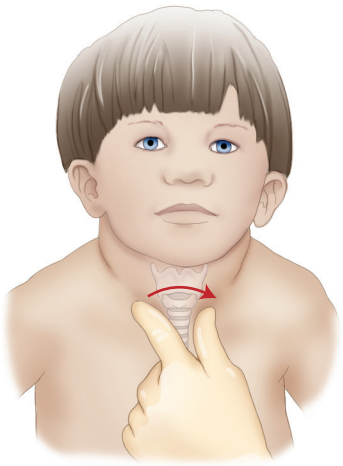


FIGURE 4-16 Technique for determining tracheal position in the older child.

PALPATION

Palpation of the chest wall and neck may be helpful in the physical examination of a child with respiratory disease. In infants and young children, palpation of the chest during quiet breathing may elicit rhonchal or **bronchial fremitus,** which are vibrations of the chest resulting from movement of air through airways partially obstructed by mucus. In an older child, palpation of the chest during normal speech may elicit **tactile fremitus,** vibrations of the chest produced by the spoken voice. Tactile fremitus may be increased over areas of the chest wall corresponding to underlying pulmonary consolidation. In an older child, assessment of chest wall excursion can be accomplished by placement of the examiner's hands on both sides of the thoracic spine, with thumbs toward the spine, and observing the motion of the hands and patient's ribs during deep inspiration. Palpation of the anterior neck may be helpful in determining whether the trachea is in the midline (Figure 4-16) and whether there are masses or adenopathy compressing the trachea.

PERCUSSION

Percussion of the chest wall may be helpful in the physical examination of an older child but is typically unrewarding in the examination of an infant or younger child. Chest percussion is performed by tapping the finger of one hand with a finger of the other hand over corresponding areas of the patient's chest, usually while the patient is sitting upright. A relatively high-pitched percussion note, or hyperresonance, suggests focal or generalized air trapping or pneumothorax. A relatively dull percussion note indicates atelectasis, consolidation, or pleural effusion. In the case of pleural effusion, changes in the level of the dull percussion note over time can be used to assess worsening or improvement.

AUSCULTATION

Auscultation involves listening to the sounds of the heart, lungs, and gastrointestinal tract, sometimes with the ears alone but more generally with a stethoscope. Breathing is normally quiet, so noises heard without the stethoscope or audible noises during "quiet" breathing are always abnormal. Grunting was previously discussed. Other audible noises include stridor, stertor, and occasionally wheezing. Abnormal chest noises, or adventitious sounds, heard with the stethoscope include crackles and wheezes.[37-39] Stridor and wheezes are sometimes further described as monophonic sounds. Wheezes may also be described as polyphonic sounds. Monophonic sounds are usually associated with upper and central airway disorders and sound similarly throughout the chest. Polyphonic sounds are usually associated with small airway disorders and sound different in different parts of the chest. Auscultation with the stethoscope should be performed while the child is calm and quiet. Intensity and symmetry of breath sounds and duration of inspiration and expiration should be noted. Prolonged inspiration suggests extrathoracic (larynx and upper trachea) airway obstruction, whereas prolonged expiration suggests intrathoracic (lower trachea, mainstem bronchi, and smaller bronchi) airway obstruction.

Stridor is a high-pitched, monophonic, audible noise that may occur during inspiration or expiration or may be biphasic.[39,40] Inspiratory stridor suggests extrathoracic airway obstruction, such as occurs in laryngomalacia, subglottic stenosis, and croup. Expiratory stridor suggests intrathoracic central airway obstruction, such as occurs in mass or vascular compression of the trachea, tracheomalacia, and bronchomalacia. Biphasic stridor typically indicates a more severe degree of laryngeal or central airway obstruction and may be associated with signs of respiratory distress. To distinguish stridor from wheezing, the examiner should place the head of the stethoscope over the neck area. If the sound is louder over the neck than over the chest, then it is most likely the result of stridor rather than wheezing. **Stertor** is a low-pitched, wet sound similar to snoring and suggests nasopharyngeal, oropharyngeal, or hypopharyngeal airway obstruction, such as occurs in adenotonsillar hypertrophy.[41,42] Audible wheezing may occur in asthma or in intrathoracic central airway obstruction, typically indicates a more severe degree of obstruction, and may be associated with signs of respiratory distress.

The classification of adventitious sounds is confusing. Most modern terminology primarily uses the term *wheezes* for continuous sounds and *crackles* for discontinuous sounds.[37-39] Continuous sounds typically last for at least 250 msec, whereas discontinuous sounds last for less than 20 msec.[37] Wheezes can be further described as inspiratory, expiratory, monophonic, polyphonic, high pitched, or low pitched. Polyphonic high-pitched wheezes typically occur in asthma, and as airway obstruction worsens, wheezes tend to progress from end-expiratory, to expiratory, to both expiratory and inspiratory sounds. The term *rhonchus* (plural, *rhonchi*) has also been used to describe a low-pitched wheeze and suggests movement of air through large airways partially obstructed by mucus. Crackles can be further described as inspiratory, expiratory, fine, and coarse. Fine crackles are less loud crackles with high-frequency components and short duration and are usually associated with distal small airway or alveolar diseases such as pneumonia or pulmonary edema. Coarse crackles are louder crackles with lower frequency and longer duration and are usually associated with medium or large airway disease such as bronchitis.[43] Where in the chest adventitious sounds are heard is also important to note and may suggest an etiology. Unilateral wheezes or wheezes heard over a specific segment or lobe suggest foreign body airway obstruction. Fine crackles heard over a specific segment or lobe suggest localized pneumonia.

NONPULMONARY EXAMINATION

In addition to examining the chest, a general examination should be done, including assessment of growth (weight, weight percentile, height, and height percentile) and examination of several other areas of the body, including the eyes, ears, nose, throat, heart, abdomen, skin, and extremities, for clues to underlying or contributing conditions (Box 4-5). Descriptions of many of the pathologic findings that may be found during a pediatric examination are outside the scope of this chapter, and the interested reader is referred to other sources. Conditions potentially associated with respiratory disease that can be detected during a general examination include significant poor growth, developmental delay, neurologic abnormalities or cerebral palsy, muscle weakness or atrophy, and adenopathy. Poor growth, manifested by weight, height, or both weight and height less than the 5th percentile for age, suggests a potentially serious chronic condition. Developmental delay, neurologic abnormalities, and muscle weakness or atrophy may result in ineffective cough, dysphagia with pulmonary aspiration, chest wall deformities, or restrictive lung dysfunction. Adenopathy may suggest immunodeficiency or an oncologic process.

Examination of the ears, eyes, nose, and throat, although usually performed by a physician, is part of the pulmonary examination and may reveal findings associated with a respiratory disease. Allergic disorders are suggested by the findings of serous otitis media; conjunctivitis; allergic shiners; Morgan-Dennie lines; nasal crease; nasal secretions; edematous, pale

Box 4-5 Nonpulmonary Examination: Findings Possibly Associated With Pulmonary Disease

GENERAL
- Poor growth (weight, height, or both less than the 5th percentile for age)
- Developmental delay
- Neurologic abnormalities or cerebral palsy
- Muscle weakness or atrophy
- Adenopathy

EARS, EYES, NOSE, THROAT
- Serous otitis media
- Conjunctivitis
- Allergic shiners
- Morgan-Dennie lines
- Nasal crease
- Nasal secretions
- Edematous, pale nasal mucosa
- Tonsillar hypertrophy
- Posterior pharyngeal mucus (postnasal drip)

HEART
- Abnormal rhythm
- Murmurs or gallop
- Prominent second heart sound

ABDOMEN
- Distention
- Hepatosplenomegaly

SKIN
- Atopic dermatitis
- Urticaria
- Poor circulation
- Hemangiomas, telangiectasias
- Cyanosis

EXTREMITIES
- Digital clubbing
- Edema
- Arthritis

nasal mucosa; and posterior pharyngeal mucus (postnasal drip). Obstructive sleep apnea is suggested by severe tonsillar hypertrophy.

Cardiac dysfunction may contribute to or be the result of pulmonary dysfunction. Findings of an abnormal rhythm, murmur, gallop, or prominent second (pulmonic) heart sound during cardiac examination suggest cardiac dysfunction and should be noted.

Evaluation of the abdomen may reveal distention or hepatosplenomegaly that can be associated with CF or may result in impaired diaphragmatic excursion with resultant restrictive lung dysfunction.

Inspection of the skin may reveal evidence of an allergic disorder, such as atopic dermatitis or urticaria; cardiac dysfunction, such as poor circulation or cyanosis; severe hypoxemia, such as cyanosis; or lesions that suggest more generalized diseases with a pulmonary component, such as hemangiomas (a benign tumor of blood vessel endothelial cells that may obstruct large airways or, if in the lung, result in right-to-left shunting of blood, causing hypoxemia) or telangiectasias (small dilated blood vessel malformations that if multiple or present in the nose may suggest hereditary hemorrhagic telangiectasia).

Inspection of the extremities may reveal evidence of cardiac dysfunction or hypoproteinemia, such as edema; immunologic disease, such as arthritis; or both. The finding of digital clubbing (Figure 4-17) in a child with any respiratory condition should strongly suggest chronic, potentially severe, and life-threatening diseases such as CF, interstitial lung disorders, or other serious lung disorders. Although digital clubbing may be familial, it is also found in cyanotic congenital cardiac disease; infective

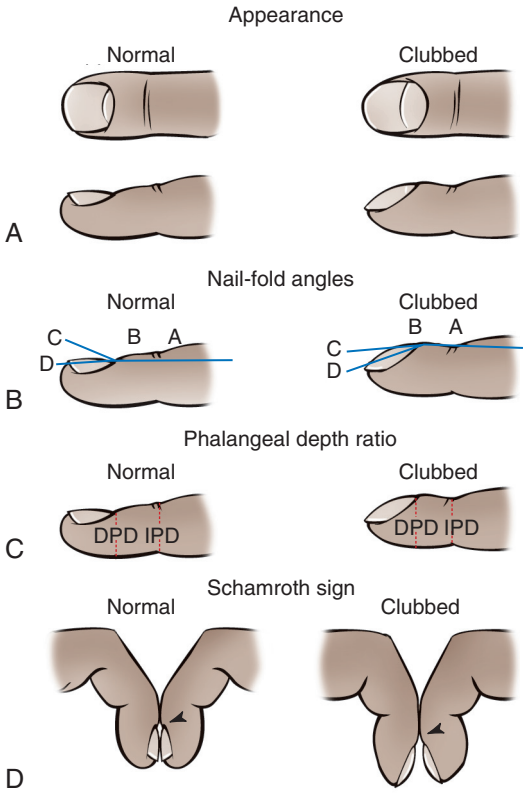


FIGURE 4-17 **A,** Normal finger, viewed from above and in profile, and the changes occurring in established clubbing, viewed from above and in profile. **B,** The finger on the left demonstrates normal profile (ABC) and normal hyponychial (ABD) nail-fold angles of 169 and 183 degrees, respectively. The clubbed finger on the right shows increased profile and hyponychial nail-fold angles of 191 and 203 degrees, respectively. **C,** Distal phalangeal finger depth (DPD)/interphalangeal finger depth (IPD) represents the phalangeal depth ratio. In normal fingers, the IPD is greater than the DPD. In clubbing, this relationship is reversed. **D,** Schamroth sign: In the absence of clubbing, opposition of the index fingers nail-to-nail creates a diamond-shaped window *(arrowhead)*. In clubbed fingers, the loss of the profile angle because of an increase in tissue at the nail bed causes obliteration of this space *(arrowhead)*.

endocarditis; cirrhosis; inflammatory bowel disease; and other infectious, neoplastic, inflammatory, and vascular disorders.[45] Thus the finding of digital clubbing should always lead to additional laboratory evaluation.

LABORATORY ASSESSMENT

Routine laboratory studies play a limited but important role in the immediate newborn period. Most laboratory abnormalities seen in the first 24 hours of life result from sepsis, abnormally high or low levels of red blood cells, red blood cell isoimmunization, or temporary derangement in the regulation of glucose metabolism.

The white blood cell (WBC) count of the newborn is usually significantly higher than pediatric or adult values. **Leukopenia,** WBCs less than 3500/mm^3, and **leukocytosis,** WBCs greater than 25,000/mm^3, suggest infection. WBCs greater than 25,000/mm^3, however, are not unusual in the immediate newborn period. Similarly, the absolute number of platelets is associated with fetal or neonatal infection. A platelet count of less than 150,000 cells/mm^3 is abnormally low and is usually seen with acute or chronic infections.

The newborn infant tends to have increased hemoglobin and hematocrit levels at birth. The fetus requires extra hemoglobin to maintain appropriate oxygen transport in the relatively low oxygen pressure of the fetal environment. The newborn's hematocrit is affected by many factors, including gestational age, the presence of placental abnormalities, the speed and mode of delivery, and the length of time after delivery that the infant remains attached to the placenta (with or without cord stripping by the obstetrician). Table 4-6 lists the range of normal values for newborns.

After completion of the history and physical examination of a pediatric patient, laboratory testing may be required for further diagnostic evaluation, objective quantification of disease severity, assessment of previous management, or longitudinal follow-up (Box 4-6). Typically, diagnostic laboratory evaluation proceeds from noninvasive to invasive studies in a stepwise progression. Noninvasive diagnostic studies that may be considered for a child with a respiratory condition include chest radiography, pulmonary function testing (spirometry, lung volume determinations, Dlco [diffusing capacity of the lungs for carbon monoxide], bronchial challenge testing [exercise, cold air, and methacholine]), exercise desaturation testing, sweat chloride analysis, complete blood cell count, serum immunoglobulins (IgG, IgA, IgM, and IgE), blood gas analysis (arterial, venous, and capillary), allergy skin testing, tuberculosis skin testing, sputum cultures (bacterial, fungal, mycobacterial, and viral), barium esophagography, chest computed tomography, chest magnetic resonance imaging, overnight polysomnography, and so on. Invasive diagnostic studies that may be considered include a 24-hour pH probe study, rigid or flexible bronchoscopy, lung biopsy (bronchoscopically directed, thoracoscopic, and open), and others. Studies used to quantitate disease severity, to assess previous management, or for longitudinal follow-up include pulmonary function testing (spirometry, lung volume determinations, Dlco, bronchial challenge testing [exercise, cold air, and methacholine]), exercise desaturation testing, sputum

Box 4-6 Laboratory Evaluation

Diagnostic
- Noninvasive
  - Chest radiography
  - Chest computed tomography
  - Chest magnetic resonance imaging
  - Pulmonary function testing (spirometry, lung volume determinations, Dlco, and bronchial challenge testing [exercise, cold air, and methacholine])
  - Exercise desaturation testing
  - Sweat chloride analysis
  - Allergy skin testing
  - Sputum cultures (bacterial, fungal, mycobacterial, and viral)
  - Overnight polysomnography
- Invasive
  - 24-hour pH probe study
  - Rigid or flexible bronchoscopy
  - Lung biopsy (bronchoscopically directed, thoracoscopic, and open)
  - Complete blood cell count
  - Serum immunoglobulins (IgG, IgA, IgM, and IgE)
  - Blood gas analysis (ABG, VBG, and CBG)
  - Tuberculosis skin testing
  - Barium esophagography

ABG, Arterial blood gas; *CBG*, capillary blood gas; *Dlco*, diffusing capacity of the lungs for carbon monoxide; *VBG*, venous blood gas.

Table 4-6 Laboratory Values in the Neonatal Patient

AGE	HgB	HcT	WBCs	PLATELETS
	(g/dl)	*(%)*	*(×1000 cells/mm^3)*	*(×1000 cells/mm^3)*
28 weeks of gestation	14.5	45	—	275
32 weeks of gestation	15	47	—	290
Term newborn	16.5	51	18.1	310
1-3 days	18.5	56	18.9	300

Hgb, Hemoglobin; *Hct*, hematocrit; *WBCs*, white blood cells.
Data from Oski FA, Naiman JL: *Hematological problems in the newborn infant*, Philadelphia, 1981, WB Saunders.

cultures (bacterial, fungal, mycobacterial, and viral), chest radiography, chest computed tomography, and others. Although pulse oximetry may be considered a laboratory evaluation in some clinical settings, because of its widespread availability it should be considered a vital sign.[46]

Clinical Highlight

A 6-year-old girl is brought by her mother to the pulmonary office because of recurrent pneumonia. This establishes the chief complaint. With only this information an extensive differential diagnosis might include CF, immunocompromise, aspiration, chronic infection, and asthma. Further questioning reveals that the child has had at least one episode of pneumonia in each of the last 4 years, usually in the winter months. Her symptoms during the acute illness include cough, fever, and dyspnea. Only one of the pneumonias resulted in hospitalization. The patient recovered completely between episodes.

At this point, the girl's growth has been good, and she does not have frequent gastrointestinal symptoms or greasy bowel movements, making CF less likely. Her mother is healthy and has no acquired immunodeficiency syndrome (AIDS) risk factors, making AIDS less likely. Each of the pneumonia episodes started with a common cold, often accompanied by wheezing. The patient has had occasional coughing when exposed to irritating smells such as cigarette smoke and cold air. During one emergency department visit, she received a nebulized medication, which greatly relieved her respiratory distress. These findings suggest that her primary disease might be asthma (Box 4-7).

The child has had no recognized exposure to tuberculosis and no foreign body aspiration history. She denies swallowing difficulty, frequent emesis (vomiting), or heartburn. She has had a red itchy rash in the elbow and knee regions in the past that her mother thinks is eczema. The patient has not had welts or hives (i.e., urticaria). The associated atopic history also points to asthma as the underlying explanation for the pneumonias.

FAMILY HISTORY

The family history may also reveal valuable clues. In the case of this 6-year-old girl, her older brother was diagnosed with asthma as a young child; there was no recognized CF, infertile males, dextrocardia, immunodeficiency, or α_1-antiprotease deficiency. This further supports asthma as a potential cause of her recurrent pneumonia.

Box 4-7 History Taking in the Pediatric Patient with Asthma

MANIFESTATIONS
- Cough
- Wheeze
- Dyspnea
- Chest pain

AGGRAVATING FACTORS
- Upper respiratory tract infections
- Exercise or activity
- Allergens or exposures
- Irritants
- Emotions

ALLEVIATING FACTORS
- Bronchodilators
- Avoidance of aggravating factors

FAILED MEDICATION TRIALS
- Antibiotics
- Decongestants
- Humidification
- Other

ASSOCIATED CONDITIONS (REVIEW OF SYMPTOMS)
- General: poor growth, activity intolerance
- Allergy/atopy: conjunctivitis, rhinitis, eczema, urticaria
- Gastrointestinal: dysphagia, dyspepsia, emesis, steatorrhea
- Pulmonary: recurrent pneumonia, foreign body aspiration
- Ear, nose, and throat: mouth breathing, snoring
- Exposure to infections: pertussis, tuberculosis, bronchiolitis, influenza, common cold

FAMILY HISTORY
- Allergic/atopic diseases: asthma, rhinitis, eczema, urticaria, food allergy
- Cystic fibrosis
- Infertile males (history of male infertility might suggest cystic fibrosis and need for further diagnostic testing)
- α_1-Antiprotease deficiency
- Dextrocardia
- Immunodeficiency states

ENVIRONMENTAL EXPOSURES
- Pets (cats, dogs, ferrets, hamsters, gerbils, birds, etc.)
- Tobacco smoke
- Visible household mold
- Areas of indoor dampness or water damage

Clinical Highlight

A 6-year-old patient with asthma was undergoing pulmonary function testing during a follow-up asthma clinic visit. She reported to the pulmonary nurse that her asthma had been under worse control over the past 2 months, especially during exercise and at night. The attending physician was prepared to prescribe a short course of oral prednisone and double the baseline dose of the inhaled corticosteroid. During administration of the inhaled bronchodilator as part of the pulmonary function test, you noticed the metered-dose inhaler technique was quite poor (despite prior demonstration of correct technique). Further questioning identified that the spacing device prescribed to improve aerosol deposition had been "lost" several weeks ago. Neither the patient nor her family realized the significance of this loss. After discovering this, you informed the asthma team about concerns that neither the inhaled steroids nor the bronchodilators were likely to be optimally deposited in the lower airways. Rather than increase the patient's exposure to corticosteroids, inhaler technique was reviewed and another spacing device was prescribed. Both the patient and her mother were reeducated about the importance of adherence and the proper technique for use of a metered-dose inhaler and spacing device.

Clinical Highlight

A 28-month-old boy is admitted to the hospital for respiratory distress and pneumonia. During the initial assessment you note that the child is somewhat thin and anxious but sitting quietly in his mother's arms. The child's pulse is 140 beats per minute, respiratory rate is 52 breaths per minute, room air oxygen saturation is 91%, and he has mild intercostal retractions. Auscultation reveals diffuse fine crackles. The child does not have clubbing. You appropriately place the child on low-flow nasal cannula oxygen. Further history reveals that the boy has had recurrent cough since he was several months of age, has had several bouts of pneumonia, and recently has developed a productive cough and lost 3 pounds. You communicate these findings to the child's physician and ask whether the child could have a chronic respiratory illness such as cystic fibrosis. After initiating appropriate immediate therapy, the physician obtains a sweat chloride analysis that is positive and refers the child to a nearby cystic fibrosis center for further evaluation and management.

In this example, your brief assessment and recognition that the child not only had an acute respiratory illness but also a probable chronic pulmonary disease led to communication with the child's physician. This communication resulted in further diagnostic testing, leading to a diagnosis and referral to more specialized care.

Key Points

- Initial stabilization of the newborn minimally involves the following:
  - Drying and warming the infant
  - Opening and clearing the infant's airway, if indicated
  - Stimulating the infant to breathe
- Direct laryngotracheal suctioning should occur in the nonvigorous (i.e., no or poor respiratory effort, heart rate <100, or poor muscle tone) meconium-stained newborn.
- Apgar score is an evaluation of newborns based on five factors: heart rate, respiratory effort, muscle tone, reflex irritability, and skin color. Apgar scoring is performed at 1 minute and 5 minutes after birth. Additional scoring may be indicated when the 5-minute Apgar is less than 7.
- Small-for-gestational-age infants have a birth weight less than the 10th percentile for gestational age. An infant whose birth weight is more than the 90th percentile is large for gestational age.
- Critical vital signs for initial assessment of the newborn include the following:
  - Heart rate (120-170 beats per minute)
  - Respiratory rate (40-60 breaths per minute)
  - Blood pressure
  - Temperature 97.6 $\pm$ 1° F (axillary) and 99.6 $\pm$ 1° F (rectal)
- Periodic breathing is normal in neonates. Apnea is diagnosed by a 20-second cessation of respiration.
- Grunting, nasal flaring, and retractions indicate respiratory distress in a normal newborn. The Silverman score provides an objective measure of newborn respiratory distress.
- Transillumination of the neonatal chest wall with a high-energy light source can rapidly diagnose a pneumothorax. A pneumothorax will "light up" brighter than normal lung tissue.
- Neurologic examination of a newborn involves observing the infant's response to the environment (bright lights and sounds), muscle tone, and presence of various reflexes (e.g., grasp, plantar grasp, Moro, and stepping reflexes).
- Examination of a pediatric patient may occur in the lap of a caregiver. A crying child is difficult to examine.
- Head bobbing is sign of respiratory distress in a small child or infant.
- Respiratory rate varies in pediatric patients with activity level but is still a sensitive indicator of the severity of underlying lung disease.

Assessment Questions

See Evolve Resources for answers.

1. What is the proper procedure to implement for an infant known to have experienced meconium aspiration before birth?
   - **A.** The obstetrician should suction the mouth, nose, and pharynx after delivery of the head, but before delivery of the shoulders.
   - **B.** Intubate immediately and aspirate the trachea using a meconium aspirator, regardless of whether the infant is vigorous.
   - **C.** Treat the infant exactly as if meconium was not present.
   - **D.** Intubate and suction only if the infant is not vigorous; otherwise, follow the normal resuscitation procedures.
2. Appropriate stimulation of a newborn includes which of the following?
   - **A.** Flicking the bottoms of the feet
   - **B.** Gently shaking the shoulders
   - **C.** Drying with a warm towel
   - **D.** Gently rubbing the back
   - **E.** A and B
   - **F.** A, C, and D
3. The Apgar score includes which of the following criteria?
   - **A.** Color
   - **B.** Evaluation of the Moro reflex
   - **C.** Heart rate
   - **D.** Reflex irritability
   - **E.** A and B
   - **F.** A, C, and D
   - **G.** C and D

4. The best indicator of an infant's overall cardiopulmonary status immediately after birth is _____.
   - **A.** Heart rate
   - **B.** Apgar score
   - **C.** Color
   - **D.** Respiratory effort
5. The ideal time to assess the gestational age of a newborn is _____.
   - **A.** Within the first 30 minutes after birth
   - **B.** Within the first hour of life
   - **C.** Within the first 12 hours of life
   - **D.** Within the first 24 hours of life
6. Ideally, gestational age is evaluated on the basis of _____.
   - **A.** The gestational duration since the mother's last menstrual cycle
   - **B.** Prenatal ultrasound evaluations
   - **C.** The Ballard scoring system
   - **D.** All of the above
7. Apnea is a pathologic condition in which breathing ceases for a period of _____ seconds or longer.
   - **A.** 10
   - **B.** 20
   - **C.** 45
   - **D.** 60
8. Signs of respiratory distress in a newborn include which of the following?
   - **A.** Vesicular breath sounds
   - **B.** Grunting
   - **C.** Nasal flaring
   - **D.** B and C
   - **E.** A and B
9. The umbilical cord normally has _____ artery(ies) and _____ vein(s).
   - **A.** 1 and 1
   - **B.** 2 and 2
   - **C.** 1 and 2
   - **D.** 2 and 1
10. An 8-month-old presents with head bobbing. Which of the following is true about head bobbing?
    - **A.** It usually suggests a brainstem lesion.
    - **B.** It is a voluntary action that can be stopped on command.
    - **C.** It usually suggests respiratory distress, airway obstruction, or decreased lung compliance.
    - **D.** It is unrelated to cardiopulmonary disease.
11. Palpation of a patient's chest produces a vibration of the chest wall during quiet breathing. This suggests partial obstruction of the large airways by mucus. The name of this sign is _____.
    - **A.** Fine crackles
    - **B.** Rhonchal or bronchial fremitus
    - **C.** Clubbing
    - **D.** Pectus carinatum
    - **E.** Stridor
12. An infant produces an audible noise that appears to be stridor. Which of the following is true about stridor?
    - **A.** It is a high-pitched, monophonic, audible noise.
    - **B.** It may occur during inspiration or expiration or may be biphasic.
    - **C.** Patients with laryngomalacia or subglottic stenosis may have inspiratory stridor.
    - **D.** Patients with a double aortic arch compressing the trachea, or tracheomalacia, may have expiratory stridor.
    - **E.** All of the above.
13. A teenager has a temperature of 38.5° C, a respiratory rate of 28 breaths per minute, increased thoracic anteroposterior diameter, minimal subcostal retractions, and fine and coarse crackles heard over the right and left upper lobes. Further evaluation reveals mild digital clubbing of the fingers. This child probably has which underlying disease?
    - **A.** Asthma
    - **B.** Gastroesophageal reflux
    - **C.** Bilateral bronchomalacia
    - **D.** Cystic fibrosis
    - **E.** Acute respiratory distress syndrome
14. In the emergency room, the respiratory therapist is asked to give a 2-year-old in respiratory distress an albuterol treatment. Pretreatment assessment reveals a mildly uncomfortable afebrile child with a respiratory rate of 36 breaths per minute, mild subcostal retractions, and expiratory wheezes best heard over the right middle and lower lobes. Posttreatment assessment is unchanged except that the respiratory rate is now 32 breaths per minute. A brief history reveals that coughing began abruptly several days ago and wheezing was noted this morning. The family has no history of atopic disease (allergic rhinitis, allergic conjunctivitis, asthma, or atopic dermatitis). This child was previously healthy with no history of chest disease. The respiratory therapist speaks with the attending physician and suggests that the child most likely has which disorder/disease?
    - **A.** Pneumonia
    - **B.** Cystic fibrosis
    - **C.** Foreign body aspiration
    - **D.** Laryngeal cleft
    - **E.** Double outlet right ventricle

REFERENCES

1. Centers for Disease Control and Prevention. *Premature Birth*. Atlanta, GA; November 7, 2016. https://www.cdc.gov/reproductivehealth/MaternalInfantHealth/PretermBirth.htm. Accessed 8/2/18.
2. Wolkoff L, Davis JM. Delivery room resuscitation of the newborn. *Clin Perinatol*. 1999;26:641.
3. Chahine AA, Ricketts RR. Resuscitation of the surgical neonate. *Clin Perinatol*. 1999;26:693.
4. Wyckoff MH, Aziz K, Escobedo MB, et al. 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, Part 13: Neonatal Resuscitation. *Circulation*. 2015;132: S543-S560.
5. Vain NE, Szyld EG, Prudent LM, et al. Oropharyngeal and nasopharyngeal suctioning of meconium-stained neonates before delivery of their shoulders: multicentre, randomized controlled trial. *Lancet*. 2004;364:597.
6. Nadkarni V, Hazinski MF, Zideman D. Pediatric resuscitation: an advisory statement from the pediatric working group of the international liaison committee on resuscitation. *Circulation*. 1997;95:2185.
7. Juretschke LJ. Apgar scoring: its use and meaning for today's newborn. *Neonatal Netw*. 2000;19:17.
8. Weinberger B, Anwar M, Hegyi T, et al. Antecedents and neonatal consequences of low Apgar scores in preterm newborns: a population study. *Arch Pediatr Adolesc Med*. 2000;154:294.
9. Jain L, Ferre C, Vidyasagar D, et al. Cardiopulmonary resuscitation of apparently stillborn infants: survival and long-term outcome. *J Pediatr*. 1991;118:778.
10. Catlin EA, Carpenter MW, Brann IV BS, et al. The Apgar score revisited: influence of gestational age. *J Pediatr*. 1986;109:865.
11. Donovan EF, Tyson JE, Ehrenkranz RA, et al. Inaccuracy of Ballard scores before 28 weeks' gestation. *J Pediatr*. 1999;135:147.
12. Sanders M, Allen M, Alexander GR, et al. Gestational age assessment in preterm neonates weighing less than 1500 grams. *Pediatrics*. 1991;88:542.
13. Ballard JL, Khoury JC, Wedig KL, et al. New Ballard score to include extremely premature infants. *J Pediatr*. 1991;199: 417.
14. Thomas P, Peabody J, Turnier V, et al. A new look at intrauterine growth and the impact of race, altitude, and gender. *Pediatrics*. 2000;106:e21.
15. Dunster K. Physiologic variability in the perinatal period. *Clin Perinatol*. 1999;26:801.
16. Rosenkrantz T. Polycythemia and hyperviscosity in the newborn. *Semin Thromb Hemost*. 2003;29:515.
17. Bhutani VK, Gourley GR, Adler S, et al. Noninvasive measurement of total serum bilirubin in a multiracial predischarge newborn population to assess the risk of severe hyperbilirubinemia. *Pediatrics*. 2000;106:e17.
18. Rigatto H, Brady JP. Periodic breathing and apnea in preterm infants: hypoxia as a primary event. *Pediatrics*. 1972;50: 219.
19. Ackerman Jr NB, Bell RE, DeLemos RA. Differential pulmonary auscultation in neonates. *Clin Pediatr*. 1982;21:566.
20. Page J, Hosking M. An approach to the neonate with sudden dysrhythmia: diagnosis, mechanisms, and management. *Neonatal Netw*. 1997;16:7.
21. Blakelock RT, Harding JE, Kolbe A, et al. Gastroschisis: can the mortality be avoided? *Pediatr Surg Int*. 1997;12:276.
22. Furdon S, Clark D. Differentiating scalp swelling in the newborn. *Adv Neonatal Care*. 2001;1:22.
23. Davis DJ. Neonatal subgaleal hemorrhage: diagnosis and management. *Can Med Assoc J*. 2001;164:1452.
24. Bodurtha J. Assessment of the newborn with dysmorphic features. *Neonatal Netw*. 1999;18:27.
25. Jones KL. *Smith's recognizable patterns of human malformation*. 4th ed. Philadelphia: WB Saunders; 1988.
26. Dennison WM. The Pierre Robin syndrome. *Pediatrics*. 1965;36:336.
27. Hashimoto BE, Filly RA, Callen PW. Sonographic diagnosis of clubfoot in utero. *J Ultrasound Med*. 1986;5:81.
28. Fernbach SA. Common orthopedic problems of the newborn. *Nurs Clin North Am*. 1998;33:583.
29. Majnemer A, Brownstein A, Kadanoff R, et al. A comparison of neurobehavioral performance of healthy term and low risk pre-term infants at term. *Dev Med Child Neurol*. 1992;34:417.
30. Glezen WP, Greenberg SB, Atmar RL, et al. Impact of respiratory virus infections on persons with chronic underlying conditions. *JAMA*. 2000;283:499.
31. DiFranza JR, Aligne CA, Weitzman M. Prenatal and postnatal environmental tobacco smoke exposure and children's health. *Pediatrics*. 2004;113:1007.
32. Morley CJ, Thornton AJ, Fowler MA, et al. Respiratory rate and severity of illness in babies under 6 months old. *Arch Dis Child*. 1990;65:834.
33. Harari M, Spooner V, Meisner S, et al. Clinical signs of pneumonia in children. *Lancet*. 1991;338:928.
34. Margolis P, Gadomski A. Does this infant have pneumonia? *JAMA*. 1998;279:308.
35. Iliff A, Lee VA. Pulse rate, respiratory rate, and body temperature of children between two months and eighteen years of age. *Child Dev*. 1952;23(4):237.
36. Rusconi F, Castagneto M, Porta N, et al. Reference values for respiratory rate in the first three years of life. *Pediatrics*. 1994;94:350.
37. Loudon R, Murphy Jr RL. State of the art: lung sounds. *Am Rev Respir Dis*. 1984;130:663.
38. Mikami R, Murao M, Cugell D, et al. International symposium on lung sounds. *Chest*. 1987;92:342.
39. Cugell DW. Lung sound nomenclature. *Am Rev Respir Dis*. 1987;136:1016.
40. Eavey RD. A sound workup for evaluating airway obstructions. *Contemp Pediatr*. 1986;3:78.
41. Tan HK, Holinger LD. How to evaluate and manage stridor in children. *J Respir Dis*. 1994;15:245.
42. Cotton RT, Reilly JS. Stridor and airway obstruction. In: CD Bluestone, SE Stool, MD Scheetz, eds. *Pediatric otolaryngology*. Philadelphia: WB Saunders; 1990:1098-1111.
43. Piirila P, Sovijärvi AR. Crackles: recording, analysis and clinical significance. *Eur Respir J*. 1995;8:2139.
44. Zitell BJ, Davis HW. *Atlas of pediatric physical diagnosis*. Philadelphia: WB Saunders; 2002.
45. Myers KA, Farquhar DR. Does this patient have clubbing? *JAMA*. 2001;286:341.
46. Mower WR, Sachs C, Nicklin EL, et al. Pulse oximetry as a fifth pediatric vital sign. *Pediatrics*. 1997;99:681.

Pulmonary Function Testing and Bedside Pulmonary Mechanics

5

Katrina M. Hynes, Carl D. Mottram

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. Define the terminology and various abbreviations used in describing specific aspects of interpreting pulmonary function tests.
2. Identify specific techniques used to elicit acceptable and repeatable results in children when performing pulmonary function tests.
3. Describe the special challenges specific to neonates, infants, and children when performing pulmonary function tests or assessing respiratory function.
4. Appraise the standard and alternative instrumentation techniques available for pulmonary function testing of newborns and children.
5. Differentiate among the infant, child, and adult chest wall and pulmonary mechanics that affect correct interpretation of pulmonary function data.
6. Compare the various techniques available for measuring airway function in both infants and children.
7. Compare the various techniques available for measuring lung volumes in both infants and children.
8. Explain the methods used to challenge, or provoke, the airways to assess more subtle lung function abnormalities or airway reactivity and their role in developing a treatment.
9. Recognize the cut point for an abnormal exhaled nitric oxide test.
10. Distinguish the difference between resistance and reactance measured during impulse oscillometry testing.
11. Describe the various tests and techniques used at the bedside to assess pulmonary function and lung mechanics in the spontaneously breathing and mechanically ventilated patient.

Key Terms

airway resistance
"all-age" reference equations
body plethysmography
bronchial provocation
cardiopulmonary exercise testing (CPET)
diffusing capacity
dynamic lung compliance
exhaled nitric oxide
functional residual capacity
hug technique
impulse oscillometry
lung compliance
pulmonary mechanics
rapid shallow breathing index
reactance
respiratory inductance plethysmography
specific conductance
spirometry
tension time index
thoracic gas volume
transpulmonary pressure
work of breathing

Pulmonary function testing (PFT) is an objective measurement of the respiratory system under various conditions of normal, disease, and stress states. Pulmonary function measurements can be used as a primary diagnostic tool or to frequently monitor disease progression by comparing previous or subsequent assessments.[1,2] PFT results corroborate a diagnosis suspected from the other components of the pulmonary assessment, primarily the patient history and physical examination. The American Thoracic Society and European Respiratory Society (ATS-ERS) publishes standards and guidelines for testing system performance characteristics, quality control, and test methodology in adults, adolescents, and preschool-aged children.[3] The pulmonary function laboratory equipment quality control program needs to follow these recommendations to ensure accurate test results regardless of the size and age of the subject being tested.

Assessing whether a specific measurement is "normal" may be complex because of the wide range of variability in normal children. Recent reference equations have been published for spirometry, diffusing capacity, and other variables that help define lung function in young subjects. The **"all-age" reference equations** published in 2012 by the European Respiratory Society Global Lung Initiative taskforce define normal values for common spirometry indices down to 3 years of age.[4] PFT measurements remain an integral component in evaluation and lengthy follow-up of children with pulmonary dysfunction over time. PFT measurements evaluate the degree of illness and quantitatively determine the efficacy of various therapeutic interventions.[8]

Laboratory testing includes measurement of lung compliance and assessment of airway caliber, lung volumes, gas exchange, and airway inflammation.[5,6] These tests can be performed in a laboratory setting or at the bedside and may include maneuvers that require active or passive participation by the subject.[7,8]

Bedside pulmonary function studies apply PFT systems in the intensive care unit at the bedside to aid in mechanical ventilator management. Mechanical ventilators now provide the opportunity to measure and display airway graphics of pressure, flow, and volume on the ventilator screen. This provides real-time displays and is useful when assessing the interaction between the ventilator and the patient. These measurements are used to optimize ventilator support and to reduce the potential complications of positive-pressure ventilation. Because of the differences in purpose, test conditions, and clinical application, these types of studies at the bedside are differentiated from standard laboratory PFT studies.

DEFINITIONS

The terminology used to describe tests that are included in specific orders may vary across institutions. "Complete pulmonary function testing" may denote an extensive testing protocol at one institution or a more select group of tests at another. Similar variations exist for "lung function survey" and "pulmonary screening." Therefore clinicians need to be familiar with the specific testing protocols within their institution.

In this chapter, the term **spirometry** represents flow–volume or volume–time measurements of basic lung function parameters. Spirometric measurements include forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), the ratio of FEV_1 to FVC (FEV_1/FVC), forced expiratory flow at 25% to 75% of vital capacity (FEF_{25-75}), and forced expiratory flow at 50% of vital capacity (FEF_{50}). Lung volumes describe the measurements of **thoracic gas volume, functional residual capacity** (FRC), residual volume (RV), total lung capacity (TLC), and the ratio of RV to TLC (RV/TLC). Other measurements, such as carbon monoxide diffusing capacity, resistance or conductance, compliance, and maximal voluntary ventilation, are considered separate tests. Sophisticated and seldom used tests are not addressed in this chapter, and more extensive texts are available for additional information.[1,2,9-12]

Bedside PFT refers to those tests often performed at the bedside, typically in the intensive care unit, including tidal volume (V_T), vital capacity (VC), minute ventilation ($_E$), peak expiratory flow rate (PEFR), and respiratory muscle strength measurements of maximal inspiratory pressure (MIP) and maximal expiratory pressures (MEP). **Pulmonary mechanics** are the interaction of forces and physical principles that determine the characteristics of gas movement into and out of the lungs. Elasticity of the lung and chest wall, resistance to flow through the airways, and the action of the respiratory muscles (diaphragm, intercostal muscles, and accessory muscles) are measurable forces affecting ventilation.

MECHANICS OF BREATHING IN NEWBORNS

With the first breaths of extrauterine life, a newborn must replace the *in utero* lung fluid with air. Surface tension forces in the fluid-filled lung require high negative pressures within the chest to establish normal air volume in the lungs. Newborns, particularly those born prematurely with respiratory distress syndrome, have low lung compliance. More pressure, or energy, is required to provide the normal amount of air volume brought into the baby's lungs with each breath. Because the newborn's ribs are mostly cartilage, the chest wall is flexible. With significant lung disease, the infant's chest wall may actually be more compliant than the lungs, causing retractions, in which the ribs and sternum distort inward during inspiration instead of expanding the lungs. The lung–thorax mechanical relationship is less of the traditional "bag in a box" analogy and more like a "bag in a bag."

The combination of **lung compliance** (C) and **airway resistance** (Raw) is the major force opposing inspiration, whereas elastic recoil is the force responsible for passive normal exhalation. When measured under static conditions (i.e., no gas flow into or out of the lungs), C is an assessment of the elasticity (compliance) of the total respiratory system (Crs).[13]

LUNG INFLATION AND TRANSPULMONARY PRESSURE

For both spontaneous and mechanically assisted breaths, the change in pressure within the airways is the driving force for gas movement into and out of the lungs. During spontaneous inspiration, moving the diaphragm and other muscles of ventilation expands the chest volume, which creates subatmospheric pressure in the thorax. During mechanically assisted breathing the ventilator applies positive pressure to the airways. Expiration is usually considered passive, but in fact the elastic recoil of the lungs and chest wall that causes gas movement out of the lungs requires energy.

Pulmonary mechanics are calculated by determining the change in pressure across the lung simultaneously with flow and volume measurements. During mechanically assisted ventilation, pressure in the airway is measured at the endotracheal tube. Gas flow and airway pressure are measured with a sealed face mask for spontaneous breathing studies. Pleural pressure may be approximated with a catheter placed in the esophagus.[13-15] The catheter is connected to a pressure transducer and either is filled with fluid or has an air-filled balloon at its tip.

Transpulmonary pressure is the pressure exerted on the lungs for gas movement; it is the difference between pleural and airway pressure. Pleural pressure measurements may not always be performed in assessing pulmonary mechanics for ventilator–patient management. In general, under these circumstances it is assumed that the pressure in the large airways equalizes to the distal airways in the lungs. In this case the compliance measurements are actually of the respiratory system, including the chest wall, rather than of the lungs alone.

NEONATAL PULMONARY FUNCTION TESTING IN THE LABORATORY

A laboratory offering PFT for infants must be prepared to meet the special needs of these patients.[12] Commercially available equipment typically uses the most technically advanced flow sensors and analyzers and may be expensive for a pulmonary laboratory to purchase. Before pursuing this type of testing, the laboratory should thoroughly evaluate its expectations, goals, and resources available to perform quality testing.[2]

Routine infant and adolescent PFTs require certain technical obstacles be overcome. The use of computers and precision electronics surmounts many of these challenges, which include high respiratory rates, the need for low dead space in the airway connection, and accurate measurements of very small gas volumes. Current instrumentation employs rapid-response gas flow sensors that are easily calibrated, remain stable, and are accurate in a measurement range that extends to the gas volumes of the smallest newborns.[1,16] A more complete discussion of equipment characteristics can be found in other sources.[2]

In infant testing, the subject may need to be lightly sedated in the laboratory for 2 to 3 hours to complete a full set of studies. Sedation carries some risk, and testing should not be viewed as routine. In a study by Heinstein et al., the nothing-by-mouth (NPO) guidelines from the hospital sedation policy allowed infants younger than 6 months to receive formula and solids for up to 6 hours, breast milk for up to 4 hours, and clear liquids for up to 2 hours before sedation. Children who are 6 months or older may receive solids and liquids for up to 6 hours and clear liquids for up to 2 hours before sedation.[17]

Some drugs may alter pulmonary mechanics or the normal characteristics of breathing. Chloral hydrate is preferred by many laboratories and can be administered as an oral solution or rectally. The recommended dosage ranges from 50 to 75 mg/kg/dose 30 to 60 minutes prior to procedure; may repeat 30 minutes after initial dose if needed to a maximum dose of 1g for infants. Although normally a safe sedative for this purpose, using chloral hydrate when oxygen saturations are reduced increases the risk of respiratory distress. The infant should be continuously monitored from the time of drug administration until discharge.[17]

A face mask is required when testing neonates and infants. To ensure accurate testing, both mask resistance and mask dead space volume should be minimized during the measurement. Caution is necessary, because using a face mask can cause trigeminal nerve stimulation and induce vagal reflexes that may alter the pattern of heart or respiratory rhythm. A physician, emergency supplies, and equipment for infant resuscitation must be readily available in the laboratory area.

PLETHYSMOGRAPHY (BABY BOX)

The principle of **body plethysmography** is similar to that of the gas concentration techniques.[18] In a closed system the product of pressure and volume is constant (Boyle's law). When performing pulmonary function testing in infants, the child is sedated and placed in the supine position. A tight-fitting mask with a small dead space volume is placed over the infant's nose and mouth. Putty is placed around the edges to create an airtight seal (Figure 5-1*B*). Rapidly moving valves may make airway occlusions at end inspiration or end expiration for determination of thoracic gas volume

FIGURE 5-1 **A,** Positioning a patient in a "baby box" plethysmograph. **B,** Close-up of sedated baby with face mask, putty to form a seal, and pneumatic belt to perform the "hug technique." (Courtesy CareFusion.)

(TGV) and Raw. The infant does not pant; however, tidal breaths may be shallow. Therefore the pressure transducers and flow sensors must be critically precise and accurate. In addition, the infant body box is relatively small, and temperature changes can drastically alter these measurements. Therefore the temperature in the box must be controlled and the air vented.

Signal-to-noise ratios are particularly critical in an infant plethysmograph. Although the child is motionless, safety features must permit rapid access to the box and the baby. The breathing apparatus should be easily removable in case the child is in distress or vomits. The advantage of plethysmography in infants is that it accurately measures TGV, the total gas in the thorax, and thus FRC may be determined. FRC is the easiest volume for the subject to reproduce consistently. Because the infant is not capable of performing a voluntary maximal inspiration or expiration, RV and TLC cannot be obtained in the traditional manner. However, if the infant pulmonary function system is capable of performing raised volumes and forced thoracic compressions, then a full set of fractional lung volumes can be estimated.[2]

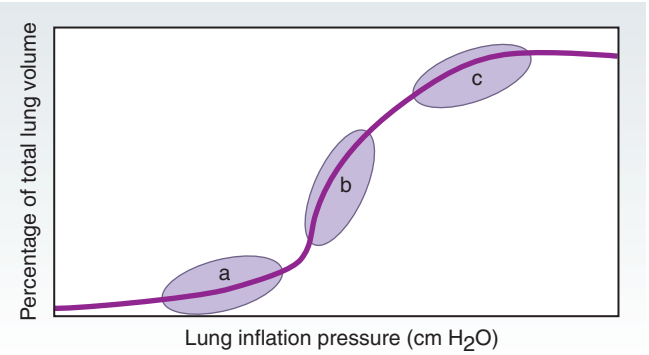


FIGURE 5-2 Volume–pressure loops of tidal breathing at various levels of functional residual capacity (FRC). *a,* Low FRC; *b,* normal FRC; *c,* elevated FRC.

FRC is the resting volume of the lung at end expiration.[5] The chest wall of newborns is very compliant, and supine FRC values are lower than adult values—approximately 20% of total lung capacity. Preterm infants with respiratory distress syndrome have an abnormally low FRC because of alveolar collapse. The low FRC value results in low lung volume, low compliance, and increased work of breathing to achieve adequate tidal volume. Figure 5-2 shows tidal volume–pressure loops at various FRC levels. Note that the slope of compliance is best, and thus work of breathing is least, at a normal FRC. Some infants maintain a dynamic FRC at this level by incorporating breathing strategies that limit the expiratory flow rate, such as expiratory grunting and increased postinspiratory diaphragmatic muscle tone. Neonates with severe respiratory distress syndrome need positive airway pressure during expiration to establish a normal FRC.

Several methods may be used to determine FRC. Systems using helium dilution and nitrogen washout techniques are basically scaled-down versions of adult systems. The helium dilution technique uses a closed-circuit system. Applying petroleum jelly to the edges of a disposable mask is helpful to ensure an airtight seal with no leaks on the infant's face. The infant breathes the helium–oxygen mixture while connected to a spirometer, until the helium concentration equilibrates between the circuit and lungs. The reduction in measured helium concentration in the circuit is equated to the FRC. The helium dilution method may be used for very sick infants with a fraction of inspired oxygen as high as 0.95.[6]

The nitrogen washout method also uses a sealed face mask. The infant breathes 100% oxygen in an open circuit, which displaces nitrogen in the lungs. The circuit must have no gas leaks. The system measures the volume of nitrogen washed out of the lungs. This method cannot measure the FRC if the infant's fraction of inspired oxygen is greater than 0.65.[19] Atelectasis may result from washout of poorly ventilated and partially obstructed areas of the lung.

The helium dilution and nitrogen washout techniques are described in further detail in the Pediatric Pulmonary Function section of this chapter.

MEASURING STATIC COMPLIANCE AND AIRWAY RESISTANCE

Static compliance (Crs) describes the elastic properties of the total respiratory system. Crs is measured during no airflow, using the passive exhalation occlusion technique, and assesses elasticity of the respiratory system.[6,18,20] Volume and pressure are measured with a pneumotachometer at two points of a passive resting exhalation. The airway is momentarily occluded at end inspiration by a shutter placed between the face mask and the pneumotachometer to stimulate the Hering-Breuer reflex. The occlusion creates an apneic pause and relaxes the respiratory muscles. Pressure is measured during the occlusion, and passive exhaled volume is measured after the shutter opens. Crs is calculated by dividing the total passive expiratory volume by the corresponding pressure change at the airway opening.

Raw reflects the nonelastic airway and tissue forces resisting gas flow. Raw is calculated from the ratio of airway occlusion pressure to expiratory flow and is described in centimeters of water per liter per second (cm H_2O/L/s). Raw is dependent on the radius, length, and number of airways and varies with volume, flow, and respiratory frequency. The small diameters of an infant's tracheobronchial tree result in high resistance to gas flow. Airway irregularities; partial blocks caused by mucus, tumor, or foreign bodies; and partial closure of the glottis can also elevate Raw. The passive exhalation occlusion technique is noninvasive and can be performed with little disturbance to the infant.[21,22] However, infants with severe lung disease have an increased respiratory drive, and it may not be possible to induce a Hering-Breuer response.[6]

Raw measurements may be derived from body plethysmograph data, using a modified infant incubator as the enclosure. Because a pulmonary plethysmograph measures lung volumes, FRC and TLC measurements are acquired along with Raw.

Another method of determining Raw is to generate random noise signals at high frequencies at the mouth while the infant is breathing normal tidal breaths through a mouthpiece or mask. This technique is known as forced oscillation and is described later in this chapter. Similar to the plethysmograph, the forced oscillation technique may be another method used to determine thoracic gas volume measurements. This technique is tolerated well by the infant and causes minimal discomfort.

Crs and Raw measurements may be useful in the following patients:

- Those receiving diuretics for chronic lung disease, such as bronchopulmonary dysplasia
- Patients undergoing high-frequency ventilation
- Those with meconium aspiration syndrome
- Those who have received extracorporeal membrane oxygenation
- Patients with respiratory syncytial virus infections and pneumonias
- Patients with diaphragmatic hernia
- Patients receiving aerosolized bronchodilator therapy

MEASURING MAXIMAL EXPIRATORY FLOW BY THE RAPID THORACIC COMPRESSION TECHNIQUE

Measuring gas flow during a forced expiratory maneuver is the conventional procedure used to evaluate airway obstruction in a cooperative infant. A relatively noninvasive technique to generate a partial expiratory flow volume (PEFV) curve in infants allows the measurement of expiratory flows during a forced maneuver in infants and small children.[3,6,18] A rapid thoracic compression or "hug" is delivered to the sleeping infant's chest and abdomen with an inflatable jacket to produce a forced expiration (Figure 5-1B). A pneumotachometer with a sealed face mask measures exhaled gas flow. The flow at the end-expiratory point of a normal resting tidal breath (FRC) is measured on the PEFV curve. This flow value, the maximal expiratory flow at FRC, is reported as liters per second (Figure 5-3). Multiple tests at various jacket inflation pressures are conducted for a "best test" assessment.

The maximal expiratory flow test can demonstrate flow limitation in airway disease and is valuable for evaluating the response to bronchodilator therapy in

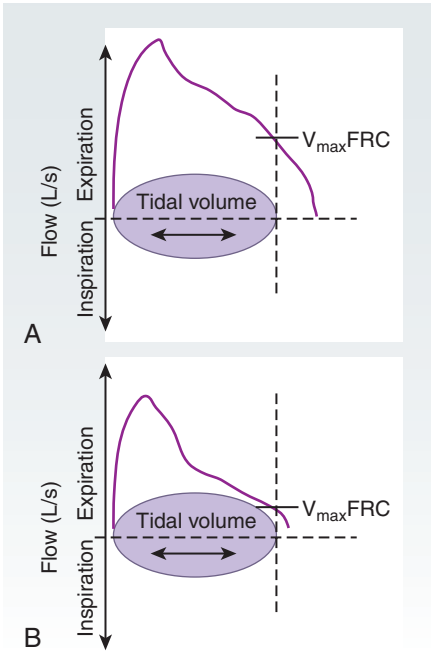


FIGURE 5-3 Partial expiratory flow volume (PEFV) curves with identification of maximal expiratory flow at FRC *(V_{max}FRC)*, demonstrating a normal resting tidal breath and one with flow limitation. **A,** Normal. **B,** Abnormal (flow limited).

infants.[23] PEFV studies are often performed before and after aerosolized bronchodilator therapy. An increase in maximal expiratory flow at FRC by at least 20% demonstrates a positive response to bronchodilator therapy. A significant number of infants with chronic lung disease have a negative bronchodilator response.[24]

Problems with the **hug technique** are uncommon in experienced hands. The clinician must avoid collapsing the upper airway as a result of hyperextending the neck, resulting in forced airflow limitation solely because of positioning. Other types of upper airway impedance may also affect the accuracy of the intrathoracic flow rates, and reflex glottis closure may complicate testing.[6]

THORACOABDOMINAL MOTION ANALYSIS BY RESPIRATORY INDUCTANCE PLETHYSMOGRAPHY

Respiratory inductance plethysmography (RIP) is a method used to indirectly measure tidal breathing over a wide age range, including infants. Compliant elastic bands are wrapped around the infant's abdomen and chest. These bands are used to analyze thoracoabdominal motion in addition to the degree to which chest and abdominal excursions are out of phase (asynchronous). Thoracoabdominal asynchrony (TAA) should increase with increased respiratory resistance (upper or lower airways, lung tissue), decreased lung compliance (parenchymal disease), and increased chest wall compliance (floppy rib cage, neuromuscular disease). RIP can be calibrated to measure V_T or uncalibrated so that the chest and abdominal signal reflect the timing and direction of volume change but not absolute volume changes. Because body movement and nonsinusoidal breathing can make accurate measurements challenging, data collection should occur during natural, quiet breathing, which most often occurs during sleep in infants. Although there are multiple limitations to take into consideration and a limited number of studies, RIP may be a useful screening tool in overall respiratory system function in infants.[3]

PEDIATRIC PULMONARY FUNCTION TESTING IN THE LABORATORY

PEDIATRIC TESTING

The greatest obstacle to obtaining satisfactory pulmonary function measurements in children lies in enlisting their cooperation and effort. Clinicians who work predominantly with children develop their own unique systems for making children comfortable and eliciting an appropriate testing effort. Conversely, pulmonary function laboratories that have limited experience with children often do not obtain satisfactory cooperation, and therefore the test results are inconclusive and the information may not be useful.

Several key factors are common to successful approaches in performing PFT on children. The testing environment or laboratory should have a warm and friendly atmosphere with pediatric-oriented pictures and toys. Each portion of the testing procedure should be carefully explained at an age-appropriate level, and the child's participation should be elicited in a playful rather than challenging fashion. For children undergoing their first PFT procedure, several efforts may be required before a satisfactory test is achieved. There is no substitute for patience and tolerance in this setting. Satisfactory performance can generally be achieved in the 5- or 6-year-old child, but some 8-, 9-, and 10-year-old children continue to have difficulty. Although uncommon, 3-year-old children may be able to do well, and good results have been reported more commonly among 4-year-old children. If the child is unable to perform satisfactorily at the first session, repeated attempts at subsequent visits should be encouraged, because most children learn quickly and often do much better at the next opportunity.

SPIROMETRY

Spirometry is a common test performed on children and requires active participation and cooperation to elicit acceptable and repeatable results. Spirometers are categorized into two general types: volume and flow. Volume spirometers collect the expired air and divide the subject's expiratory time to derive flow. These spirometers are large because they are required to measure up to 8 L of air.[25] Flow-based spirometers use a pneumotachometer, or some other flow-sensing device, to measure flow, which in turn is multiplied by the subject's expiratory time to calculate volume. Flow spirometers are more common because they are inherently smaller than a volume spirometer and can easily be integrated into a variety of testing systems. An assortment of flow-based spirometers are available, including handheld devices, standalone systems integrated with a computer or laptop, and spirometers that are a component of a complex testing system that might include a body plethysmograph.

The FVC maneuver performed during spirometry is composed of three major components: the deep breath, the initial blast, and exhaling until empty. The latter two, however, are inconsequential if the subject does not take a deep breath. Demonstrating test performance before testing can greatly enhance the success rate of getting results that represent the subject's true lung function. The practitioner can use visual aids to help the child understand the test expectations. In Figure 5-4, the child uses a pinwheel to practice the technique needed for spirometry testing. This fun, interactive method demonstrates to the young subject the need for both a quick initial blast out and also to sustain "the blow" to keep the pinwheel spinning as

FIGURE 5-4 A child practices blowing out using a pinwheel before spirometry testing. (Courtesy Katrina Hynes.)

long as possible. Some spirometers are integrated with computers and have software with interactive incentive screens. These screens, through a variety of methods (e.g., blowing out candles on a cake), give feedback to the young child to blast hard and fast and keep blowing until completely empty.

The following are the ATS-ERS acceptability criteria for a maneuver:

- Free from artifact
  - Cough during the first second of exhalation Figure 5-8A
  - Glottis closure that influences the measurement Fig 5-8 B
  - Early termination or cutoff
  - Effort that is not maximal throughout
  - Leak
  - Obstructed mouthpiece
- Good start
  - Extrapolated volume of 5% of FVC or 0.15 L, whichever is greater Fig 5-8 C
- Satisfactory exhalation
  - Duration of 6 seconds (3 seconds for children younger than 10 years old) or
  - A plateau in the volume–time curve

The maneuver is considered "usable" if there is no cough in the first second and/or glottis closure that influence the measurement.[25] Usable maneuvers typically underestimate the subject's VC, so usable variables would include peak flow, $FEV_{0.5}$, and FEV_1.

The traditional volume–time spirogram (Figure 5-5) is used to calculate timed flows such as FEV_1 and FEF_{25-75} and measure the FVC. It is also used to assess the end-of-test criteria of reaching a plateau.

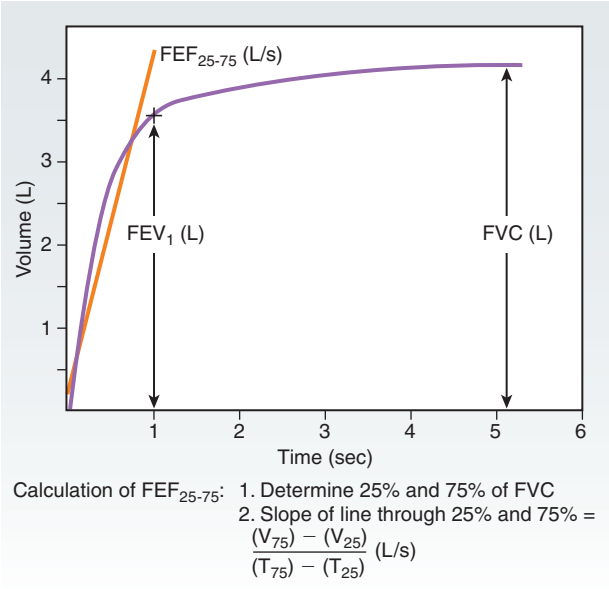


FIGURE 5-5 A normal standard volume–time spirometry graph depicting the forced vital capacity *(FVC)*, forced expiratory volume in 1 second *(FEV_1)*, and forced expiratory flow between 25% and 75% of vital capacity *(FEF_{25-75})*.

Flow–Volume Loop

The flow–volume loop and its specific measurements are shown in Figure 5-6. The flow–volume curve is useful in identifying the quality of the maneuver, and its shape can be characteristic of a specific disease process. One advantage to the flow–volume representation is its clear depiction of whether subjects exhale to RV or whether they terminate their effort prematurely (Figure 5-7). "Early termination" is assessed by how gradual flow approaches zero and the duration of the exhalation effort displayed on the volume–time graph. An example of early termination is glottis closure, which can be common in young patients (Figure 5-8B). Other acceptability indicators, such as cough in the first second (Figure 5-8A) and excessive back extrapolation volume (Figure 5-8C), are easily identified by the effect on the flow–volume curve. In addition, the shape of a flow–volume loop may be of value in

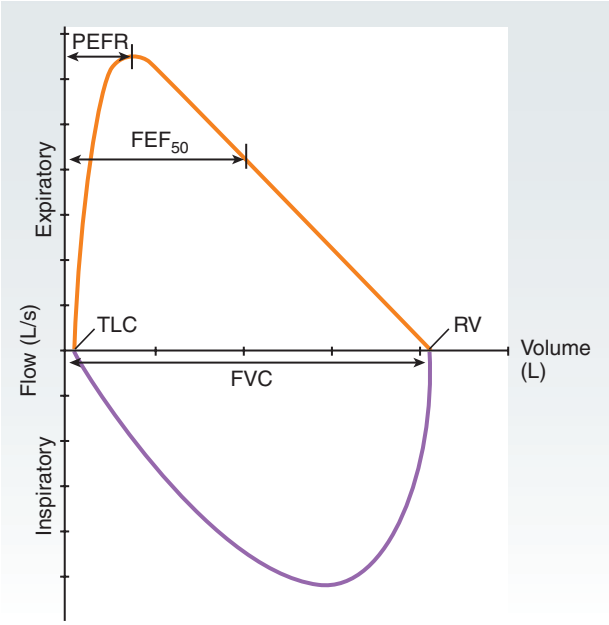


FIGURE 5-6 Normal flow–volume loop showing both the expiratory and inspiratory loops. The usual flow rates are identified. Note that no forced expiratory volume in 1 second *(FEV_1)* is evident because there is no time axis. *FEF_{50}*, Forced expiratory flow at 50% of vital capacity; *FVC*, forced vital capacity; *PEFR*, peak expiratory flow rate; *RV*, residual volume; *TLC*, total lung capacity.

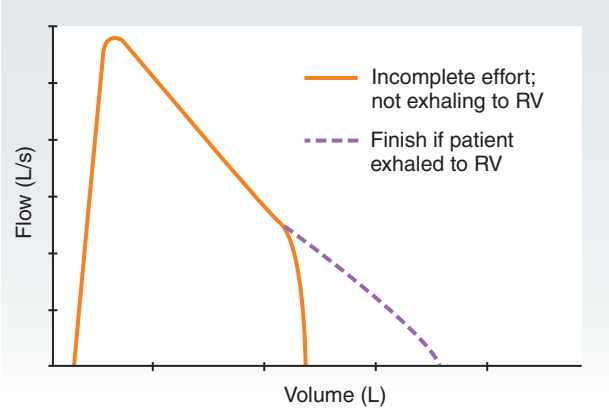


FIGURE 5-7 This expiratory flow–volume loop demonstrates the patient's failure to exhale completely to residual volume *(RV)*. This will artificially decrease FVC and increase FEF_{50}.

determining extrathoracic and intrathoracic sources of airway obstruction. Flow–volume loops that demonstrate fixed airway obstruction show a plateau on both inspiratory and expiratory phases of the loop (Figure 5-9A). Flow limitation on the inspiratory portion of the loop is characteristic of an extrathoracic obstruction (Figure 5-9B). This is common in children with vocal cord dysfunction (VCD). Flow limitation on the expiratory part of the loop demonstrates an intrathoracic obstruction (Figure 5-9C). A simple mnemonic for determining variable obstruction is, "What's in is out, what's out is in." In other words, a variable inspiratory obstruction affects the expiratory portion of the flow–volume curve, and a variable expiratory obstruction affects the inspiratory portion of the flow–volume curve.[2]

Some obstructions may also show a flutter, or irregular flow pattern, on either portion of the loop; this may be secondary to redundant tissue of the upper airway.

Forced Vital Capacity, Forced Expiratory Volume, and the Ratio

The most common measurements from spirometry include the FVC, FEV_1, and FEV_1/FVC ratio. These measurements are reproducible for many disease states in adult patients, such as chronic obstructive pulmonary disease. Physiologists were concerned, however, that the FVC and FEV_1 might be relatively preserved despite the presence of moderately severe small airway disease, and thus significant lung disease might be missed by using only these measurements. Because small airways less than 2 mm in diameter contribute only a small part of the total lung resistance, 20% or less, these tiny airways have been described as the "silent zone" of the lung. In an effort to measure their function more independently, without the large airway functions obscuring the measurements, the "maximal mid-expiratory flow rates" are calculated.[9] In current terminology, this is the FEF_{25-75} or the FEF_{50}.

Forced Expiratory Flow at 25% to 75% and at 50% of Vital Capacity

Although the FEF_{25-75} and FEF_{50} have been supported as reflecting the function of smaller airways, their measurement is considerably more variable than that of the FEV_1 or FVC.[5,12,25] This decreases their usefulness in distinguishing normal from abnormal and requires a considerably larger change to be considered physiologically significant, as opposed to just the normal variability found from one measurement to another.[3] In addition, if the child does not fully exhale to RV, FEF_{25-75} may be artificially elevated because of reduced VC.

Reference Values and Relevant Change

To interpret the test results, the laboratory needs to select a reference set and know the variability and clinically significant change for the most common spirometric and lung volume measurements in children (Table 5-1). The ERS Global Lung Initiative (GLI) has established the "all-age" reference set down to the age of 3 years and should be considered the preferred reference equations in this age range.[4] Furthermore, the interpreter should be aware of the effects associated with changes in VC and expiratory time on midflow variables (e.g., FEF_{25-75}) when interpreting these variables. Many childhood lung diseases, such as asthma and cystic fibrosis, have their roots in the distal airways; thus variables that are more sensitive, although more variable, may enhance the overall interpretation

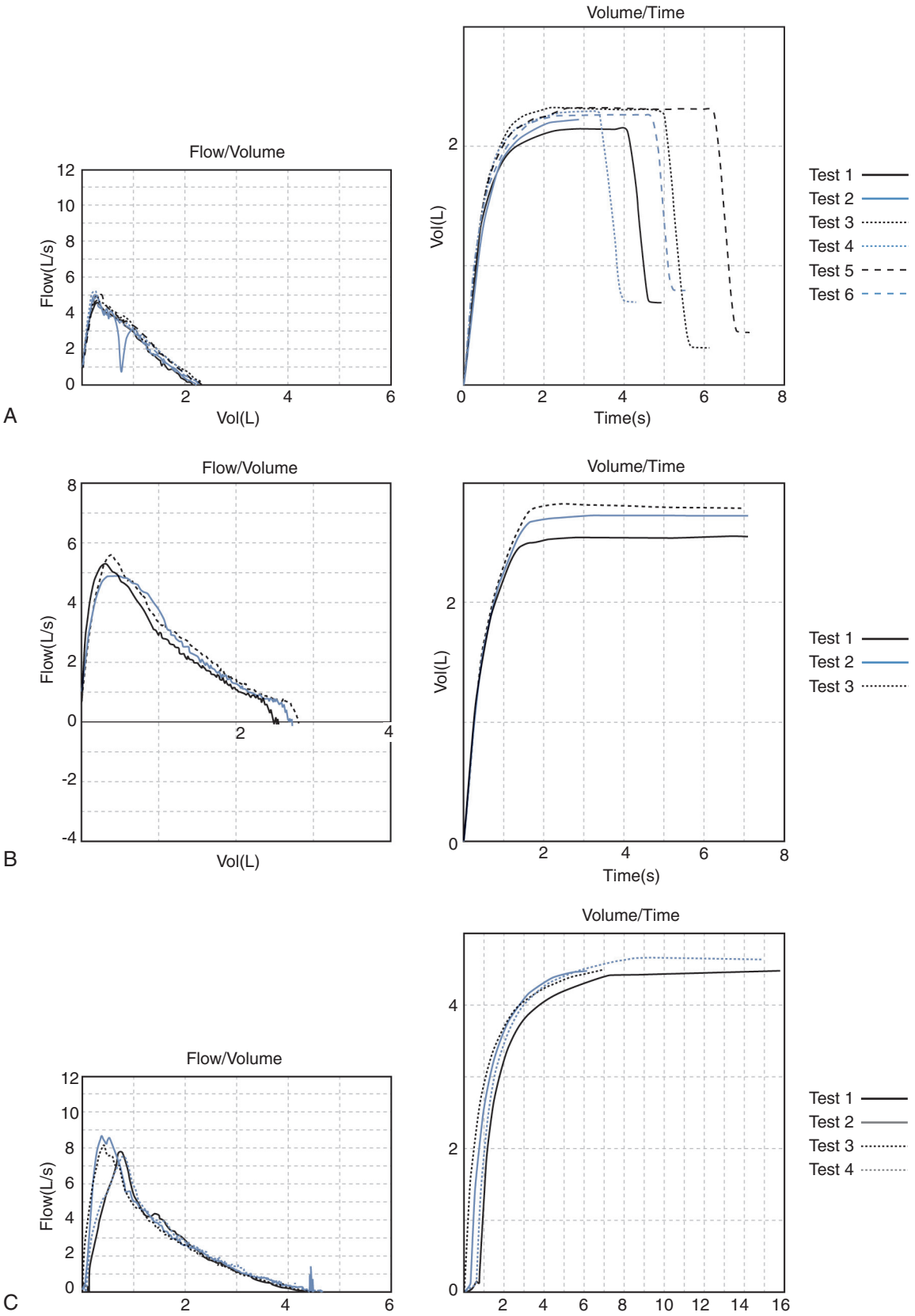


FIGURE 5-8 Common acceptability errors in spirometry. **A,** Cough in the first second in one of four maneuvers; this will interfere with proper measurement of FEV_1. **B,** Early termination consistent with glottis closure in all three maneuvers; this will typically yield an underestimation of FVC. **C,** Excessive back extrapolation volume in two of the four performed maneuvers; this will cause an overestimation of FEV_1 in the affected maneuvers. (From Mottram C: *Ruppel's manual of pulmonary function testing,* ed 11, St. Louis, 2018, Elsevier.)

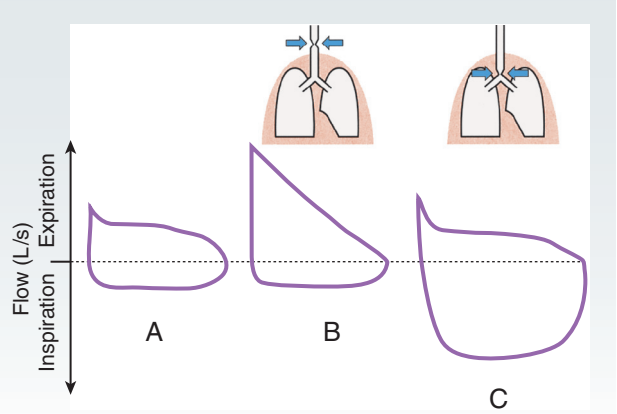
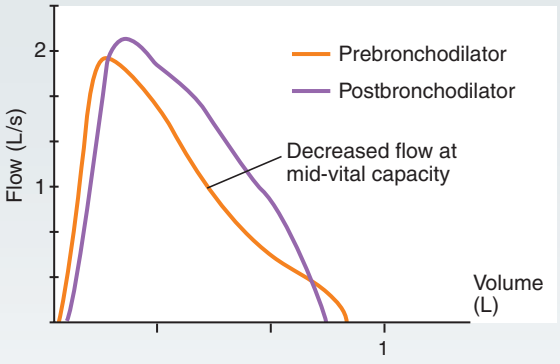


FIGURE 5-9 Flow–volume loops showing various forms of airway obstruction. **A,** Fixed obstruction; **B,** variable extrathoracic obstruction; **C,** variable intrathoracic obstruction. An easy mnemonic is *What's in is out, out is in.* In other words, if it affects the expiratory loop, it is inside the chest (variable intrathoracic), and if it affects the inspiratory loop, it is outside the chest (variable extrathoracic).



	Predicted	Prebronchodilator	Postbronchodilator	% Change
FVC (L)	0.89	0.81 (91)	0.78 (87)	−3
FEV_1 (L)	0.87	0.72 (83)	0.78 (89)	+8
FEV_1 : FVC (%)	95	88	100	
PEFR (L/s)	2.13	1.78 (83)	2.18 (102)	+22
FEF_{50} (L/s)	1.66	0.90 (54)	1.53 (92)	+70

FIGURE 5-10 Prebronchodilator and postbronchodilator expiratory loops produced by a 5-year-old patient with asthma. The prebronchodilator curve is slightly concave with respect to the volume axis, which is not evident on the postbronchodilator curve. The FEF_{50} is the only prebronchodilator measurement below the expected normal range of variability; it increased by 70% after bronchodilator therapy. *FEF_{50},* Forced expiratory flow at 50% of vital capacity; *FEV_1,* forced expiratory volume in 1 second; *FVC,* forced vital capacity; *PEFR,* peak expiratory flow rate.

Table 5-1 Pulmonary Function Measurements in Children

	VARIABILITY	IMPORTANT CHANGE
Measurement	(%)	(%)
FVC	5-7	>10
FEV_1	8	>15
FEV_1/FVC	—	—
FEF_{25-75}	15	>30
FEF_{50}	15	>30
TLC	7	>10
RV	7	>10
RV/TLC	7	—

FEF_{25-75}, Forced expiratory flow at 25% to 75% of vital capacity; *FEF_{50},* forced expiratory flow at 50% of vital capacity; *FEV_1,* forced expiratory volume in 1 second; *FVC,* forced vital capacity; *RV,* residual volume; *TLC,* total lung capacity.

Table 5-2 Characterization of Obstructive and Restrictive Patterns in Pulmonary Function Testing

MEASUREMENT	OBSTRUCTIVE	RESTRICTIVE
FVC	Normal or decreased	Decreased
FEV_1	Decreased	Decreased
FEV_1/FVC	Decreased	Normal or increased
TLC	Normal or increased	Decreased
RV	Increased	Normal or decreased
RV/TLC	Increased	Normal or increased

FEV_1, Forced expiratory volume in 1 second; *FVC,* forced vital capacity; *RV,* residual volume; *TLC,* total lung capacity.

of the test. An abnormality isolated to the measurement of FEF_{25-75} or FEF_{50} is uncommon but more likely in children than adults. Therefore most pediatric PFT centers pay careful attention to this variable as an early indicator of obstructive disease. Figure 5-10 demonstrates the potential importance of these measurements in a child with asthma.

Spirometry Values

Spirometry values are commonly used to determine whether a disease has a restrictive or obstructive pattern. Table 5-2 demonstrates the expected changes with each pattern. The primary difference is whether the FEV_1/FVC ratio is decreased or preserved. The most common chronic diseases in children—asthma, cystic fibrosis, and bronchopulmonary dysplasia—are obstructive. Obstructive diseases produce a concave shape or scoop to the flow–volume curve (Figure 5-11C). Most restrictive defects in children are related to an abnormal chest wall configuration or neuromuscular weakness rather than to interstitial fibrosis, as seen in adults. Caution must be used in describing restrictive lung disease on the basis of spirometry alone, because complete lung volumes are not measured. If the child did not take a deep breath, the FVC will be artificially decreased and mimic the restrictive pattern. Therefore if restrictive lung disease is a concern, the therapist

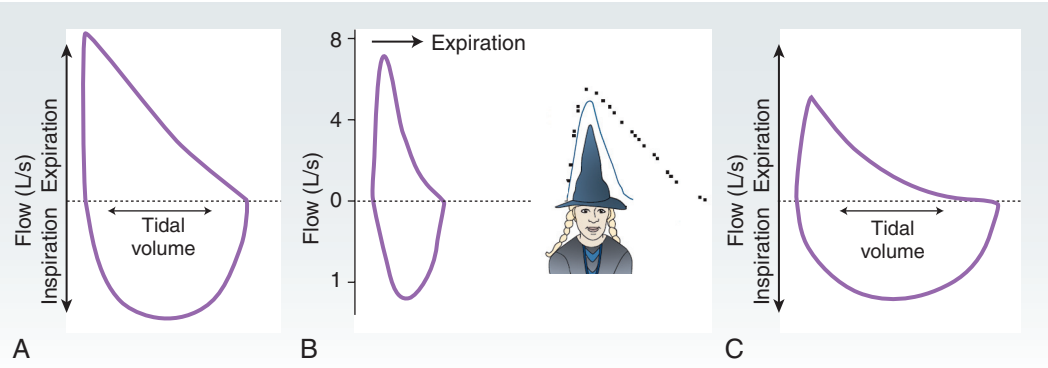


FIGURE 5-11 Patterns in flow–volume loops. **A,** Normal. **B,** Restrictive (also known for its characteristic "witch's hat" shape). **C,** Obstructive (concave).

should consider performing one of the lung volume studies described in the next section. The restrictive pattern is typically characterized by preserved flows with a reduction in the volume. This produces a visual pattern that has been described as a "witch's hat" (Figure 5-11B).[2]

Diffusing Capacity

The **diffusing capacity** of the lung (DLCO), also referred as transfer factor of the lung (TLCO), assesses the functionality of the alveolar–capillary interface. To perform the test the child must exhale to RV within 12 seconds, then rapidly inspire to TLC. The patient is then asked to hold his or her breath for 8 to 12 seconds, exhaling quickly once the breath-hold-time (*t*BH) is complete. It is important that the inspired volume of gas (VI) be at least 90% of the largest VC in the same pulmonary function testing session.[26] A maneuver may be deemed acceptable when the VI/VC is at least 85% but less than 90% if the VA is within 200 mL or 5% of the highest VA (among acceptable DLCO maneuvers), whichever is greater.[26] Two acceptable efforts that are repeatable within 2 mL/minute/mm Hg are required; the mean of acceptable maneuvers is reported. A maximum of five DLCO efforts should be performed.[26]

Abnormalities in DLCO may reflect pathologic changes in the lung and are often correlated with outcome.[27] A reduction in the DLCO might indicate problems with perfusion of the pulmonary capillary bed, bleeding within the lung, or thickening or damage of the alveolar–capillary membrane interface. Indications for testing in the pediatric population that may produce a reduced DLCO include pulmonary fibrosis (primary disease or secondary to radiation treatment or chemotherapy), immunologic disorders (scleroderma, systemic lupus erythematosus), bronchiolitis obliterans, pulmonary edema, and hematologic disorders. An abnormally high DLCO may be seen in pediatric patients with acute hemorrhagenous bleeds, such as pulmonary vasculitis.[2] The single-breath DLCO procedure requires subjects to hold their breath for 8 to 12 seconds, which may be challenging for the very young. The 2017 ERS-ATS DLCO technical standard for Single-Breath Carbon Monoxide Uptake in the Lungs expects DLCO systems have rapid analyzer technology (RGA).[26] These advanced systems have a 0% to 90% response time of less than 150 ms, allowing the technologist to identify when dead space has been cleared and makes testing possible in subjects with a VC less than 1 L. DLCO has been successfully performed on young children; however, as with all pulmonary function testing, it depends on the subject's maturation rather than the age. Reference values have been established for pediatric patients.[28] Kim and colleagues published regression equations in healthy children of Western European descent, ages 5 to 19.[29]

LUNG VOLUMES

In contrast to the relative simplicity of spirometry, lung volume measurements are somewhat more involved and more difficult to perform. They include FRC, RV, TLC, RV/TLC ratio, and TGV. With the child sitting, the same techniques described earlier are used to measure lung volumes. These methods include helium dilution, nitrogen washout, and body plethysmography.[29,30-32]

Helium Dilution Method

The helium dilution method of calculating FRC measures only the gas that is in direct communication with the central airways. Helium dilution is described as the closed-circuit technique, because the subject rebreathes within a closed system (typically a bag). This technique uses the principle that the concentration of a gas in one volume is proportional to the concentration of that same gas in another volume, provided there is no production or consumption of the measured gas. Therefore knowing the concentration of the gas inside the lungs and outside, as well as knowing the external volume, allows calculation of the lung volume. The volume of gas in the lung at end expiration (FRC)

mixes and equilibrates with a known amount and concentration of helium (usually 5% to 10%) in a closed breathing circuit. The challenge for young children is keeping a tight seal on the mouthpiece during the test, because any leak will make the results invalid. The child breathes on the test system until helium equilibration is achieved. Helium equilibration is considered to be complete when the change in helium concentration is 0.02% for 30 seconds.[30] Testing time is typically less than 3 minutes but can last up to 10 minutes in a subject with severe airway obstruction.

Nitrogen Washout Method

The nitrogen washout method of calculating FRC also measures only the gas that is in direct communication with the central airways. Nitrogen washout is described as the open circuit technique, because the subject's air is measured and expelled from the system. The child breathes 100% oxygen for up to 7 minutes via a mouthpiece, which displaces nitrogen in the lungs. The circuit must have no gas leaks. The system measures the volume of nitrogen washed out of the lungs. On the basis of the starting alveolar concentration of nitrogen, the computer uses a regression equation to calculate the volume of air in the lungs at end expiration, which is the FRC.[2]

Plethysmography

Body plethysmography requires that the patient sit in an airtight acrylic glass box, commonly called a body box. There are three types of body plethysmographs: volume, flow, and pressure. Most of the currently available body boxes are the latter, which uses a constant-volume, pressure-variable technique (Figure 5-12A).[31] During constant-volume body plethysmography, the child voluntarily pants against a closed shutter (Figure 5-12B). Using Boyle's law, the change in pressure

FIGURE 5-12 **A,** Three different vendor body plethysmographs. (Courtesy CareFusion, nSpire, and MGC Diagnostics.) **B,** Child supporting cheeks, panting, while performing lung volumes using a body box. (Courtesy Katrina Hynes.)

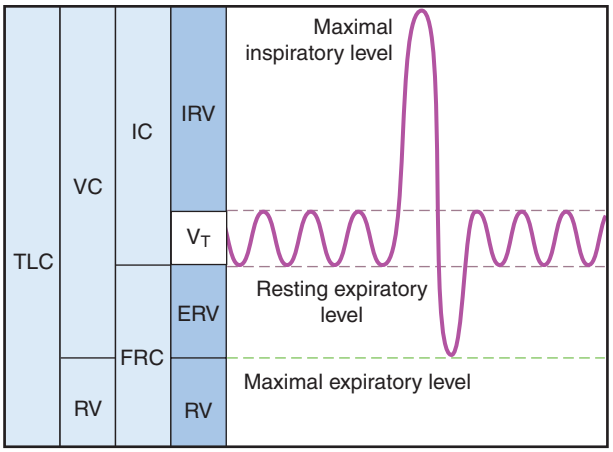


FIGURE 5-13 Graphic display of a simple spirogram depicting the subdivisions of lung volumes and capacities. *ERV,* Expiratory reserve volume; *FRC,* functional residual capacity; *IC,* inspiratory capacity; *IRV,* inspiratory reserve volume; *RV,* residual volume; *TLC,* total lung capacity; *VC,* vital capacity; *V_T,* tidal volume. (Modified from Comroe Jr J, Forster R, Dubois A, et al: *The lung: clinical physiology and pulmonary function tests,* ed 2, St. Louis, 1962, Mosby.)

against the closed shutter attached to a pneumotachometer is used to calculate a volume measurement, the TGV. TGV is measured at a known FRC value rather than on the basis of assumed values. TLC, the inspiratory capacity, is obtained by spirometry and added to the FRC. To calculate the RV, the expiratory reserve volume is subtracted from the FRC (Figure 5-13). In addition to measuring lung volumes, body plethysmography measures resistance and **specific conductance** (see below).

Several potential errors are common when children perform these tests. If they are uncomfortable and anxious, pediatric patients may breathe at a slightly higher lung volume. If they are unable to start spirometry at TLC or exhale to RV, the values of inspiratory capacity and expiratory reserve volume will be incorrect. Therefore it is important to demonstrate the maneuver and make the child completely comfortable and relaxed.

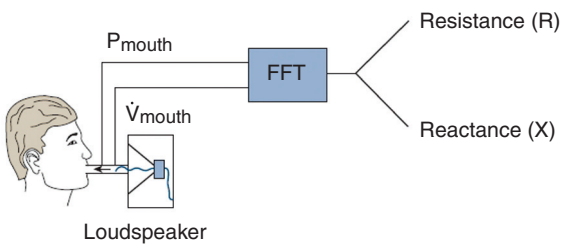
Lung volume measurements are most useful in revealing restrictive lung diseases, in which they are decreased. It is critical to determine whether the lung volumes are smaller than expected because of a musculoskeletal problem (e.g., scoliosis and kyphosis), muscle weakness (e.g., Duchenne's muscular dystrophy and spinal muscular atrophy), or lung parenchymal disease (e.g., idiopathic pulmonary fibrosis). If it can be established that the patient's FVC as measured by spirometry correlates well with the TLC as measured on the basis of lung volumes, spirometry may be sufficient for most patients' follow-up.

In addition to lung volumes, measuring maximal inspiratory and expiratory pressures helps assess overall respiratory muscle strength and augments volume measurements when assessing patients with muscle weakness.

Airway Resistance. The body plethysmograph also allows the measurement of Raw and the volume-associated parameters of specific airway resistance (sRaw) and conductance (sGaw). Raw is the pressure difference per unit flow as gas flows into or out of the lungs. The reciprocal of airway resistance (1/Raw) is conductance (Gaw). If obtained during lung volumes, the derivation of sRaw and sGaw can be calculated. Because some patients have changes in sGaw without changes in FEV_1 or FVC after a bronchodilator, and such changes are believed to be clinically significant, measuring bronchodilator response by sGaw may be more sensitive than relying on spirometry indices only, although a change of 35% to 40% is required. The measurement may also be helpful in pediatric patients who cannot perform acceptable spirometry. Reference values have been published in children for ages 3 to 10 years.[33]

IMPULSE OSCILLOMETRY

Impulse oscillometry (IOS), also referred to as the forced oscillation technique (FOT), is a method to evaluate airway caliber using a miniature loudspeaker to produce oscillations within the airway (Figure 5-14A). The pressure oscillations generated are of two types: those in phase with airflow, termed resistance (Rrs); and those "out of phase" with airflow, termed **reactance** (Xrs). Impulse oscillometry is a simple test that does not require the active cooperation of the child, and studies have shown IOS can be performed successfully in 3- to 6-year-olds with asthma.[34] Typical measured frequencies include 5, 10, 15, and 20 hertz (Hz), and reference equations have been published in children.[34] Current guidelines state that technologists and therapists can achieve competency after 10 to 15 supervised tests where they learn to recognize patient and technical problems that can occur during testing.[3] For this procedure the child should be seated, wear a nose clip, and firmly support the cheeks and mouth floor. The child is then instructed to breathe calmly and avoid obstructing the mouthpiece with his or her tongue. Practice tests and sometimes distracters, such as a movie, can assist in achieving quiet tidal breathing in a young patient (Figure 5-14B). The data acquisition should cover several breathing cycles, typically lasting 10 to 20 seconds. IOS can be used to assess the bronchodilators, with cut points ranging from a 10% to 30% decrease in Rrs5. Response to methacholine using IOS has been described. In one study an Rrs5 increase of 45% compared with the baseline showed the optimal combination of sensitivity and specificity (0.72 and 0.73, respectively).[35]



A

B

FIGURE 5-14 Components of the impulse oscillometry (IOS) apparatus. **A,** A loudspeaker generates flow signals consisting of many pulsations. These pulsations are delivered to the mouth while mouth pressure *(P)* and flow *(V)* are measured. The computer then calculates resistance (*R*) and reactance (*X*). **B,** A 5-year-old boy performing IOS. The patient is using a nose clip, supporting the cheeks, and making a tight seal with the lips at the mouthpiece of the IOS apparatus. The therapist uses a movie as a distracter during the test procedure so the young boy breathes calmly throughout the data acquisition period.

Clinical Highlight

Impulse Oscillometry

A 4-year-old girl presents with a history of coughing and wheezing. Current height is 109.4 cm; weight is 20 kg. Currently she is taking the following medications:

- Albuterol 0.083% nebulized solution, 3 mL by inhalation every 4 hours as needed
- Flovent HFA 44 μg/actuation aerosol, two puffs by inhalation two times a day

Her impulse oscillometry results were as follows:

AIRWAY REACTIVITY	BASELINE	POST-BRONCHODILATOR	PERCENT CHANGE
R5Hz (kPa/L/sec)	1.28	0.87	−32%

BRONCHIAL PROVOCATION (CHALLENGE) TESTING

Challenge testing, also known as **bronchial provocation,** may be used in documenting bronchial hyperreactivity. [2,6,36-38] This can help solidify the diagnosis of hyperreactive airway disease, or asthma, in a patient whose symptoms may not be typical of asthma. Alternatively, for the patient who has symptoms that might mimic asthma, the lack of bronchial oversensitivity may help initiate the search for an alternative explanation. Bronchoprovocation tests are classified as direct or indirect, based on their mechanism of action. Common agents such as methacholine act directly on the smooth muscle cells of the airways to cause bronchoconstriction and airway hyperresponsiveness (AHR). Indirect bronchoprovocation tests, such as mannitol and adenosine monophosphate (AMP), act through inducing the release of bronchoconstricting mediators. Another indirect test such as hyperventilation, either at rest or during exercise, results in heat and water loss from the airway, which provokes a bronchospasm in susceptible patients.

Methacholine and mannitol are two very common inhalation challenge agents that have well-described protocols.[2] In methacholine testing, a test is considered positive if the FEV_1 falls more than 20% from baseline.[3,37,38] The concentration of the challenge drug is used as a marker of the degree of bronchial reactivity and is called the PD20, the provocative dose that produces a 20% fall in FEV_1. For example, a patient with highly reactive asthma may have a fall in FEV_1 of 20% with a methacholine concentration of 0.25 mg/mL. A patient with mild asthma may experience a 20% fall in the FEV_1 at 10 mg/mL. In mannitol testing a 15% decline in FEV_1 is considered a positive response.

Antigen inhalation is rarely used as a challenge because of the difficulty in quantifying the dose of antigen to administer. Furthermore, antigen inhalation carries the risk of a late-phase reaction 6 to 8 hours after the challenge, at which time the patient is unlikely to be near a medical facility for therapeutic intervention.

An alternate indirect method is an exercise challenge test. The driving forces for bronchoconstriction during exercise are primarily low humidity and low air temperature as precipitators of airway water loss. Providing an environment of no humidity in the laboratory is typically accomplished by using a tank of compressed air, a bag reservoir, and a directional valve system. The exercise test is performed specifically with the intent of eliciting a hyperreactive response. This is achieved by rapidly increasing the workload via treadmill or cycle ergometer until reaching a target heart rate (85%-90% of predicted), or minute ventilation

(40%-60% of MVV) within spirometry is performed after a brief cool-down in 5-minute increments. A 10% fall on FEV_1 is considered a positive response. Some laboratories use hyperventilation while having the patient breathe cold air, without exercise, as the provocation test.

The Clinical Highlight, *Positive Methacholine Challenge in a 7-Year-Old Girl with Chronic Cough*, shows a positive methacholine challenge test in a 7-year-old girl evaluated for a chronic cough. This positive study led to therapy for asthma and ultimately resolved her cough. Interestingly, her previous spirometric measurements were normal and showed no improvement after bronchodilator therapy. The responses to exercise and cold air are measured by the duration of the challenge as well as the work performed during the exercise test. If other test parameters are used, such as the peak expiratory flow rate or specific Raw, different critical levels of positivity are used.

CARDIOPULMONARY EXERCISE TEST

Cardiopulmonary exercise testing (CPET) is performed in the pediatric age group to evaluate symptoms that only occur during exercise or as a more general assessment of the patient's exercise tolerance in specific disease states.[2] The American Heart Association (AHA) has published guidelines on CPET in the pediatric age group and lists the common reasons for testing.[39] Box 5-1 expands on the AHA reasons to include specific disease states that might necessitate evaluation using CPET.

Current technology and testing devices easily adapt to the young subject. Cycle ergometers typically used in pediatric testing can be modified to varying body sizes using saddle height, crank-shaft length, and handlebar adjustments (Figure 5-15). This allows testing in subjects as young as 5 years of age. Ventilatory and metabolic responses to exercise can be assessed using small, close-proximity pneumotachometers, which can be positioned using mouthpieces or mask adaptations. Traditional measurements of electrocardiogram and

Clinical Highlight

Positive Methacholine Challenge in a 7-Year-Old Girl With Chronic Cough*

METHACHOLINE		PULMONARY FUNCTION		
CONCENTRATION (Mg/Ml)	CUMULATIVE DOSE (Mg/Ml)	FVC (L)	FEV_1 (L)	PERCENT CHANGE IN FEV_1
Saline	0	1.51 (83% predicted)	1.4 (82% predicted)	—
Methacholine				
0.025	0.125	1.51	1.38	–1%
0.25	1.375	1.64	1.53	+9%
2.5	13.875	1.54	1.39	–1%
10	63.875	1.33	1.07	–24%
Albuterol	—	1.41	1.26	–10%

FEV_1, Forced expiratory volume in 1 second; *FVC*, forced vital capacity.
*In a methacholine challenge test, the patient first breathes aerosolized saline (as a baseline), followed by a breathing test. The subject then takes five breaths of methacholine at a low concentration, followed by another breathing test. The process continues with increasing concentrations of methacholine until there is a 20% change in lung function or the maximal amount of methacholine has been inhaled. Albuterol, a bronchodilator, is then administered to help open the airways.

Box 5-1 Common Reasons for Pediatric Exercise Testing and Specific Clinical Applications

- Evaluate specific signs and symptoms induced by exercise
- Assess or identify abnormal responses to exercise
- Assess efficacy of specific medical or surgical treatments
- Assess functional capacity for athletic and vocational activities
- Evaluate prognosis
- Establish baseline data for rehabilitation

SPECIFIC CLINICAL APPLICATIONS

- Cardiac disorders
- Aortic stenosis
- Cardiomyopathy
- Tetralogy of Fallot, Ebstein's anomaly
- Coarctation of the aorta
- Prolonged QT syndrome
- Pulmonary
- Asthma
- Cystic fibrosis
- Chest wall (e.g., pectus excavatum)
- Vocal cord dysfunction
- Others
- Obesity
- Neuromuscular disease
- Exercise-induced syncope (e.g., postural orthostatic tachycardia syndrome [POTS])

FIGURE 5-15 **A,** A cycle ergometer with adjustable pedal crank shafts to test smaller patients. **B,** An 8-year-old child on a cycle ergometer with a face mask interface to a pneumotachometer to measure exhaled air. (Courtesy Katrina Hynes.)

blood pressure responses can be correlated to responses in oxygen consumption (Vo_2), minute ventilation (e), and other metabolic derivatives to evaluate exercise tolerance, ventilatory limitation, and inappropriate breathing strategies. The physiologic responses to exercise are well defined in the pediatric age group but are beyond the scope of this chapter.[2] The Clinical Highlight regarding the 14-year-old girl demonstrates the use of the test in evaluating a teenage subject with symptoms during exercise.

The subject exercised on a cycle ergometer to a maximal workload of 160 watts. This appeared to be a

Clinical Highlight

The patient is a 14-year-old girl. She is an athlete who participates in cross-country running and figure skating.

History of present illness includes a 1-year history of dyspnea. The patient reports that "I can't catch my breath" with activity. She had been treated empirically with albuterol but still complained of her symptoms.

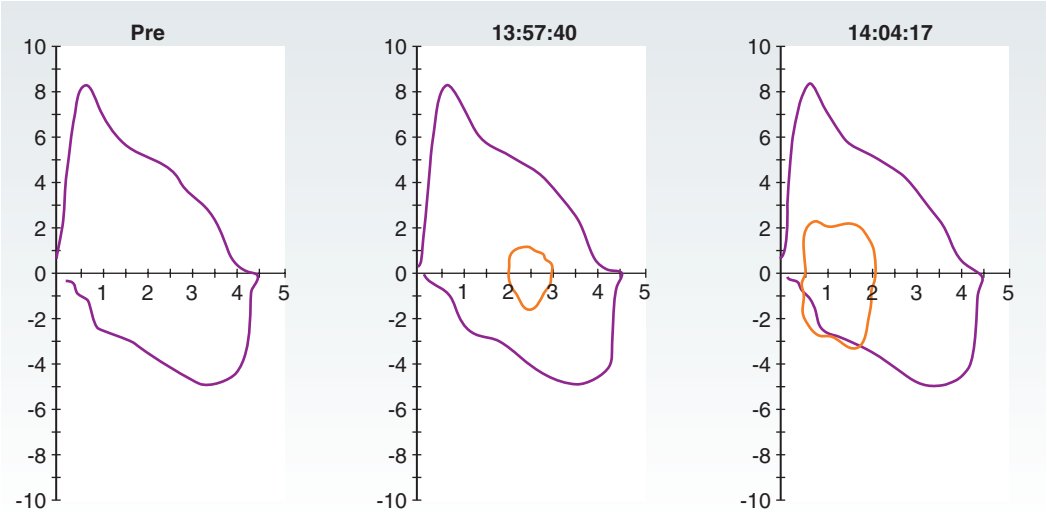
- Medications: Albuterol 2 puffs before activity
- Current evaluation included the following:
  - Methacholine challenge: negative
  - Exhaled nitric oxide: 10 ppb

A cardiopulmonary exercise test was ordered to further evaluate her symptoms, which occur with exercise.

CPET RESULTS

EXERCISE		REST	MAXIMUM	PREDICTED	PERCENT PREDICTED
Workload	watts		160	190	84
Time	min:s		12.3		
Spo_2	%	98	98		
Vo_2	L/min	0.384	1.945	2.331	83
Vo_2/kg	mL/kg		32		
R		0.75	1.00		
Cardiac Function					
Heart rate	bpm	58	191	199	96
Blood pressure (cuff)	mm Hg	100/64	146/60	170/88	86/68
Oxygen pulse	Vo_2/HR	7	10	11	91
Ventilation					
Minute ventilation	L/min	11.9	74.2	160.0	46
Respiratory rate	per min	10	45		
Tidal volume	L	0.367	1.650		
VT/FVC	%	8	33	45-50	

HR, Heart rate; *Spo_2,* oxygen saturation by pulse oximetry; *Vo_2,* oxygen consumption; *VT/FVC,* tidal volume/forced vital capacity ratio.



maximal exercise test based on heart rate criterion. The subject has normal exercise tolerance with a maximum oxygen consumption (Vo_{2max}) of 83% predicted. The heart rate and blood pressure response were within the normal range, and the electrocardiogram did not show any signs of arrhythmia or ischemic changes. Minute ventilation increased to 74 L/min. There was no evidence of ventilatory limitation (e/maximum voluntary ventilation), although she used an inappropriate breathing strategy with small tidal volumes (Vt/FVC 33%) and higher breathing frequencies to increase her minute ventilation. Gas exchange assessed using pulse oximetry was normal (Spo_2 98%). Flow–volume loops obtained during CPET also demonstrated an improper breathing strategy, with the subject moving up in lung volumes during exercise and also showing evidence of variable extrathoracic obstruction (truncation and up-sloping inspiratory curve) suggestive of vocal cord dysfunction (VCD). The subject did exhibit audible stridor at peak exercise. The interpretation was that she had normal exercise tolerance with evidence of VCD and inappropriate breathing strategy.

EXHALED NITRIC OXIDE

Exhaled nitric oxide (ENO) is a biomarker of airway inflammation and is a simple and noninvasive test for diagnosing and monitoring asthma in children. The fraction of nitric oxide (FE_{NO}) can be measured with either a chemiluminescent or electrochemical analyzer and is reported in parts per billion (ppb). Analyzers can be independent portable devices or integrated with data acquisition software, which allows for incentive programs to help the child maintain the required flow, pressure, and duration of each maneuver (Figure 5-16). The child should refrain from eating or drinking (except water) for 2 hours before testing. Spirometric maneuvers have been shown to transiently reduce ENO levels. As a result, it is recommended that ENO analysis be performed

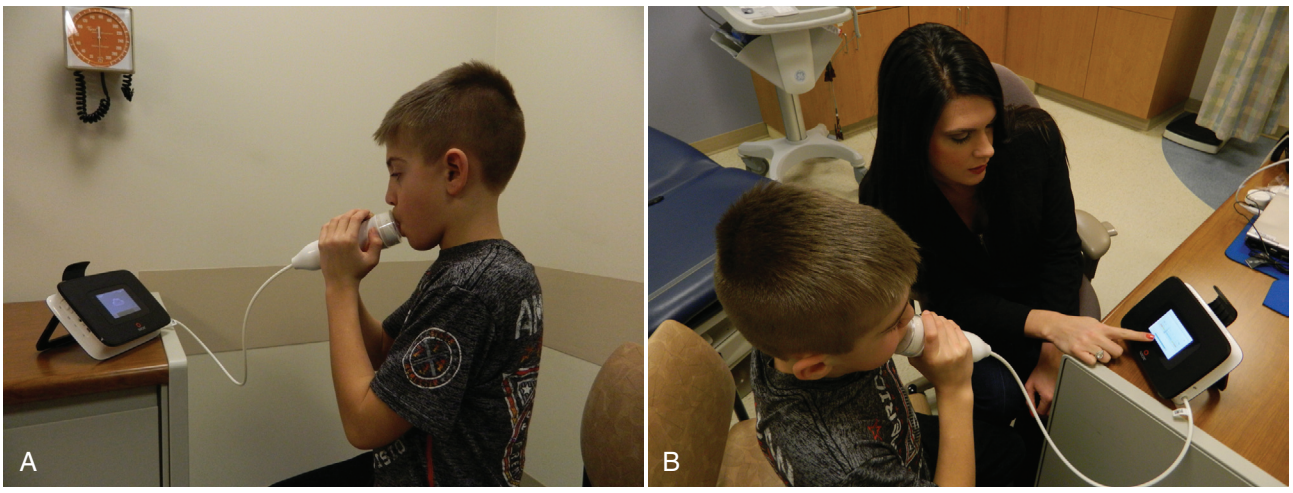


FIGURE 5-16 **A,** A 9-year-old boy successfully performing an exhaled nitric oxide test. **B,** Therapist passively coaching a 9-year-old boy using an incentive program. (Courtesy Katrina Hynes.)

before spirometry.[40] According to current interpretation guidelines, a value less than 20 ppb can be used to indicate that eosinophilic inflammation and responsiveness to corticosteroids is less likely.[41] A value greater than 35 ppb in children can be used to indicate that eosinophilic inflammation is present; in symptomatic patients there is a high likelihood the child will respond to inhaled corticosteroids.[41] FE_{NO} values between 20 ppb and 35 ppb should be interpreted cautiously.[41]

MEASURING PULMONARY MECHANICS AT THE BEDSIDE

TIDAL VOLUME

VT is the gas volume (in milliliters) inhaled and exhaled during each resting breath. Often VT is indexed to body weight and reported as milliliters per kilogram (ml/kg). Some PFT systems report inspired and expired VT values separately, whereas some combine the two values. Infants in a neonatal intensive care unit may not normally inhale the same volume as they exhale for any given breath. This is visible in flow–volume and pressure–volume loops that are not closed. Typically, an average of at least 10 resting breaths is a better method of reporting VT. Infants receiving positive-pressure ventilation may have a gas leak around the uncuffed endotracheal tube. In this case, it is more accurate to report expired VT. Some PFT systems report leakage as a percentage of exhaled to inhaled VT, which is helpful in determining the delivered effective tidal volume. A system used for ventilator patient management should report VT values for spontaneous and ventilator-delivered breaths separately.[42]

Respiratory Frequency

Most PFT systems report respiratory frequency, or rate, as breaths per minute. If the child or infant is intubated and receiving mechanical ventilation, the system should report spontaneous and ventilator breaths separately. Often, increased respiratory frequency is one of the first signs of reduced compliance, increased resistance, or fatigue.

Minute Ventilation

Minute ventilation is the volume of gas inspired and expired each minute by the infant or child. It is reported as liters per minute (L/min) or as liters per minute per kilogram (L/min/kg) of body weight and is the product of VT and respiratory frequency. Viewing spontaneous and ventilator-delivered breathing separately or as a fraction of the total minute volume indicates the mechanical contribution of ventilation. This is helpful in assessing progress in weaning of a patient from assisted mechanical ventilation.

Rapid Shallow Breathing Index

The **rapid shallow breathing index** (RSBI) is a value that integrates two variables to determine the efficiency of tidal breathing. The RSBI is the ratio of spontaneous respiratory rate to VT: Divide the respiratory rate by VT (in liters) to calculate the index. A calculated value less than 100 to 105 is predictive of a successful extubation in adults.[43,44] The RSBI has less predictive value when applied to children and infants.[45-47] Factors such as age, endotracheal tube size, agitation, sedation, and duration of mechanical ventilation all contribute to the success of extubation and the usefulness of the RSBI as a pediatric weaning tool. The RSBI can be a useful tool in evaluating relative increases or decreases in work of breathing and monitoring an infant before and after extubation. For infants and children, the RSBI equation is normalized for body size by dividing the VT by weight. The resulting unit of measure becomes breaths per milliliter per kilogram and allows easier comparison among the various measurements.[43,46,48] Because of the range of normal respiratory rates and tidal volumes, no single RSBI value will predict extubation success in the pediatric population.

Inspiratory and Expiratory Times

PFT systems measure inspiratory and expiratory times (TI and TE) by gas flow. The reported values will be different from the set, or duty cycle, times of a mechanical ventilator. Some systems also calculate the inspiratory-to-expiratory TI/TE ratio or inspiratory time percent (TI/TTOTAL) from measured time.

Lung Compliance

At the bedside, compliance is measured by the same technique as in the PFT laboratory. When making bedside measurements, it is important to know the compliance test conditions to interpret the meaning of the reported value. *Specific lung compliance* describes compliance when it is measured at a known level of total lung volume. When measuring compliance under static conditions by airway occlusion, compliance is similar to the value derived in the laboratory and assesses Crs. **Dynamic lung compliance** (Cdyn) is measured during resting tidal breathing and is affected by Raw.

There are some limitations to Cdyn measurement. This value reflects true compliance only when measuring transpulmonary pressure during spontaneous breathing with an esophageal catheter. Most centers do not routinely place an esophageal catheter for ventilator management studies. Instead, if the graph demonstrates that gas flow reaches zero at the end of inspiration and expiration, it is assumed that pressure has equalized from the proximal airway to the lungs. Compliance varies at different points of total lung volume, which is usually unknown during dynamic testing.

Airway Resistance

During bedside testing, the best evaluation of Raw also uses transpulmonary pressure measurements.

A high Raw value is visualized on the pressure–volume loop, described later, as a bowing out of the curve from the line of idealized compliance, or slope of the curve. The presence of an endotracheal tube with a small inner diameter is an airway obstruction causing Raw to be high. Changes in mechanical ventilator settings greatly affect Raw values, as do airway impairments such as secretions, bronchospasm, and edema. Bedside measurements of Raw usually preclude techniques used in the laboratory and are derived from the passive occlusion technique.

Time Constants

Respiratory time constants, tau (τ), are the mathematical product of compliance and resistance expressed as seconds, because all the units of pressure and volume measurement cancel out except time. A time constant is an interval over which a given change occurs, as a percentage of total change. Three time constants are required to reach 95% of inflation or exhalation. T_I, or inflation time, and T_E should be at least three times the respiratory time constants for optimal inspiration or expiration to occur.[49]

PRESSURE, FLOW, AND VOLUME OVER TIME

Most infant PFT systems graphically display measured airway (or transpulmonary) pressure, inspired and expired gas flow rates, and V_T on appropriate scales over a horizontal time axis on the screen as the data are collected by the computer. This type of graphic display is also a component of most neonatal mechanical ventilators. Figure 5-17 shows a scalar tracing of pressure, flow, and volume over time. Pressure (see Figure 5-17, *top tracing*) is either transpulmonary pressure or airway pressure measured at the endotracheal tube connection with the ventilator circuit. Gas flow at the airway (see Figure 5-17, *middle tracing*) shows the inspiratory flow rate as a downward deflection and the expiratory flow rate as an upward deflection, with the center line being zero flow. V_T (see Figure 5-17, *bottom tracing*) portrays inspiration as upward, with a return to the baseline as volume is exhaled. The vertical dashed lines delineate the change from inspiration to expiration for each breath. Breaths are numbered from left to right; 1, 2, 4, and 5 are mechanically ventilated. Breath 3 is a spontaneous breath, with a lower V_T than the ventilator-delivered breaths.

FLOW–VOLUME LOOPS

During bedside testing, flow–volume loops are typically generated during tidal breathing.[32,50] The peak of expiratory flow normally occurs within the first one-third of expiratory volume. Flow–volume loops that show decreased flow with relatively normal volume indicate an obstructive process in the airways; loops with decreased volume and normal flow suggest a restrictive disorder.

PRESSURE–VOLUME LOOPS

Graphically displaying a tidal breath with pressure change (airway or transpulmonary) on the horizontal axis and volume on the vertical axis also forms a loop. Spontaneous breathing is evidenced by a negative pressure change, and mechanical ventilator breaths display pressure in the positive direction. If the action of inhalation had only the elastic forces of lung tissue to overcome, the pressure–volume graph would not be a loop, but rather a straight line between the beginning and end points of inspiration (the dashed line in Figure 5-18). The pressure–volume loop bows out from that line of pure compliance, mostly because of pressure needed for gas flow through narrow, resistive airways. The loop meets the line of ideal compliance at the end points of a tidal breath, where gas flow is zero. The slope of the line, and of the loop as a whole, depends on compliance. The more compliant the lung, meaning less pressure needed for normal V_T, the more vertical the pressure–volume loop appears.

Lung Overdistention

Ventilator-induced lung injury and pulmonary barotrauma are major complications of positive-pressure

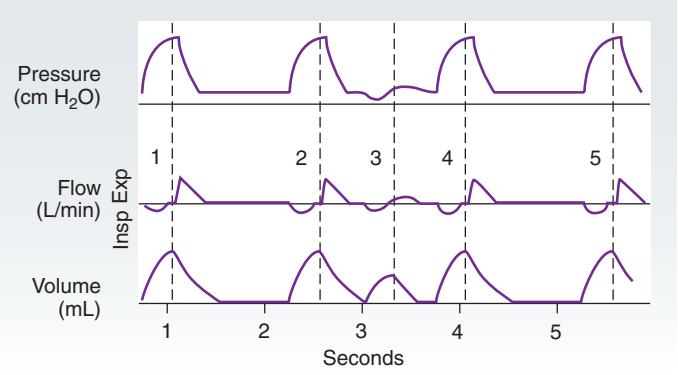


FIGURE 5-17 Tracing of pressure, flow, and volume over time (in seconds). *Exp,* Expiration; *Insp,* inspiration.

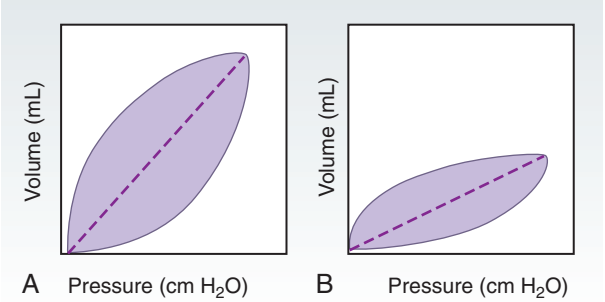


FIGURE 5-18 Pressure–volume loops demonstrating normal and decreased lung compliance. **A,** Normal lung compliance. **B,** Decreased lung compliance.

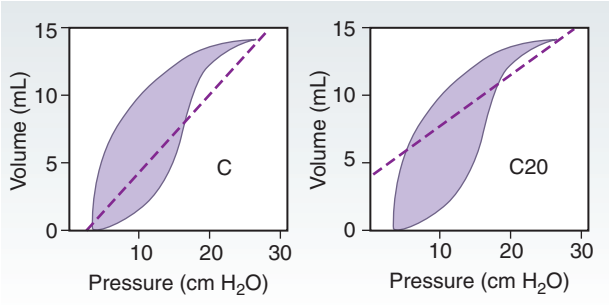


FIGURE 5-19 Pressure–volume loops demonstrating overdistention. Note the "penguin" or "bird's beak" appearance in the shape of the loops. These loops demonstrate idealized slopes *(dashed lines)* for change in compliance for the entire breath *(C)* and change in compliance in the last 20% of inspiratory pressure *(C20)*. The C20:C ratio identifies lung overdistention.

ventilation in all patient populations. Applying excessive distending airway pressures results in a characteristic distortion in the appearance of the normal pressure–volume loop (Figure 5-19). To visualize this, imagine blowing up a balloon. At first it is necessary to blow hard (i.e., apply a large amount of pressure) to get any volume into the balloon. It then seems easier to push additional volume into the balloon as it expands. Finally, as the balloon reaches its expansion limit—that is, starts to overdistend—it again becomes more difficult to blow up. In other words, the compliance of the balloon or lung changes with total volume.

Applying additional pressure to an overdistended lung produces little or no increase in delivered volume and is hazardous to the patient. Lung overdistention is quantified by comparing compliance change in the last 20% of inspiratory pressure (C20) with compliance change for the entire breath (C), in the ratio C20/C (see Figure 5-19). A C20/C value less than 0.8 indicates lung overdistention during mechanical ventilation. Gas exchange can be improved in mechanically ventilated neonates with lung overdistention by reducing peak inspiratory pressure.[51]

Work of Breathing

The calculated **work of breathing** is determined as the integral of esophageal pressure for a given tidal volume and reflects the amount of energy required by the patient to breathe. Work of breathing is usually indexed to body weight, reported as grams-centimeters per kilogram (g-cm/kg) or as joules per liter (J/L). Work of breathing measurement has proven particularly useful when evaluating new ventilator techniques and response to various therapies.

OTHER BEDSIDE TESTS

Other common pulmonary function measurements performed at the bedside are vital capacity, peak expiratory flow rate, and maximal inspiratory pressure, often referred to as *negative inspiratory force (NIF)*. These measurements require a respirometer or pneumotachometer, a peak flow meter, and an NIF meter. The values are helpful in a variety of clinical situations, including weaning from mechanical ventilation, evaluating neuromuscular disorders such as myasthenia gravis or muscular dystrophy, and evaluating treatment for reactive airways.

Each of these measurements depends on patient cooperation and effort, which makes it challenging with children and prevents their use for infants. Pediatric patients may need to be older than 4 or 5 years of age to perform some of these tests because of equipment limitations. Also, the child must be able to understand the instructions and use the correct technique to perform the tests. The therapist must thoroughly explain the technique for each maneuver and provide a chance for practice before actually collecting the data. It is imperative that clinicians record their impression of the child's understanding and effort with the actual measurements.

Vital Capacity

VC is the maximal amount of gas that can be expired after a full inspiration. The patient inhales to TLC and then exhales completely through a respirometer or other measuring device. VC values are effort dependent, and the child must cooperate completely when asked to perform the maneuver. Incomplete effort will result in an artificially low value, which may lead to misdiagnosis. Forced vital capacity differs from VC in that during the FVC maneuver the patient exhales as forcefully and rapidly as possible after a maximal inspiration. FVC is usually the same as a slow VC, except in patients who experience airway collapse with rapid, forceful expiration.

Peak Expiratory Flow Rate

PEFR is the maximal achievable flow during a rapid, forced expiration. The PEFR is used primarily to monitor patients with hyperreactive airways. It is generally measured with handheld devices that sense flow against a turbine, through a variable orifice, or against a spring-loaded diaphragm. With increasing flow rates, an indicator advances linearly on a scale that reveals the PEFR, usually as liters per minute. Note that the PEFR on the flow–volume loop measures the same function as the peak flow meter, air flow in the large airways, but is reported as liters per second. The PEFR measurement made during the recording of a flow–volume loop is an actual measurement of air flow. Because the handheld peak flow meter measures only the inertia from the initial blast of air, the value is not identical to the value reported during an flow–volume loop measurement.

Portable peak flow meters are used extensively in the study and management of patients with asthma. A significant decrease in the individual's baseline PEFR

may indicate worsening asthma and the need for therapeutic interventions. In addition, measuring PEFR before and after bronchodilator administration evaluates the effectiveness of the therapy.[52]

Portable handheld models are inexpensive and easy to use at home, at school, or in an office. When using handheld peak flow meters, care must be taken to avoid partial occlusion of the flow exit orifice during exhalation. Partial occlusion decreases the amount of flow required to raise the flow indicator, resulting in overestimation of PEFR. This measurement can also be erroneously high if the patient uses a "spitting" action during exhalation.[6,53]

Maximal Respiratory Pressures

Maximal respiratory pressures, both inspiratory and expiratory, are tests that can be used to measure the degree of muscle weakness in a child who suffers from a congenital or acquired neuromuscular disorder (e.g., muscular dystrophy, Guillain–Barre syndrome) or a thoracic deformity such as pectus excavatum. MIP (or PI_{max}), also called *negative inspiratory force,* is the maximal negative pressure, expressed as centimeters of water (cm H_2O), generated after exhaling to RV and inspiring maximally against an occlusion. Likewise, MEP or (PE_{max}), also called *positive expiratory force,* is the maximal positive pressure, expressed as cm H_2O, generated after inspiring to TLC and maximally expiring against an occlusion. A small fixed leak is introduced into the system to eliminate excessive positive pressure that could be caused by the cheeks during an MEP maneuver and glottis closure during the MIP maneuver. The pressure-measuring device is required to record pressures from −200 cm H_2O to +200 cm H_2O. A maximal plateau pressure held for 1 to 2 seconds is recorded. The best effort of three that vary less than 20% or 10 cm H_2O, whichever is greater, should be reported.

MIP is an important measure to help differentiate weakness from other causes of restrictive lung disease. It can be an important differentiating point for children and young adults with various neuromuscular diseases. These patients usually have a combination of scoliosis and muscle weakness, both of which might contribute to reduced lung volumes. Measuring MIP helps in determining how much reduction might be caused by weakness. Because many neuromuscular diseases are progressive, MIP helps document this progression. MIP may also indicate the patient's physical ability to take a deep breath and is often measured when weaning a patient from mechanical ventilation is being considered.

A low MEP is associated with a patient's inability to cough effectively. Individuals with excessive mucus–producing diseases such as cystic fibrosis or chronic bronchitis are unable to clear secretions effectively. A low MEP can also be representative of air trapping in patients with emphysema.

Complex Bedside Measurements

Automated and computer monitors allow the measurement of more complex breathing variables at the bedside. Usually these measurements are useful for weaning a child from mechanical ventilation, but they may also be helpful when evaluating the pulmonary status of a neuromuscular patient.

An example of such a measurement is the P0.1, pronounced "P one hundred." It is similar to MIP but measures the negative pressure generated in the first 100 msec. P0.1 appears to be more indicative of the ability to sustain respiratory drive and predict successful extubation or weaning from mechanical ventilation.

Another such measure is the **tension time index** (TTI), which may assist in predicting successful weaning from mechanical ventilation. The TTI is the product of the inspiratory time–to–cycle time ratio and the integrated area under the pressure curve throughout the respiratory cycle. TTI can be measured both invasively and noninvasively. The TTI of the diaphragm (TTdi) is an invasive measurement of the load capacity ratio of the diaphragm. The respiratory muscle time index (TTmus) is a noninvasive measurement of the load on all respiratory muscles. In a study by Harikumar and colleagues, a TTmus value greater than 0.18 and a TTdi value greater than 0.15 had sensitivities and specificities of 100% in predicting extubation failure. Invasive and noninvasive measurements of TTI may provide an accurate prediction of extubation outcome in mechanically ventilated children.[54]

Key Points

- Pulmonary function testing is a vital part of the diagnosis and management of many respiratory diseases in both the intensive care unit and outpatient laboratory.
- Obtaining reliable pulmonary function data from infants and pediatric subjects may be challenging but provides extremely valuable insight into their respiratory mechanics.
- Traditional diagnostic tools such as spirometry, lung volume measurement techniques (e.g., plethysmography and dilution methods), diffusing capacity, and provocation tests are used in assessing lung function.
- A multitude of other diagnostic test modalities (e.g., impulse oscillometry, exhaled nitric oxide, CPET, etc.) may be used to identify and manage the care of infant and pediatric patients.

- Understanding the physiologic principles of the tests and their specific application across a variety of clinical arenas is a useful skill set of the neonatal and pediatric practitioner.
- The continued advancement of pulmonary diagnostic technology and its application by skilled clinicians has dramatically enhanced the reliability and accuracy of pulmonary function testing in these age groups.

Assessment Questions

See Evolve Resources for answers.

1. When interpreting pulmonary function test results in children, assessing whether values are "normal" is complicated by _____.
   - **A.** Applying the process of obligatory miniaturization
   - **B.** The wide range of variability in normal children
   - **C.** Lack of predicted normal values
   - **D.** A and C
   - **E.** B and C
2. Why do inspiratory retractions distort the ribs and sternum inward during distressed breathing in a premature newborn?
   - **A.** Negative inspiratory pressures exceed transpulmonary pressure.
   - **B.** The chest wall is compliant and does not expand the lungs.
   - **C.** The specific conductance of the lungs is higher than the recoil of the chest wall.
   - **D.** Time constant differences result in a lag between lung expansion and chest wall movement.
   - **E.** None of the above.
3. Airway resistance (Raw) reflects the nonelastic airway and tissue forces resisting gas flow. How is Raw calculated?
   - **A.** By dividing the peak ventilating pressures by the peak flow rate
   - **B.** Using a modified Fick equation for gas flow
   - **C.** From the ratio of airway occlusion pressure to expiratory flow
   - **D.** Using a tonometer and paramagnetic analyzer
   - **E.** By dividing the ratio of upper airway flow by lower airway compliance
4. Which of the following are possible tests that may be used to determine lung volume in an infant?
   - **I.** Functional residual volume
   - **II.** Helium dilution
   - **III.** Plethysmography
   - **IV.** Thoracic gas volume
   - **V.** Nitrogen washout
     - **A.** II, III, and V
     - **B.** I, III, and V
     - **C.** II and IV
     - **D.** III and IV
     - **E.** IV and V
5. What is the difference between pleural pressure and airway pressure?
   - **A.** End-expiratory pressure
   - **B.** Hyperinflation pressure
   - **C.** PD20
   - **D.** Isovolume pressure
   - **E.** Transpulmonary pressure
6. Which of the following are considered a complication of using a face mask during infant pulmonary function tests?
   - **I.** Trigeminal nerve damage
   - **II.** Vagal reflex stimulation
   - **III.** Increased lung compliance
   - **IV.** Increased dead space volume
   - **V.** Recurrent pharyngeal nerve damage
     - **A.** I, II, and IV
     - **B.** I, III, and IV
     - **C.** II and IV
     - **D.** II, III, and V
     - **E.** III, IV, and V
7. What is one advantage to using a flow–volume loop instead of volume–time spirometry?
   - **A.** A flow–volume loop is not dependent on patient cooperation or effort.
   - **B.** Volume–time spirometry causes early fatigue in children.
   - **C.** Flow–volume measurements are easier to record.
   - **D.** A flow–volume loop displays early termination of the exhalation effort.
   - **E.** Time–volume displays are not real-time measurements.
8. How are spirometric values affected if a child fails to begin exhalation at 100% of total lung capacity?
   - **A.** Reported tidal volume value is higher than the actual value.
   - **B.** Reported FEF_{50} value is higher than the actual value.
   - **C.** Reported FVC value is lower than the actual value.
   - **D.** Reported PEFR value is higher than the actual value.
   - **E.** All values are reported accurately.
9. Measuring flow from airways less than 2 mm in diameter is determined by evaluating _____.
   - **A.** The maximal midexpiratory flow rates
   - **B.** The forced expiratory flow at 25% to 75% of exhalation
   - **C.** The forced expiratory flow at 50% of exhalation
   - **D.** B and C
   - **E.** A, B, and C
10. When using a handheld peak flow meter, a 6-year-old patient with asthma partially occludes the exit orifice of the meter. On the basis of the flow meter results, the physician may _____.
    - **A.** Erroneously prescribe the wrong medication dose because the value reported is lower than the actual value
    - **B.** Prescribe the correct medication dose because there is no effect on the actual value
    - **C.** Not prescribe medication because the value reported is higher than the actual value
    - **D.** Prescribe a medication dose that is proportionate to the erroneous reduction in peak flow
    - **E.** None of the above

REFERENCES

1. Majaesic CM, Jones R, Dinu IA, et al. Clinical correlations and pulmonary function at 8 years of age after severe neonatal respiratory failure. *Pediatr Pulmonol*. 2007;42:829.
2. Mottram CD. *Ruppel's Manual of Pulmonary Function Testing*. 11th ed. St. Louis: Elsevier; 2017.
3. Beydon N, Davis SD, Lombardi E, et al. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. *Am J Respir Crit Care Med*. 2007;175:1304.
4. Quanjer PH, Stanojevic S, Cole TJ, the ERS Global Lung Function Initiative, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012;40:1324-1343.
5. Miller MR, Crapo R, Hankinson J, et al. An official American Thoracic Society/European Respiratory Society statement: general considerations for lung function testing. *Eur Respir J*. 2005;26:153.
6. Davis S, Johnson R, Flucke R, et al. American association for respiratory care clinical practice guideline: infant/toddler pulmonary function tests. *Respir Care*. 2008;53(7): 929-945.
7. Hanrahan JP, Tager IB, Castile RG, et al. Pulmonary function measures in healthy infants. *Am Rev Respir Dis*. 1990;141: 1127.
8. Rosenfeld M, Pepe M, Longton G, et al. Effect of choice of reference equation on analysis of pulmonary function in cystic fibrosis patients. *Pediatr Pulmonol*. 2001;31:227.
9. Hyatt RE. Expiratory flow limitation. *J Appl Physiol*. 1983; 55:1.
10. Castile R. Novel techniques for assessing infant and pediatric lung function and structure. *Pediatr Infect Dis J*. 2004;23: S246-S253.
11. Seed L, Wilson D, Coates AL. Children should not be treated like little adults in the PFT lab. *Respir Care*. 2012; 57(1):61-71.
12. Blonshine SB. Pediatric pulmonary function testing. *Respir Care Clin North Am*. 2000;6:27.
13. Bhutani VK, Sivieri EM. Pulmonary function and graphics. In: Goldsmith JP, ed. *Assisted ventilation of the neonate*. 4th ed. Philadelphia: WB Saunders; 2003:293-309.
14. Talmor D, Sarge T, O'Donnell CR, et al. Esophageal and transpulmonary pressures in acute respiratory failure. *Crit Care Med*. 2006;34:1389.
15. Saslow JG, Aghai ZH, Nakhla TA, et al. Work of breathing using high-flow nasal cannula in preterm infants. *J Perinatol*. 2006;26:476.
16. Frey U, Stocks J, Coates A, et al. Specifications for equipment used for infant pulmonary function testing: ERS/ATS Task Force on Standards for Infant Respiratory Function Testing, European Respiratory Society/American Thoracic Society. *Eur Respir J*. 2000;16:731.
17. Heistein LC, Ramaciotti C, Scott WA, et al. Chloral hydrate sedation for pediatric echocardiography: physiologic responses, adverse events, and risk factors. *Pediatrics*. 2006;117: e434.
18. Stocks J, Godfrey S, Beardsmore C, et al. European Respiratory Society/American Thoracic Society: Plethysmographic measurements of lung volume and airway resistance: ERS/ATS task force on standards for infant respiratory function testing. *Eur Respir J*. 2001;17:302.
19. Tepper RS, Asdell S. Comparison of helium dilution and nitrogen washout measurements of functional residual capacity in infants and very young children. *Pediatr Pulmonol*. 1992;13:250.
20. Brar G, Geiss D, Brion LP, et al. Respiratory mechanics in very low birth weight infants during continuous versus intermittent gavage feeds. *Pediatr Pulmonol*. 2001;32:442.
21. Katier N, Uiterwaal CS, de Jong BM, et al. Passive respiratory mechanics measured during natural sleep in healthy term neonates and infants up to 8 weeks of life. *Pediatr Pulmonol*. 2006;41:1058.
22. Katier N, Uiterwaal CS, de Jong BM, et al. Feasibility and variability of neonatal and infant lung function measurement using the single occlusion technique. *Chest*. 2005;128: 1822.
23. Maynard RC, et al. Partial forced expiratory flow (PFEF) measurements in premature infants at discharge. *Pediatr Res*. 1991;29:324.
24. Becker MA, Donn SM. Real-time pulmonary graphic monitoring. *Clin Perinatol*. 2007;34:1.
25. Miller MR, Hankinson J, Brusasco V, ATS/ERS Task Force, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26: 319-338.
26. Graham BL, Brusasco V, Burgos F, et al. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. *Eur Respir J* 2017;49.
27. Ginsberg JP, Aplenc R, McDonough J, et al. Pre-transplant lung function is predictive of survival following pediatric bone marrow transplantation. *Pediatr Blood Cancer*. 2010;54: 454-460.
28. Koopman M, Zanen P, Kruitwagen CL, et al. Reference values for paediatric pulmonary function testing: the Utrecht dataset. *Respir Med*. 2011;105:15-23.
29. Kim YJ, Hall GL, Christoph K, et al. Pulmonary diffusing capacity in healthy Caucasian children. *Pediatr Pulmonol*. 2012;47:469-475.
30. Gappa M, Pillow JJ, Allen J, et al. Lung function tests in neonates and infants with chronic lung disease: lung and chest-wall mechanics. *Pediatr Pulmonol*. 2006;41:291.
31. Wanger J, Clausen JL, Coates A, et al. Standardization of the measurement of lung volumes. *Eur Respir J*. 2005;26:511.
32. Pfaff JK, Morgan WJ. Pulmonary function in infants and children. *Pediatr Clin North Am*. 1994;41:401.
33. Kirkby J, Stanojevic S, Welsh L, et al. Reference equations for specific airway resistance in children: the Asthma UK initiative. *Eur Respir J*. 2010;36:622-629.
34. Nowowiejska B, Tomalak W, Radlin J, et al. Transient reference values for impulse oscillometry for children aged 3–18 years. *Pediatr Pulmonol*. 2008;43:1193-1197.
35. Schulze J, Smith HJ, Fuchs J, et al. Methacholine challenge in young children as evaluated by spirometry and impulse oscillometry. *Respir Med*. 2012;106:e627-e634.
36. Godfrey S, Cohen S, Avital A, et al. Timing and nature of wheezing at the endpoint of a bronchial challenge in preschool children. *Pediatr Pulmonol*. 2005;39:262.
37. Wanger J, Blonshine S, Foss C, et al. AARC Guideline: Methacholine challenge testing. *Respir Care*. 2001;46(5): 523-530.
38. Crapo RO, Casaburi R, Coates AL, et al. Guidelines for methacholine and exercise challenge testing—1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med*. 2000;161:309.
39. Paridon SM, Alpert BS, Boas SR, et al. Clinical stress testing in the pediatric age group: a statement from the American Heart Association Council on Cardiovascular Disease in the Young, Committee on Atherosclerosis Hypertension, and Obesity in Youth. *Circulation*. 2006;113: 1905-1920.
40. American Thoracic Society/European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide. *Am J Respir Crit Care Med*. 2005;171:912-930.
41. Dweik RA, Boggs PB, Erzurum SC, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric

oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med*. 2011;184:602-615.
42. Mammel MC, Fisher JB, Bing DR, et al. Effect of spontaneous and mechanical breathing on dynamic lung mechanics in hyaline membrane disease. *Pediatr Pulmonol*. 1990;8:222.
43. Berg KM, Lang GR, Salciccioli JD, et al. The rapid shallow breathing index as a predictor of failure of noninvasive ventilation for patients with acute respiratory failure. *Respir Care*. 2012;57(10):1584.
44. Vassilakopoulos T, Zakynthinos S, Roussos C. The tension–time index and the frequency/tidal volume ratio are the major pathophysiologic determinants of weaning failure and success. *Am J Respir Crit Care Med*. 1998;158:378.
45. Chatila W, Jacob B, Guaglionone D, et al. The unassisted respiratory rate–tidal volume ratio accurately predicts weaning outcome. *Am J Med*. 1996;101:61.
46. Venkataraman ST, Khan N, Brown A. Validation of predictors of extubation success and failure in mechanically ventilated infants and children. *Crit Care Med*. 2000;28:2991.
47. Farias JA, Alía I, Esteban A, et al. Weaning from mechanical ventilation in pediatric intensive care patients. *Intensive Care Med*. 1998;24:1070.
48. Thiagarajan RR, et al. Predictors of successful extubation in children. *Am J Respir Crit Care Med*. 1999;160:1562.
49. Kamlin C, Davis PG. Long versus short inspiratory times in neonates receiving mechanical ventilation. *Cochrane Database Syst Rev*. 2004;18(4):CD004503.
50. Lucangelo U, Bernabé F, Blanch L. Respiratory mechanics derived from signals in the ventilator circuit. *Respir Care*. 2005;50:55.
51. Kuschel C. Ventilation graphics and respiratory function monitoring. *Newborn Serv Clin Guideline*. http://www.adhb.govt.nz/newborn/teachingresources/ventilation/RespiratoryFunctionMonitoringAndGraphics.htm. June 2003.
52. Slieker MG, van der Ent CK. The diagnostic and screening capacities of peak expiratory flow measurements in the assessment of airway obstruction and bronchodilator response in children with asthma. *Monaldi Arch Chest Dis*. 2003;59:155.
53. Nair SJ, Daigle KL, DeCuir P, et al. The influence of pulmonary function testing on the management of asthma in children. *J Pediatr*. 2005;147:797-801.
54. Harikumar G, Egberongbe Y, Nadel S, et al. Tension-time index as a predictor of extubation outcome in ventilated children. *Am J Respir Crit Care Med*. 2009;180(10):982-988.

Radiographic Assessment

6

Nina Kowalczyk

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. Recognize differences in radiographic positions and projections that affect the appearance of the visualized anatomy.
2. Identify the uses of alternative imaging modalities.
3. Identify normal chest structures.
4. Examine a chest radiograph for proper placement of endotracheal tubes and vascular catheters.
5. Identify the pathologies most commonly visualized on soft tissue images of the neck.
6. List the most common causes that lead to radiographic evaluation of the newborn chest.
7. Describe how atelectasis affects the individual lobes of each lung.
8. Describe the radiographic appearance of cystic fibrosis.
9. List the complications of chest trauma, and identify the placement of support devices.

Key Terms

air bronchogram
atelectasis
barium swallow
bronchiectasis
cellulitis
chest wall hematoma
computed tomography
costal cartilaginous deformities
croup
diaphragmatic motion
dysphasia
epiglottitis
esophagram
foreign body aspiration
hila
horizontal fissure
major fissure
mass effect
mediastinal masses
mediastinum
minor fissure
oblique fissure
patent ductus arteriosus
picture archiving and communication system (PACS)
pleural effusions
pneumatocele
pneumomediastinum
pneumothorax
position
projection
pulmonary interstitial emphysema
retropharyngeal cellulitis
silhouette sign
spine sign
superficial masses
thymus gland
tracheoesophageal fistula
tracheomalacia
vascular ring

Radiographic assessment of the chest and airway is often critical for patient evaluation by the respiratory care practitioner: the position of lines and tubes can be accurately determined; visualized lung fields on the radiographs can be correlated with the physical examination; and airways can be assessed for patency and abnormalities. Conventional radiography remains the most common imaging modality in the pediatric population, and in most instances the pediatric thorax can be adequately assessed with conventional radiography. In some cases, however, further sectional imaging evaluation may be required using **computed tomography** (CT). Concerns regarding ionizing radiation dose to infants and children must be considered when ordering chest radiographs and CT examinations, especially in very ill children who have repeated studies over a relatively short period of time. In such instances, sonographic evaluation of the lungs and

pleura may be indicated. Technologic advancements leading to higher resolution ultrasonic transducers have allowed sonography to become a useful alternative in imaging the lungs and pleura, while adhering to the ALARA (as low as reasonably achievable) radiation safety principle supported by the "Image Gently" campaign initiated by the Alliance for Radiation Safety in Pediatric Imaging.[1]

RADIOGRAPHIC IMAGING

Conventional chest radiographs may be obtained with a mobile radiographic unit at the patient's bedside or by using stationary radiographic equipment in the radiology department. To ensure the highest-quality images, radiographic examinations should be performed on stationary radiographic units whenever possible. It is critical to pay close attention to careful positioning, radiographic technique, and adequate inspiratory effort when imaging the chest, because these factors are often quite difficult to control in pediatric patients. Mobile radiographs should only be obtained when it is not safe or feasible to transport the patient to the radiology department. Mobile radiography is most commonly used when imaging neonates and patients in critical care units. Digital radiography has been widely adopted across the United States; it allows images to be viewed on monitors within the patient unit or on a computer via a **picture-archiving and communication system (PACS),** an electronic network to manage digital images.

Patient **position** and the radiographic **projection** are critical conditions to consider when evaluating a radiographic image. *Position* refers to the arrangement of the patient's body (e.g., erect, supine, recumbent), and *projection* refers to the path of the x-ray beam (e.g., posteroanterior [PA], meaning entering through the body's posterior surface and exiting the anterior surface). The standard projections for chest radiography are the erect PA and left lateral obtained on full inspiration.[2] The PA and anteroposterior (AP) projections demonstrate chest anatomy in relation to right and left sides of the body. With the addition of the lateral projection, most commonly a left lateral, the anatomic structures can also be visualized from anterior to posterior. This allows the structures to be examined three-dimensionally. When imaged with stationary radiographic equipment within the radiology department, a PA projection is obtained with the patient in an upright position with his or her chest against the radiographic imaging device. The x-ray tube is placed behind the patient's back with the x-ray beam projected through the patient in a posterior-to-anterior path. An upright left lateral projection of the chest is also obtained with the patient's arms raised above his or her head to avoid superimposition of the arms within the lung apices. The x-ray beam is projected through the patient in a right side–to–left side path. These positions place the heart close to the image receptor and prevent engorgement of the heart and great vessels. However, when the radiograph is performed at the patient's bedside with mobile radiographic equipment, the image receptor is placed behind the patient's back and the x-ray tube is placed in front of the patient's chest. This obtains a frontal view in the AP projection, with the beam passing from anterior to posterior. Whenever possible, mobile chest radiographs are obtained with the patient in a seated position to place the thorax erect, but in some cases, such as in neonates, the image must be obtained with the patient lying flat on his or her back. An AP projection causes magnification of structures such as the heart because it places the anatomy further from the image receptor. When the chest radiograph is obtained with the patient in a supine position, the abdominal organs rise, the lungs cannot be fully distended, and the heart appears enlarged. Therefore knowledge of how the frontal view is obtained (anteroposterior vs. posteroanterior) is useful in evaluating heart size.

Although most chest radiographs are performed with PA and left lateral projections, other projections may contribute additional information. The lateral decubitus position is a frontal projection performed with the patient lying on either the right side (right lateral decubitus) or on the left side (left lateral decubitus). The downward side can be evaluated for presence of fluid, such as a mobile pleural effusion, and the upward side will demonstrate free air, such as in the case of a **pneumothorax** (air in the pleural cavity). Decubitus chest radiographs may also be used if a foreign body is lodged in a bronchus, causing air trapping. The downward-side lung normally loses volume but may remain expanded when a foreign body obstructs airflow out of the bronchus.

As mentioned earlier, chest radiography is usually performed on full inspiration. Forced expiratory images are used in assessing the presence of a pneumothorax and to evaluate for foreign body aspiration in small children. When assessing foreign body aspiration in very young patients, the radiographer may gently add pressure to the abdomen during expiration. If an obstruction is present, the affected lung does not decrease in size, but remains normal to hyperexpanded (Figure 6-1). In older and cooperative children the radiographer will have the patient inspire and expire without assistance while the radiographs are obtained. Oblique views are usually rotated 45 degrees from the frontal position. They are typically used in the evaluation of rib fractures and to better evaluate the entire heart border.

Although the thoracic trachea and mainstem bronchi are demonstrated on chest radiographs, soft tissue AP and lateral projections of the neck allow evaluation

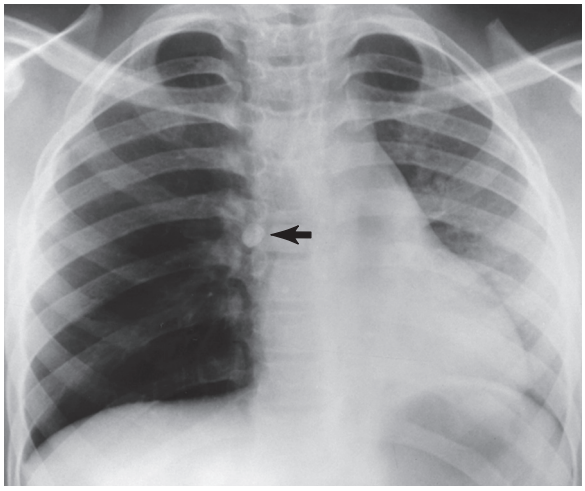


FIGURE 6-1 This expiratory frontal chest radiograph shows a normal decrease in left lung volume. A tooth *(arrow)* obstructs the right mainstem bronchus and causes air trapping in the right lung.

of the extrathoracic airway. These images may show **mass effect** on the airway from a retropharyngeal abscess or can show distortion of the tracheal caliber caused by croup and subglottic stenosis.

Real-time imaging of the airway by fluoroscopy will show the dynamic collapse of tracheal walls known as **tracheomalacia.** If a **barium swallow,** also known as an **esophagram,** is performed as well, the presence of a **vascular ring** (in which the trachea and esophagus are encircled by connected segments of the aortic arch and its branches) or **tracheoesophageal fistula** (an abnormal connection between the trachea and the esophagus) can be excluded. Swallowing studies are performed with the assistance of a speech therapist, using various consistencies of barium-impregnated food to determine which the patient is unlikely to aspirate.

CT creates sectional images of the chest that can be viewed in multiple imaging planes: transverse, sagittal, and coronal. Volumetric CT offers the advantage of imaging the entire chest with one breath hold, which allows better evaluation of the chest, especially the diaphragm area. However, the radiation dose associated with CT is much higher than the radiation dose received from a conventional chest radiograph. Therefore the use of CT in imaging pediatric patients is limited. CT of the chest is the method of choice for the evaluation of pulmonary adenopathy. Standard radiographs are only about 50% sensitive to chest disease, typically displaying only advanced pathologic conditions.[2] CT of the neck is also appropriate in older children with a palpable neck mass, whereas ultrasound of the neck is preferable in patients younger than 14 years because it does not expose the child to ionizing radiation. However, if the mass is located in the retropharyngeal area, an enhanced CT of the neck is appropriate for pediatric patients of all ages.[3]

SONOGRAPHIC IMAGING

Because the ultrasonic waves are not transmitted well through the lungs or bony structures within the thorax, sonography is not the modality of choice in many instances. However, because sonography is free from ionizing radiation, it is most valuable in assessing **costal cartilaginous deformities, superficial masses** within the adipose tissue, infections within the chest wall such as **cellulitis, pleural effusions,** traumatic or postoperative **chest wall hematomas,** and anomalies of the **thymus gland** and **diaphragmatic motion.**[4] Ultrasonic findings relative to diaphragmatic excursion and paralysis correlate highly to fluoroscopic evaluation and reduce the patient's exposure to ionizing radiation. Sonography has the ability to demonstrate very small amounts of fluid not visible on conventional chest radiography; therefore it is quite useful in the evaluation of pleural effusions. It is also superior to CT in characterizing the pleural fluid within the chest by the presence or absence of echoes within the fluid.[4,5]

Additionally, ultrasound demonstrates a high degree of accuracy in demonstrating a pneumothorax and evaluating **mediastinal masses.**[5] Normally, the thymus gland should visualize as homogeneous echoes and can be differentiated from other mediastinal masses by its sonographic appearance. Ultrasound is also often used to guide biopsies of mediastinal masses.[4]

NORMAL CHEST ANATOMY

The normal structures that are visualized on a chest radiograph are distinguishable because of differences in the absorption of the x-ray beam by the organs and tissues within the thoracic cavity. Bone and metallic orthopedic hardware appear bright white because of greater x-ray absorption and less exposure of the image receptor. In contrast, air has little beam absorption, and therefore well-expanded lungs appear relatively black. Soft tissue organs and fluid usually appear as shades of gray in between the white bones and black lungs. However, incorrect exposure of the image receptor may alter the normal gray scale. Digital radiographic images are automatically rescaled to allow proper image contrast and brightness, and the image can be manipulated by the clinician after it is processed.

By using specialized tools available for adjusting images on a PACS monitor or computer, the image may be manipulated to enhance visualization of the lung detail and to clarify the presence of abnormal collections of free air. Adjusting the window level controls the brightness of the image on the monitor, and adjusting the window width changes the gray scale on the monitor. This is helpful in evaluating the soft tissue structures within the chest and neck. The zoom features are particularly useful to help magnify specific

areas on the radiographic image. Inversion of the image sometimes will clarify the tip position of small catheters. Because of the complexity of image retrieval and portrayal with a PACS, instruction is usually provided to the clinicians by the PACS administrators from the radiology department.

A chest radiograph is a two-dimensional representation of a three-dimensional object. When an x-ray beam passes through the chest, the densities of all the structures it encounters are summated. Thus a flat object such as plate-like **atelectasis** (collapse of all or part of the lung) may add little to the opacity of the chest in one projection but may appear opaque when viewed on edge in another projection. Pulmonary vessels appear as white dots when viewed in cross section but are fainter when viewed as tubes.

Differences in tissue density allow the viewer to discriminate between different structures. The heart, which is composed of soft tissue of muscle density, is clearly demarcated by a distinct edge from the adjacent air-filled lung. However, if the lung becomes denser from loss of air, as in atelectasis, or if the alveoli become filled with pus, as in pneumonia, the sharp edge between the heart and the lung is no longer apparent. The sign caused when two normal structures lose their distinct edge and blend imperceptibly is widely known as the **silhouette sign** (Figure 6-2).

The normal structures that the respiratory care practitioner must evaluate on all chest radiographs are the heart, lungs, and airways (Figure 6-3). Other structures that may be important in a specific patient include the diaphragm, soft tissues, bones, and organs in the upper abdomen. Although the heart is centrally located within the chest, it lays in an oblique plane; thus the left ventricle normally projects into the left hemithorax. As mentioned earlier, it is important to remember that the heart size may be magnified by anteroposterior projection and decreased lung expansion. Pulmonary bronchi, arteries, and veins form confluent areas on either side of the heart called the right and left pulmonary **hila.** Enlargement of the hila may be caused by increased caliber of the pulmonary vessels or enlarged lymph nodes. The side of the aortic arch should also be noted. Normally the aortic arch is on the left and causes a prominent bulge of the superior mediastinum and a mild indentation on the trachea.

The **mediastinum** is composed of the heart, aorta, main pulmonary artery and proximal branches, origins of the great vessels from the aorta, the superior vena cava, and the thymus. It may appear differently in chest radiography depending on the child's age, developmental stage, and health. Thymic tissue is usually prominent in the neonate and becomes less apparent with age because of regression of the thymus and growth of surrounding structures. Because it is an anterior mediastinal structure, the thymus in a small child fills the anterior clear space normally seen on the lateral projection of a teenager or adult. On the AP or PA projection it may only cause widening of the superior mediastinum. When the thymus projects away from the mediastinum, typically into the right upper lung, it appears as a "sail" with a sharp inferior margin. The lateral margins often have a characteristic wavy contour (Figure 6-4). Unlike a pathologic mass such as lymphoma, the normal thymus does not exert mass effect on the trachea. It is important to note that changes in the mediastinal contour are common after cardiac surgery, because the thymus gland is often removed during the surgical procedure. In such

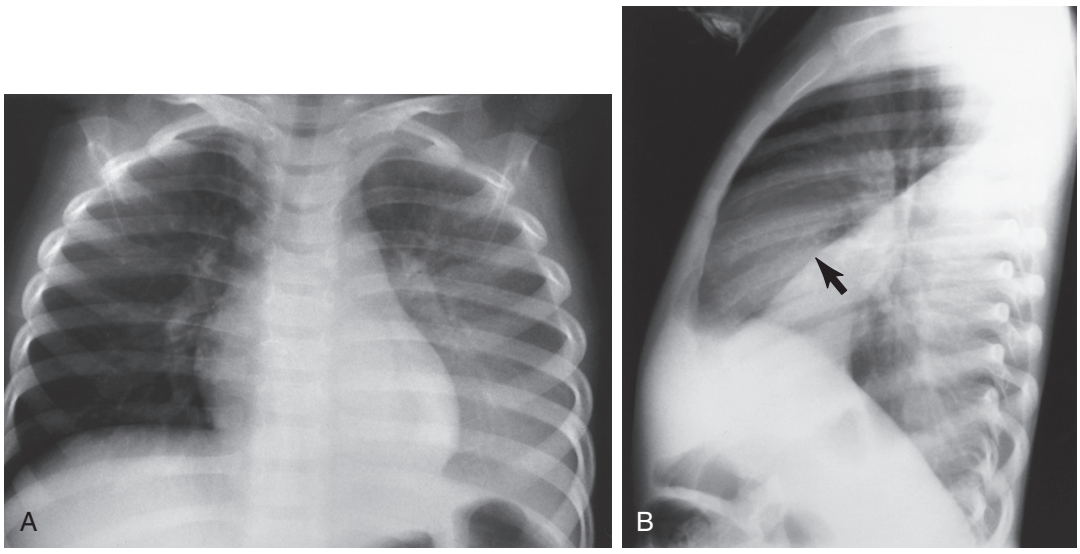


FIGURE 6-2 **A,** Left lower lobe pneumonia abuts the diaphragm, leading to nonvisualization of the normal edge of the diaphragm. The cardiac border is demarcated because the *lingula* (a segment of the upper lobe of the left lung) is normally aerated. **B,** Only the right hemidiaphragm is visualized, because the left is obscured by the left lower lobe pneumonia. The major fissure appears as an edge *(arrow).*

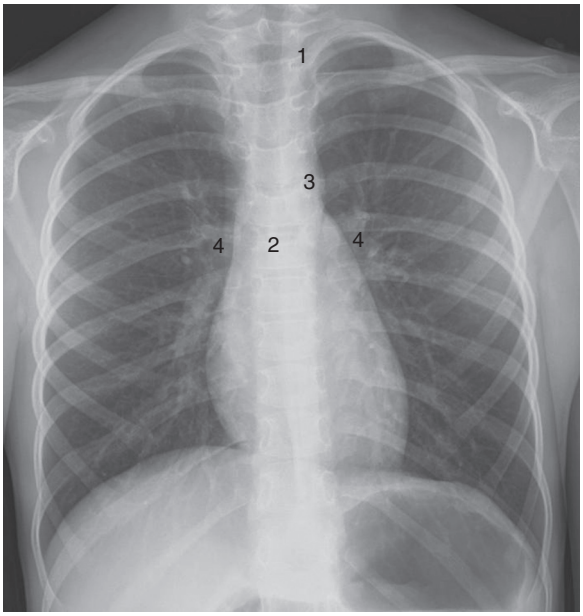


FIGURE 6-3 Normal frontal view of the chest demonstrating the thoracic inlet *(1)*, the carina (the point at which the trachea splits into the two mainstem bronchi) *(2)*, the aortic arch *(3)*, and the pulmonary hila *(4)*.

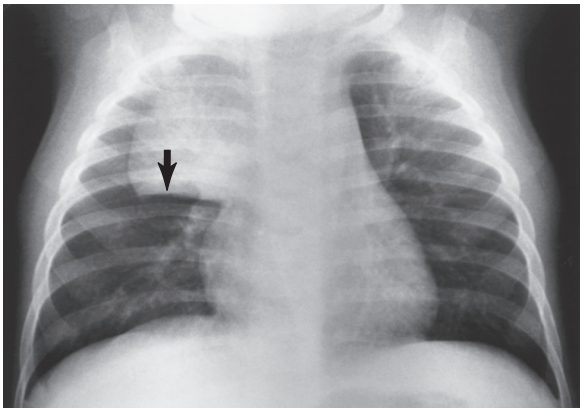


FIGURE 6-4 The normal thymus abuts the minor fissure (arrow) and has a curved lateral margin.

instances, CT of the chest may be used for further investigation. In addition to thymus gland variations, other congenital or acquired abnormalities such cardiac and vascular malformations, as well as previous thoracic surgeries, can alter the mediastinal appearance.[6]

The right lung is divided into three lobes and the left lung into two lobes. Both lungs have upper and lower lobes, but the right lung also has a middle lobe. The lingula of the left upper lobe may be thought of as corresponding to the right middle lobe, at least in location. A frontal view of the chest primarily demonstrates the upper and middle lobes of the lungs. Separating the upper and lower lobes, the **major fissures** (also called **oblique fissures**) extend diagonally on the lateral projection in an anteroinferior-to-posterosuperior plane. Fluid in the fissures increases their visibility. The posterior lobes are visualized on the lateral projection of the chest. The **minor fissure** (also called the **horizontal fissure**) separates the middle lobe from the right upper lobe. It is horizontal in orientation on both frontal and lateral projections and terminates at the major fissure on lateral projection.

Lung density is greatly affected by the degree of inspiration. Poor inspiration will cause crowding of pulmonary vessels and airways, leading to an overall increase in lung density. When comparing the present chest radiograph with a prior image, the depth of inspiration should be taken into account and excluded as a cause of the change in appearance of both the lungs and size of the heart (Figure 6-5). When viewing infant and pediatric radiographs, body rotation may be difficult to avoid. Evaluating thoracic symmetry helps when interpreting the loss of lung volume or increased density in the rotated patient.

Careful evaluation of the position and caliber of the trachea, the laterality of the aortic arch, and mainstem bronchi should be conducted for evidence of abnormal displacement or distortion by an adjacent mass or the presence of a vascular anomaly. Pneumomediastinum

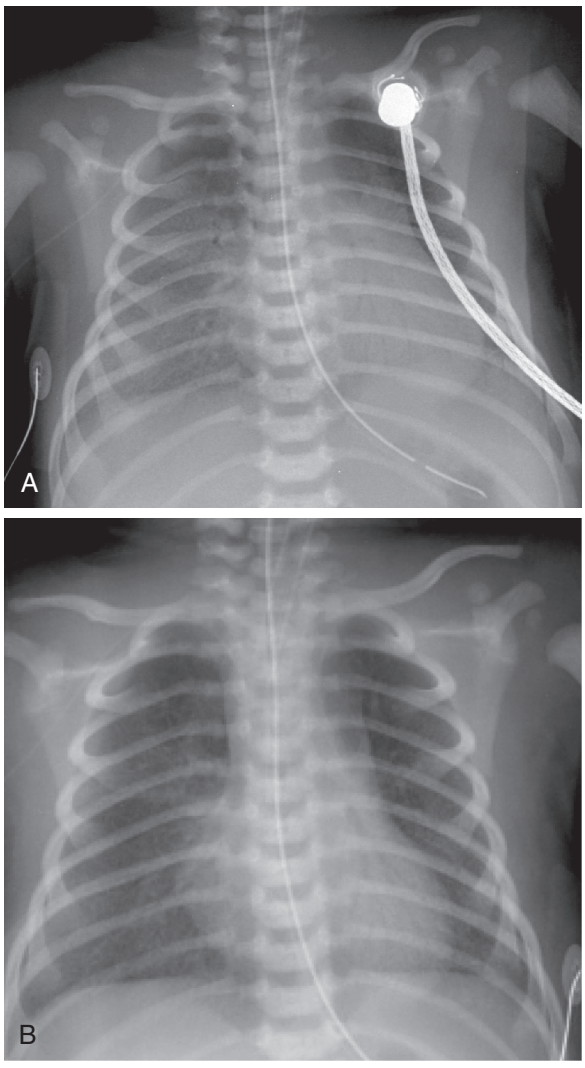


FIGURE 6-5 **A,** Infant with respiratory distress syndrome on a lower ventilator setting. **B,** The same infant on a higher ventilator setting.

may occur after tracheostomy tube placement and must be diagnosed quickly, because the tension on the heart may have fatal consequences. A posterior pneumomediastinum will appear as a collection of air over the heart shadow, often termed a *vanishing heart*.[6] Truncation of a mainstem bronchus is often a sign of a mucous plug when the lung is collapsed. Although the right hemidiaphragm is usually slightly higher than the left because of the underlying liver, the position of the diaphragm may indicate hemidiaphragm paralysis or abdominal pathology. Congenital fusion anomalies may be seen in the neonatal rib cage, and rib fractures may contribute to difficult ventilation in a trauma patient.

POSITIONING OF LINES AND TUBES

Chest radiography is considered the gold standard in assessing endotracheal tube placement. The frontal chest radiograph can readily be used to assess the proper placement of the endotracheal (ET) tube, which should be positioned in the midtracheal region between the inferior clavicular border and the carina.[7,8] If the tip is located above the clavicular border, the ET tube is too shallow. If the tube is at the carina or in one of the mainstem bronchi, overaeration of one lung and atelectasis of the opposite lung may result. The position of the head, especially in a neonate, may result in a significant change in position of the ET tip: The tip will advance toward the carina when the head is flexed.

If a chest radiograph is obtained for suspected esophageal intubation, the stomach, small bowel, and esophagus will be distended with air while the lungs will be underinflated. Although usually not necessary, a lateral projection would demonstrate the ET in the more posterior esophagus. The lateral projection may be more useful for showing adequate tracheal positioning and length in long-term placement of a tracheostomy tube.

A chest tube is inserted through the chest wall between the ribs to allow drainage of air (e.g., pneumothorax) or fluid (e.g., pleural effusion or hemothorax) from the thoracic cavity. Those placed lower on the chest wall are usually for fluid drainage; those placed higher are usually for air removal. Chest tubes are designed with a radiopaque-impregnated material, making them visible on a conventional chest radiograph. A Blake drain can also be used for drainage of pericardial and pleural spaces, especially after cardiac surgery. These silicone tubes are also radiopaque, and they are more comfortable for patients compared with traditional chest tubes.[7]

Various vascular catheters are visible on radiographic evaluation. The positions of vascular catheters should be radiographically evaluated and repositioned if necessary. Umbilical venous catheters (UVC) are commonly used for solution infusions, central venous pressure monitoring and venous blood gas monitoring, medication administration, and total parental nutrition in the neonate. This catheter is placed through the umbilical vein to the inferior vena cava, with the tip ideally located in the inferior right atrium or right atrial junction.[7] Umbilical arterial catheters (UAC) are commonly used for arterial blood pressure monitoring, arterial blood gases, exchange transfusions, and blood sampling in the neonate. This catheter is inserted through the umbilical artery and takes a path through the internal iliac artery to the common iliac artery to its final placement within the aorta, ideally at the T6-T10 level above the celiac, superior mesenteric, and renal arteries.[7] A pulmonary artery catheter is a multilumen catheter that serves to evaluate cardiac function. The pulmonary artery catheter measures pulmonary wedge pressure, reflecting left atrial pressure, and it is positioned in the pulmonary artery. Central venous catheters (CVC) are primarily used for parental nutrition and medication administration. They are further classified as temporary nontunneled catheters or long-term tunneled peripherally inserted catheters (PICC) or implantable ports.[7] Proper insertion of an internal jugular catheter, commonly used for administration of intravenous fluids and central venous pressure (CVP), places the tip of the catheter in the distal superior vena cava just above the right atrium. PICC lines are common for both neonates and children needing long-term venous access for blood draws, nutrition, medications, or chemotherapeutic administration. They may be inserted in the veins of the upper extremity or scalp, with the tip located in the superior vena cava close to the right atrium. Indwelling central venous catheters such as a Port-a-Cath are usually inserted via the internal jugular or subclavian vein with the tip of the catheter placed in the superior vena cava.[7] Port access devices are placed under the skin, just below the clavicle.[1] If the tip of the catheter is in the right atrium, arrhythmia may result. Pneumothorax and new ipsilateral pleural effusion could result from error in catheter placement.

AIRWAY OBSTRUCTION

The adenoids are posterior to the nasopharynx on the lateral neck radiograph. The palatine tonsils are best seen between the oropharynx and nasopharynx. Enlargement of these normal lymphoid structures are a major cause of sleep-related apnea. An acute infection can also cause adenoidal and tonsillar enlargement, leading to airway obstruction (Figure 6-6).

Croup (laryngotracheobronchitis) is the most common cause of upper airway obstruction in children, with a peak incidence in infants and children 6 months to 5 years of age.[5] Most cases are virally induced (parainfluenza) and cause inspiratory stridor with a barking cough. Frontal and lateral neck radiographs may show the characteristic subglottic narrowing below the vocal cords with loss of the normal "shouldering"

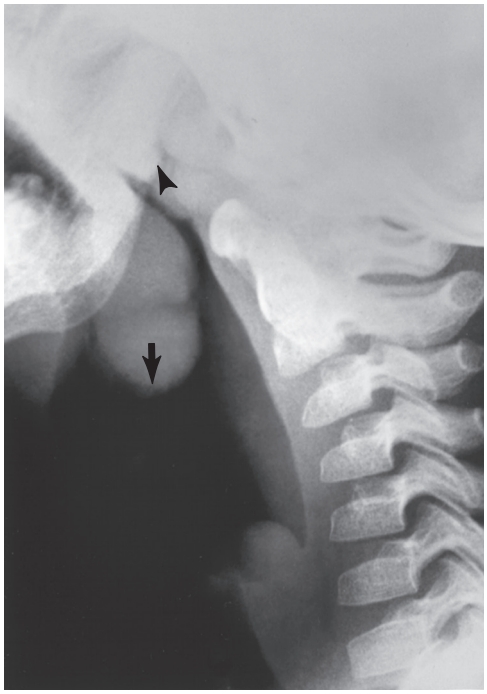


FIGURE 6-6 Enlarged tonsils *(arrow)* appear to hang down into the hypopharynx. The nasopharynx *(arrowhead)* is narrowed from enlarged adenoids located posterior and superior.

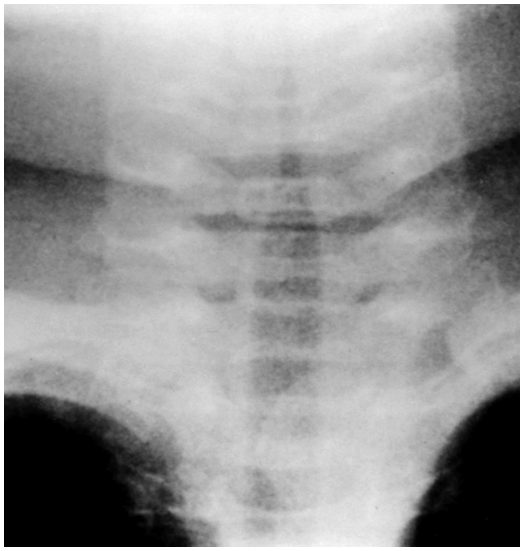


FIGURE 6-7 "Steepling" of the subglottic airway is caused by croup.

of the airway and resultant "church steeple" appearance. The hypopharynx usually appears overdistended (Figure 6-7).

Whereas croup usually improves within a few days of supportive therapy, **epiglottitis** is a life-threatening disease causing acute inspiratory stridor, fever, and **dysphasia** (speech impairment). The usual pathogen is *Haemophilus influenzae*, and the risk of infection is now greatly reduced by immunization programs. The diagnosis should be made by physical examination or by direct visualization through a scope. If a lateral

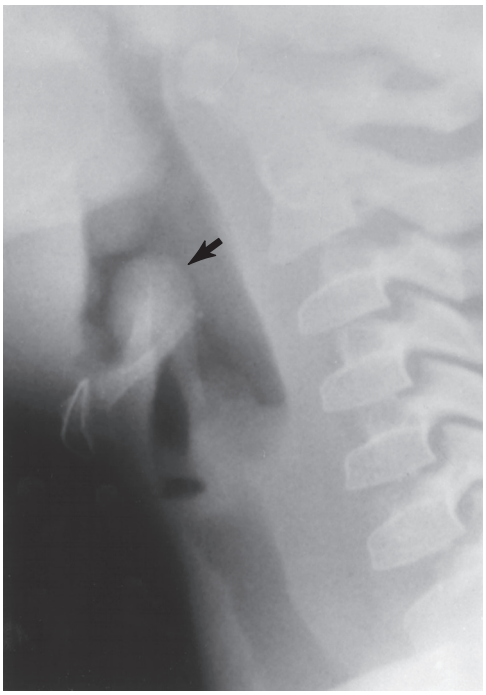


FIGURE 6-8 An enlarged epiglottis *(arrow)* appears as a "thumb" projecting into the airway.

radiograph of the neck is obtained, the epiglottis is enlarged (referred to as the *thumb sign*), and the aryepiglottic folds are thickened, with overdistention of the hypopharynx. The radiograph is performed upright in the position most comfortable for the patient to breathe. Because safety of the child is of primary concern, the radiograph should be performed portably in the emergency department, where intubation can be performed quickly if necessary (Figure 6-8).

Retropharyngeal cellulitis and abscess are usually preceded by an upper respiratory infection, often with cervical adenopathy (enlargement of the cervical lymph nodes). Spread of infection along lymph channels leads to enlargement of the retropharyngeal (prevertebral) soft tissues on the lateral neck radiograph with forward displacement and bowing of the airway (Figure 6-9). As discussed earlier, CT is the imaging modality of choice for distinguishing cellulitis from an abscess, which will appear as a walled-off fluid collection needing surgical drainage.

Foreign body aspiration is the sixth most common cause of accidental death in children.[9] Often a child being evaluated for stridor has aspirated a foreign body, such as a peanut, into the bronchus and the airway is blocked, or the child has ingested an object such as a coin into the esophagus, causing compression of the trachea. The following anatomic areas within the esophagus tend to be prime locations for blockage by a foreign body: the area posterior to the cricoid cartilage at the level of C6 near the esophageal sphincter; the area where the distal aortic arch descends posterior in the midesophagus at the level of T4; and in the distal esophagus where it narrows near the lower esophageal

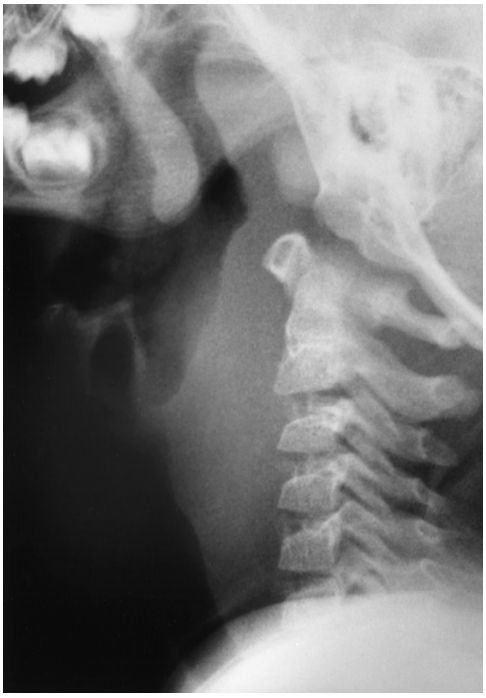


FIGURE 6-9 The hypopharynx and trachea are displaced away from the cervical spine by a retropharyngeal abscess.

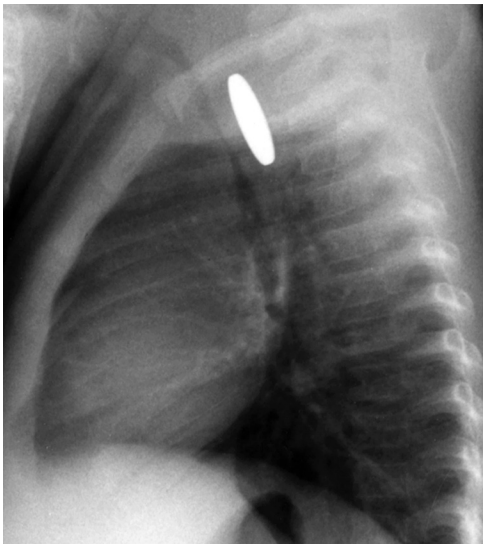


FIGURE 6-10 Edema from a coin in the upper esophagus causes marked narrowing of the adjacent trachea. The child presented with stridor and difficulty with swallowing.

sphincter.[10] If the child is suspected of ingesting a coin or other object, a lateral radiograph of the neck, AP and lateral projections of the chest, and a frontal view of the abdomen may be obtained to locate the object (Figure 6-10). However, almost 90% of foreign bodies are not visible on a conventional AP and lateral chest radiograph. Non-radiopaque objects that are aspirated may be difficult to see unless outlined by air in the trachea or bronchi. Forced expiratory chest radiographs are most useful in demonstrating the air trapping that may result when a foreign body is aspirated into a bronchus. In some instances, decubitus radiographs or fluoroscopy may be warranted. Most recently, CT of the neck and chest have been shown to provide superior imaging of foreign objects, especially indirect evidence of an obstruction such as air trapping and atelectasis.[9]

Tracheomalacia is diagnosed when the thoracic trachea abnormally collapses during expiration, leading to an expiratory wheeze. Although this may be seen in premature infants, other associations include tracheoesophageal fistula and vascular rings. The abnormal collapse may be easily demonstrated by airway fluoroscopy, which may be combined with a barium swallow to exclude a fistula or ring.[9]

RESPIRATORY DISTRESS IN THE NEWBORN

The various causes and conditions that can result in respiratory distress in the newborn may be combined under the mnemonic *CHAMPS* (Box 6-1).

One of the most common causes of respiratory distress in newborns is transient tachypnea of the newborn. Conditions that decrease the thoracic squeeze to clear the lungs of fluid at delivery include cesarean section, mild or moderate prematurity, maternal diabetes, and precipitous delivery. The radiographic findings usually show mild vascular congestion with pulmonary edema and small pleural effusions. The chest radiograph clears rapidly by 24 hours and is usually normal by 48 to 72 hours of age with conservative treatment.

Respiratory distress syndrome (RDS), or hyaline membrane disease, occurs in premature infants, particularly those younger than 36 weeks of gestation. It is caused by a deficiency in pulmonary surfactant and deficiency in alveolar surface area for gas exchange in the immature lungs.[3] By lowering the surface tension in the alveoli, surfactant prevents atelectasis. When surfactant is deficient, the chest radiograph shows the characteristic pattern of low lung volumes with a ground-glass or granular pattern of alveolar collapse surrounding **air bronchograms** (air-filled bronchus against surrounding opacified alveoli, indicating alveolar disease) (Figure 6-11).

Artificial surfactant given through the endotracheal tube may lead to rapid improvement demonstrated radiographically, but it may also lead to asymmetrical patterns of aeration if distributed unevenly. Gradual improvement over 1 week occurs with mild or moderate cases of RDS, but severe disease usually results in the chronic lung changes of bronchopulmonary dysplasia. This chronic disease is characterized by coarse, linear

Box 6-1 Respiratory Distress in the Newborn

C: Cardiac, congenital anomalies
H: Hyaline membrane disease
A: Airway
M: Meconium aspiration
P: Pneumonia
S: Surgical lesions

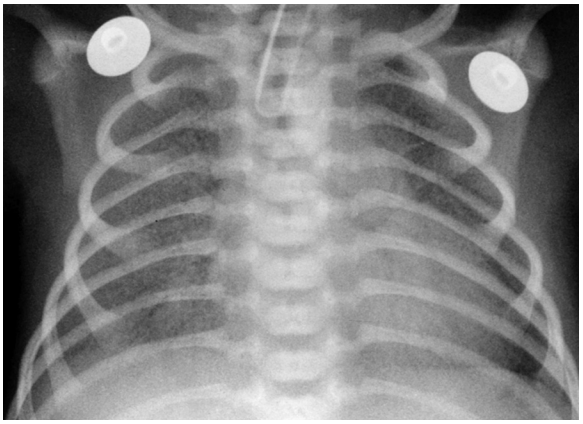


FIGURE 6-11 Even after intubation, the lungs are hypoinflated and have a granular pattern with faint air bronchograms in this infant with respiratory distress syndrome.

areas of scarring or atelectasis interspersed with areas of air trapping and shifting atelectasis. Both RDS and bronchopulmonary dysplasia may produce a variety of air leaks related to mechanical ventilation, including pneumothorax, **pneumomediastinum,** and **pulmonary interstitial emphysema.**

Pneumothoraces are the most common air leaks and are caused when air dissects in the pleural space surrounding the lung. On an AP supine chest radiograph, air is usually seen lateral to the lung but may be subpulmonic (between the lung and diaphragm) or medial (next to the heart), in the latter case mimicking a pneumomediastinum (Figure 6-12). If the hemithorax appears hyperlucent or the lateral costophrenic margin is too clearly visualized, a decubitus view or cross-table lateral view (patient supine with x-ray beam parallel to the table and passing through the patient from one side to the other side) may be helpful to exclude a pneumothorax. An upright, PA chest radiograph is preferred in older children in whom the pneumothorax accumulates above the lung apex.

When air dissects into the mediastinal tissues, it is called a *pneumomediastinum.* This air elevates the

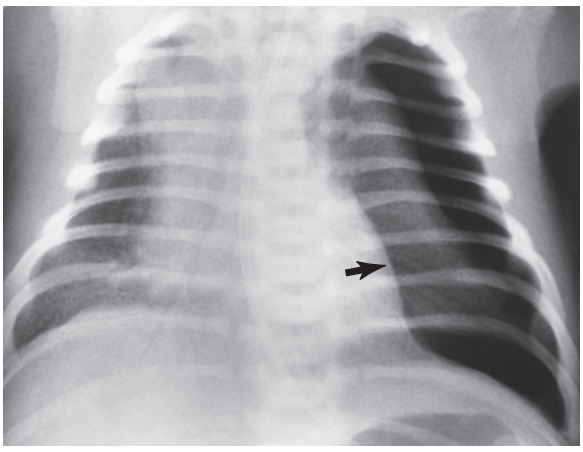


FIGURE 6-12 This large left pneumothorax appears black and outlines the partially collapsed left lung and left cardiac border *(arrow).*

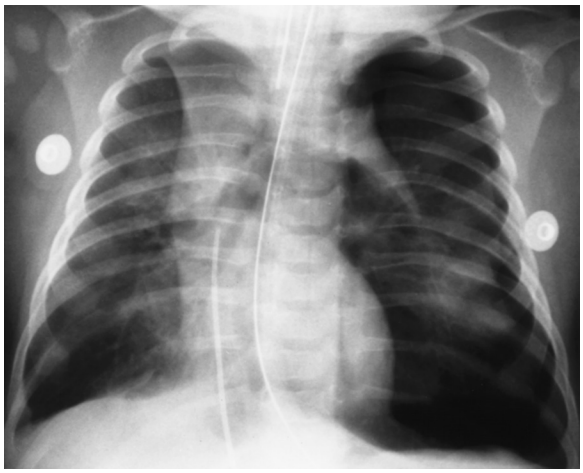


FIGURE 6-13 A pneumomediastinum elevates the left lobe of the thymus to produce a "spinnaker sail" in this child, who also has a large left pneumothorax.

thymus, producing a "spinnaker sail" appearance, and may dissect under the heart, leading to a continuous diaphragm appearance (Figure 6-13). A lateral decubitus image may cause a medial pneumothorax to shift to the elevated lateral pleural space, which distinguishes it from a pneumomediastinum. Air in a pneumopericardium surrounds only the heart and does not extend around other mediastinal structures such as the aorta. Neither a medial pneumothorax nor a pneumopericardium will elevate the thymus.

Pulmonary interstitial emphysema results from air dissecting within the interstitium of the lung. This condition appears as a diffuse pattern of random, small radiolucent bubbles combined with an irregular network of branching radiolucencies. Distribution is variable from entire lung to lobar to segmental. Interestingly, the pattern of involvement may shift from one lobe of one lung to another lobe in the other lung (Figure 6-14).

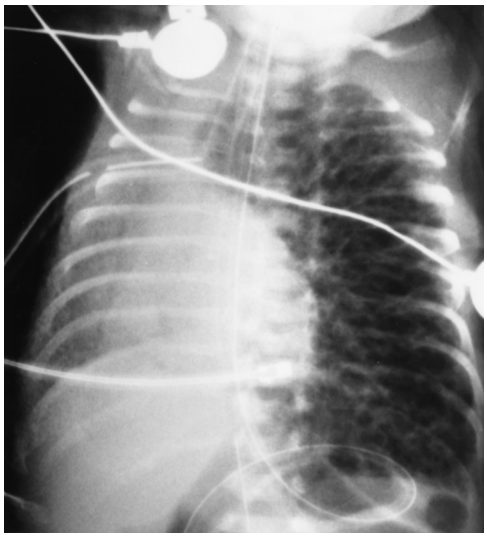


FIGURE 6-14 Massive pulmonary interstitial emphysema throughout the left lung causes shift of the mediastinum to the right and downward displacement of the left hemidiaphragm.

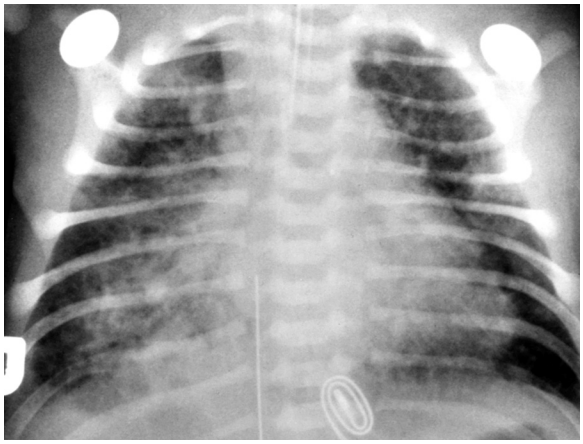


FIGURE 6-15 Meconium aspiration appears as a coarse, asymmetrical pattern. Enlargement of the heart may be secondary to fluid overload in this infant.

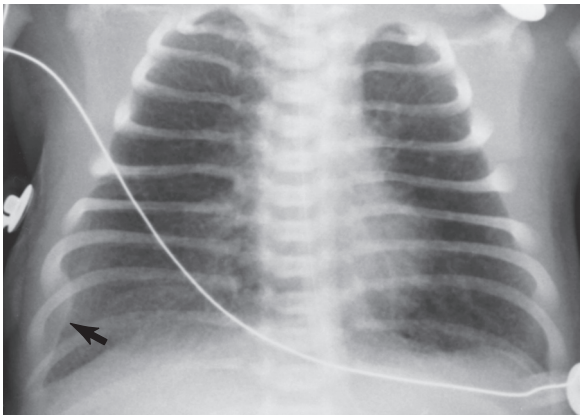


FIGURE 6-16 Group B streptococcal pneumonia presented in this infant with hyperinflation, small right pleural effusion *(arrow)*, and a hazy infiltrative pattern.

The radiographic appearance of RDS can also be complicated by the superimposition of a **patent ductus arteriosus** (in the newborn, a failure of the connection between the aorta and the pulmonary artery to close) or hemorrhage. The appearance of pleural effusions with increased heart size and edema several days after birth suggests patent ductus arteriosus. Whiteout of a lung or lobe without volume loss may result from pulmonary hemorrhage.

Although meconium staining of amniotic fluid occurs in 12% of deliveries, only 2% of these newborns develop meconium aspiration syndrome. Predisposing factors are postmaturity, intrauterine stress, and small size for gestational age. The aspirated meconium produced by the bowel plugs bronchi and produces a chemical pneumonitis. The chest radiograph is characterized by coarse, patchy opacities secondary to atelectasis from bronchial obstruction alternating with areas of hyperinflation (Figure 6-15). The severity of the radiographic abnormalities does not always correlate with the clinical severity of the disease. Likewise, an infant with relatively mild radiographic findings may be worse clinically because of persistent pulmonary hypertension. Pneumothoraces and pneumomediastinum develop in about 25% of infants with meconium aspiration syndrome. Resolution of the radiographic findings may take several weeks.

Although a variety of organisms may cause neonatal pneumonia, the most common is group B *Streptococcus*, which is usually acquired by the fetus before birth. Premature rupture of the membranes and maternal infection are predisposing factors. The radiographic findings are variable and may mimic other disease entities. For example, pneumonia may have a pattern resembling RDS; however, the presence of pleural effusions is rare in RDS but common in neonatal pneumonia (Figure 6-16). Treatment is usually begun on the basis of the clinical assumption of pneumonia, with the radiographs used to monitor progress of the disease.

Two surgical entities that may cause a cystic appearance in the lung are congenital diaphragmatic hernia and cystic adenomatoid malformation. In congenital diaphragmatic hernia, bowel herniates through the defect in the diaphragm, leading to a "cystic" appearance as the loops fill with air. If the stomach herniates as well, placement of a nasogastric tube may confirm the diagnosis. Because the bowel is in the chest, the abdomen will appear scaphoid (concave). Most hernias occur on the left. Patient outcome depends on the degree of pulmonary hypoplasia caused by compression of the developing lung tissue (Figure 6-17).

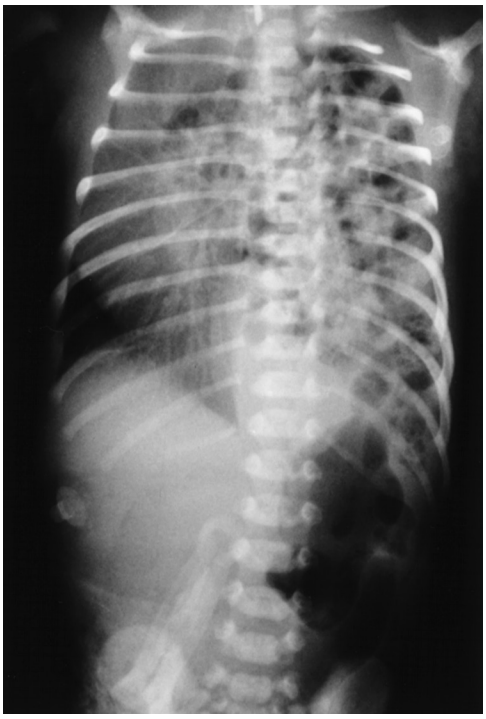


FIGURE 6-17 Multiple "cysts" in the left hemithorax are air-filled loops of bowel that herniated through a defect in the left hemidiaphragm. The abdomen is scaphoid from decreased bowel content.

Cystic adenomatoid malformation is a derangement in normal pulmonary tissue development, leading to cysts ranging from millimeters to several centimeters in size. Initially the cysts are fluid filled, but they become air filled over the first day or two of life. A large dominant cyst could mimic congenital lobar overinflation, whereas cysts appearing to fill one lung could mimic congenital diaphragmatic hernia. The presence of a normal amount of bowel in the abdomen would make a hernia unlikely.

ATELECTASIS

Atelectasis is caused by an absence of air in the lung parenchyma from myriad causes, including bronchial obstruction or extrinsic compression. Most atelectasis is subsegmental in extent and appears as discoid or plate-like opacities, often radiating from the hila or located just above the diaphragm. Segments, lobes, and entire lungs may be collapsed, or atelectatic. This loss of volume may shift fissures toward the area of atelectasis, cause a mediastinal shift toward the affected side, and elevate the ipsilateral diaphragm. Crowding of the pulmonary vascular and interstitial markings in the affected region will occur. The other lung or adjacent lobes may become more lucent secondary to hyperexpansion.

When atelectasis occurs in the right upper lobe, the minor fissure and posterior half of the major fissure shift upward. The collapsed right upper lobe appears as a triangular wedge of opacity adjacent to the superior mediastinum on the frontal radiograph and as a triangular wedge at the apex in the lateral radiograph. Because no minor fissure is present on the left, collapse of the left upper lobe appears different from the right, with the major fissure shifting in an anterior direction. The collapsed left upper lobe on frontal projection appears as opacity in the upper two-thirds of the lung that obscures superior mediastinal and left cardiac borders and lacks a sharply defined border with the aerated lower lobe (Figure 6-18). In lateral projection the left upper lobe collapses adjacent to the anterior chest wall, with the major fissure defining the edge against the lower lobe. Isolated lingular atelectasis obscures the left cardiac border.

Right middle lobe collapse is commonly seen in children with asthma and causes the major and minor fissures to approximate. The resultant triangular wedge or plate-like opacity is most diagnostic in lateral projection and extends from the hilum to the anterior chest wall (Figure 6-19). It is less defined in frontal projection and may appear as a vague loss of the right-side cardiac border.

Both right and left lower lobe atelectasis cause downward and posterior displacement of the major fissure. The lower lobe collapses toward the posterior aspect of the diaphragm on the lateral view and retrocardiac adjacent to the spine on the frontal view. The sharp border of the adjacent diaphragm becomes obscured in both projections. In the lateral radiograph the normally more lucent-appearing lower thoracic vertebral bodies appear denser than normal, because the x-ray beam must penetrate through the adjacent collapsed lower lobe. This increased density of the lower thoracic vertebral bodies has been termed the **spine sign.** Left lower lobe collapse is commonly seen in postoperative patients, especially those who have undergone cardiothoracic surgery.

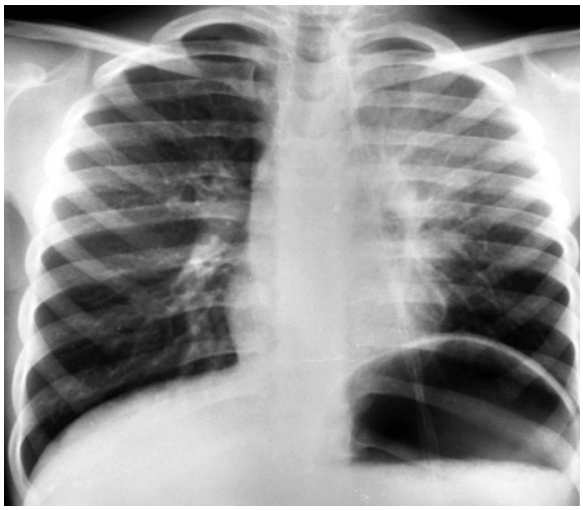


FIGURE 6-18 Left upper lobe collapse causes elevation of the left hemidiaphragm and crowding of the left ribs from volume loss. The cardiac and superior mediastinal borders are indistinct because of the "silhouette sign," whereas the diaphragm remains demarcated by the aerated left lower lobe.

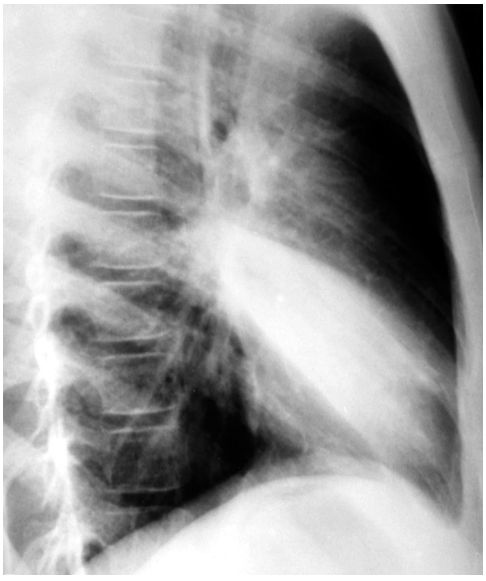


FIGURE 6-19 A collapsed right middle lobe appears as a triangular wedge of increased density extending anteriorly and inferiorly toward the anterior chest wall and diaphragm.

The previously described silhouette sign is useful in localizing suspected atelectasis. The right cardiac border loses its sharp definition with right middle lobe atelectasis, whereas the left border is associated with lingular pathology. The diaphragmatic border is lost when atelectasis or other pathology occurs in the adjacent lower lobe.

PNEUMONIA

Viruses are the most common cause of pneumonia in children, especially in the outpatient population. Often, bacterial pneumonias are superimposed over viral infections, but they may also be seen in hospitalized patients. Fungal and less common infections should be suspected in immunocompromised patients.

Infections may involve primarily the airways, mainly the peripheral airspaces, or a combination of both. Bronchiolitis in younger children and bronchitis in older children are viral infections of the airways leading to a radiographic appearance of bronchial wall thickening. Hyperinflation of the lungs and linear areas of atelectasis secondary to airway plugging by mucus are often associated with airway inflammation.

Patchy areas of poorly defined parenchymal opacification characterize bronchopneumonia. The inflammation in the airways extends outward to involve the adjacent air spaces. The opacities may be caused by the air space inflammation as well as by atelectasis from associated mucous plugging of the peripheral airways. Air bronchograms occur when the open airways are surrounded by consolidated or collapsed air spaces. Both viral and bacterial pneumonias can cause a bronchopneumonia pattern. Although it may mimic other pulmonary diseases, *Mycoplasma* presents typically as a bronchopneumonia.

Filling of the peripheral air spaces with an infectious exudate causes a dense, consolidated appearance. The involvement may be limited to a segment of lung or spread to involve the entire lobe. Bacterial infections are usually the cause of consolidated, or lobar, pneumonia.

Pneumonia may be associated with hilar adenopathy and pleural effusions. When the pleura becomes infected, the resulting empyema may need to be surgically drained. Although decubitus radiographs may be able to differentiate an uncomplicated mobile pleural effusion from loculated fluid or thickening, both ultrasound and CT can be used to better characterize the pleural fluid. Pulmonary abscesses are rare complications, but **pneumatoceles** (thin-walled, air-filled cavities in the lungs) may occur after staphylococcal pneumonia. Round pneumonias are usually of pneumococcal origin (Figure 6-20).

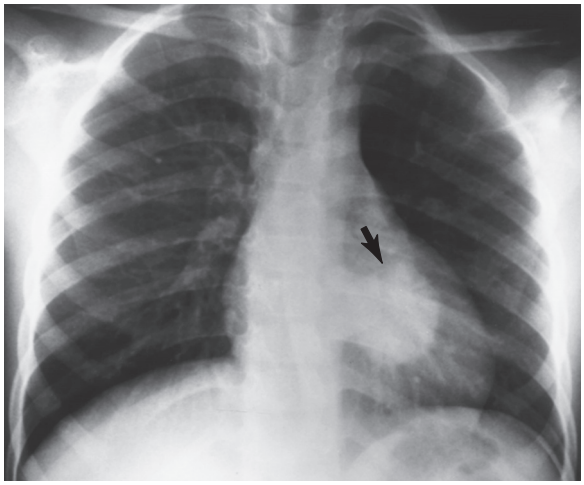


FIGURE 6-20 Round pneumonia *(arrow)* in the left lower lobe simulates a mass.

The American College of Radiology (ACR) has developed appropriateness criteria for imaging pediatric patients who present with a fever with an unknown source.[3] Although the source of a fever may be determined medically through patient evaluation, history, and laboratory tests, chest radiographs are considered appropriate in the acute evaluation of infants and children with a fever without a source, especially if the patient displays chest symptoms. Chest radiographs may also be appropriate for evaluation of a pediatric patient who does not have chest symptoms but does have a fever, oxygen saturation of 95% or lower, and a white blood cell count of 20,000/mm^3 or more.[3]

ASTHMA

Asthma is caused by recurrent bronchospasm of the large intrathoracic airways, leading to wheezing and labored breathing. Chest radiographs are usually obtained to exclude the presence of pneumonia causing the acute episode. Typical findings are hyperinflation and bronchial wall thickening. Mucous plugging of the airways may lead to atelectasis and focal air trapping. Atelectasis is the usual cause of a focal opacity in the lung. Pneumomediastinum occurs in a small percentage of children evaluated for an acute asthma attack and is a cause of acute chest pain.[12]

CYSTIC FIBROSIS

Cystic fibrosis is a genetic disorder affecting the function of exocrine glands, causing increased viscosity of the respiratory mucus. This mucus is difficult to clear from the airways, leading to obstruction and promotion of bacterial infection. Cystic fibrosis involves many organs in addition to the respiratory system. In

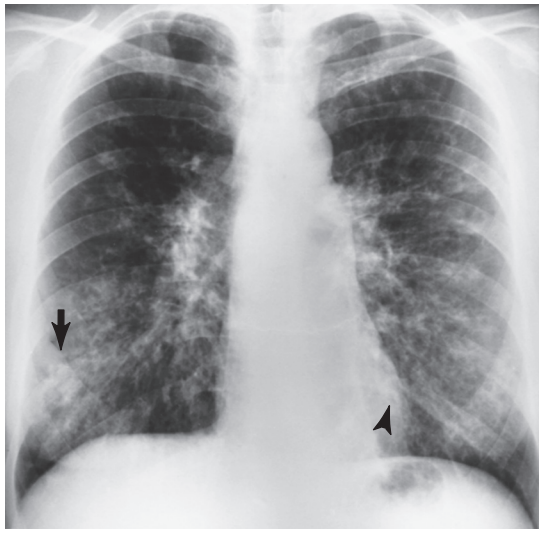


FIGURE 6-21 Coarse interstitial markings, hyperinflation, bronchiectasis, mucous plugging *(arrow)*, atelectasis *(arrowhead)*, and enlarged pulmonary hila are all demonstrated in this child with cystic fibrosis.

the respiratory system, evidence suggests that the lungs are histologically normal at birth. Pulmonary damage is initiated by gradually increasing secretions from the hypertrophy of bronchial glands, leading to obstruction of the bronchial system. The resultant plugging promotes staphylococcal infection, followed by more tissue damage, as well as atelectasis (collapse of lung tissue) and emphysema. Early childhood radiographs may show nonspecific findings of airway disease with peribronchial thickening, atelectasis, and air trapping. These early changes are similar to the chest radiographs of a patient with asthma. As the disease progresses, fingerlike mucoid impaction of the airways may be demonstrated along with abnormal dilation of the airways, called **bronchiectasis,** lobar atelectasis, scarring, pulmonary artery and right ventricular enlargement, and overinflation of the lung and chest wall. Recurrent infections are common. Striking hyperinflation is seen in older patients, often with enlarged hila from pulmonary hypertension (Figure 6-21). Current guidelines from the American Cystic Fibrosis Foundation suggest consideration of annual chest radiographs in addition to pulmonary function testing (PFT) to evaluate lung damage.[13]

ACUTE RESPIRATORY DISTRESS SYNDROME

Although originally described in adults, acute respiratory distress syndrome may occur in children as well. These patients present initially with either sepsis, pneumonia, near drowning, inhalation injury, aspiration, or trauma. The acute lung insult can lead to increased capillary permeability, pulmonary edema, surfactant inactivation, alveolar filling, and

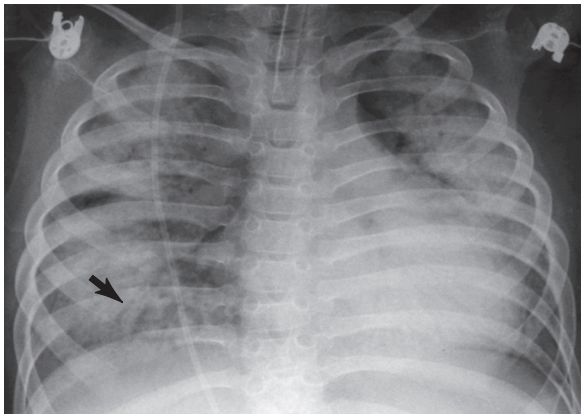


FIGURE 6-22 Pneumonia was the precipitating precursor to acute respiratory distress syndrome, with densely consolidated lungs and air bronchograms *(arrow)*.

reduced lung compliance. This leads to profound hypoxemia and acute respiratory distress syndrome. The disease passes through stages of acute lung injury, exudative alveolitis, fibroproliferative repair, and finally recovery if the patient survives. The mortality rate is high. Pneumothoraces and pneumomediastinum are common complications (Figure 6-22).[14]

CHEST TRAUMA

When an injured child is evaluated in the emergency department, initial radiographs to screen for trauma usually include an AP projection of the chest. Lines and tubes inserted at the accident site or on arrival in the emergency department should be assessed for position and effectiveness. A right mainstem intubation may lead to collapse of the left lung. The position of a chest tube may not be optimal for evacuating a pneumothorax, and the nasogastric tube may need to be advanced into the stomach.

Consolidation in a patient with blunt trauma may result from pulmonary contusion with hemorrhage into the air spaces. Aspiration leading to patchy consolidation in the upper lobes should be considered in patients who have lost consciousness. Laceration of the lung may lead to cysts in the parenchyma, as well as a pneumothorax. The rib cage should be evaluated for fractures, especially adjacent to an area of lung injury. Multiple contiguous rib fractures may result in a flail chest (three or more rib fractures resulting in paradoxical motion of the chest wall with respiration) with associated ventilation difficulties (Figure 6-23).

Widening of the superior mediastinum suggests hemorrhage, which could be venous or related to aortic injury. Traumatic aortic rupture is rare in children, unlike in adults. Small children have prominent thymic tissue, as mentioned earlier in this chapter,

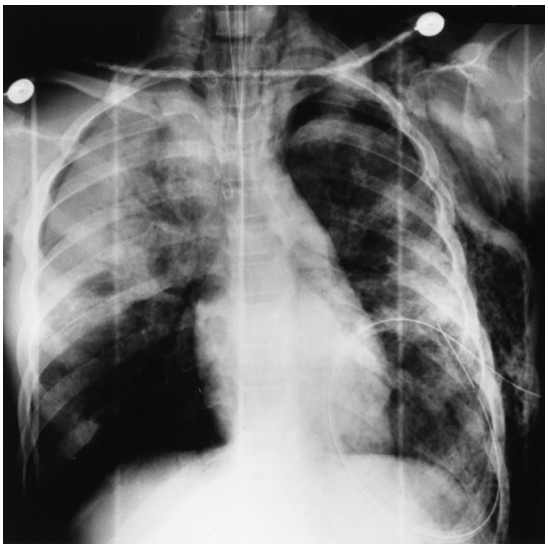


FIGURE 6-23 Trauma to the chest resulted in extensive bilateral air leaks and densely consolidated pulmonary contusions. Multiple rib fractures are present.

and this should be excluded as the cause of mediastinal widening. Tracheal and bronchial fractures are rare but cause massive air leaks. Enlargement of the cardiac silhouette from a traumatic pericardial effusion is rare.

When significant chest injury is suspected clinically or demonstrated on chest radiographs, CT of the chest more clearly demonstrates the extent of the injury than conventional radiographs. These are often rapidly performed in conjunction with imaging of the abdomen. Lung and mediastinal injury and placement of chest tubes can be further clarified. More injury is often shown by chest CT examination than was suspected on chest radiographs. Not uncommonly, small pneumothoraces are found by sonography or CT that cannot be seen on conventional radiographs. CT angiography of the chest has supplanted catheter aortography for exclusion of aortic injury.

Key Points

- *Position* refers to the arrangement of the patient's body, and *projection* refers to the path of the x-ray beam.
- The PA and AP projection demonstrates chest anatomy in relation to right and left sides of the body. The lateral projection demonstrates the anatomic structures from anterior to posterior. The lateral decubitus position is a frontal projection performed with the patient lying on either the right or left side.
- The normal structures that are visualized on a chest radiograph are distinguishable because of differences in the absorption of the x-ray beam. Bone and metallic orthopedic hardware appear white, well-expanded lungs appear relatively black, and soft tissue organs and fluid usually appear as shades of gray.
- The endotracheal tube should be located between the thoracic inlet and the carina.
- The tip of the UVC should be located in the inferior right atrium or right atrial junction. The tip of the UAC should be within the aorta at the T6-T10 level above the celiac, superior mesenteric, and renal arteries. The tip of an internal jugular catheter for CVP should be in the distal superior vena cava just above the right atrium. The tip of PICC lines placed in the upper extremities should be located in the superior vena cava close to the right atrium. The tip of indwelling central venous catheters such as a Port-a-Cath should be placed in the superior vena cava.
- Chest radiography is appropriate in neonates to evaluate for a fever without a source, RDS, pneumonias, congenital diaphragmatic hernias, and cystic adenomatoid malformation.
- Atelectasis may affect segments, lobes, or the entire lung. The collapsed right upper lobe appears as a triangular wedge of opacity adjacent to the superior mediastinum in the frontal radiograph and as a triangular wedge at the apex in the lateral radiograph. The collapsed left upper lobe appears as opacity in the upper two-thirds of the lung, obscuring the superior mediastinal and left cardiac borders on the frontal projection and the left upper lobe collapsing adjacent to the anterior chest wall on the lateral projection. Right middle lobe collapse is best visualized on the lateral projection as a triangular wedge or platelike opacity extending from the hilum to the anterior chest wall. Both right and left lower lobe atelectasis cause downward and posterior displacement of the major fissure.
- The radiographic appearance of cystic fibrosis in early childhood demonstrates nonspecific findings of airway disease with peribronchial thickening, atelectasis, and air trapping. As the disease progresses, fingerlike mucoid impaction of the airways may be demonstrated along with bronchiectasis, lobar atelectasis, scarring, pulmonary artery and right ventricular enlargement, and overinflation of the lung and chest wall.
- Chest trauma resulting in pulmonary contusion often is demonstrated radiographically as consolidation from hemorrhage into the air spaces. Aspiration pneumonia demonstrated as patchy consolidation in the upper lobes should be considered in the patient with loss of consciousness. Laceration of the lung may lead to pneumothorax, atelectasis, and cyst formation within the lung parenchyma. Multiple contiguous rib fractures may result in a flail chest with associated ventilation difficulties. To reduce patient radiation dose, sonography is an alternative imaging modality in cases of chest trauma.

Assessment Questions

See Evolve Resources for answers.

1. A mother states that she found her 18-month-old child choking near an open can of peanuts. Which set of chest radiographs would most likely suggest airway obstruction?
   - **A.** Frontal and bilateral oblique
   - **B.** Frontal inspiratory and frontal forced expiratory
   - **C.** Frontal and lateral
   - **D.** Frontal and left-side-down lateral decubitus
2. The normal thymus has a characteristic appearance with which of the following radiographic findings?
   - **I.** Displacement of the trachea to the opposite side of the mediastinum
   - **II.** Appearance of a sail
   - **III.** Wavy margins
     - **A.** I and II only
     - **B.** I and III only
     - **C.** II and III only
     - **D.** I, II, and III
3. A pneumothorax is suspected on the left in a child's portable radiograph from the intensive care unit. Which of the following may better image and confirm a suspected pneumothorax?
   - **I.** Cross-table lateral
   - **II.** Upright frontal
   - **III.** Left-side-down decubitus
   - **IV.** Right—down decubitus
     - **A.** I, II, and III only
     - **B.** I, II, and IV only
     - **C.** I, III, and IV only
     - **D.** II, III, and IV only
4. Subglottic edema causing a "church steeple" appearance of the trachea on the frontal neck radiograph is characteristic of which infection?
   - **A.** Retropharyngeal abscess
   - **B.** Epiglottitis
   - **C.** Adenoiditis
   - **D.** Croup
5. Before intubation, the chest radiograph of a premature newborn reveals low lung volumes and diffuse ground-glass opacification of the lungs. These radiographic findings are most characteristic of _____.
   - **A.** Meconium aspiration
   - **B.** Respiratory distress syndrome
   - **C.** Bronchopulmonary dysplasia
   - **D.** Transient tachypnea of the newborn
6. The initial chest radiograph of a neonate in severe respiratory distress and who has a scaphoid abdomen reveals multiple round air-filled structures in the left side of the chest, displacing the mediastinum to the right. The most likely cause is _____.
   - **A.** Congenital adenomatoid malformation
   - **B.** Pulmonary interstitial emphysema
   - **C.** Congenital diaphragmatic hernia
   - **D.** Staphylococcal pneumonia
7. Left lower lobe collapse (atelectasis) is associated with which of the following radiographic findings?
   - **I.** Loss of the left-side heart border
   - **II.** Loss of the left hemidiaphragm border
   - **III.** Increased retrocardiac density
   - **IV.** "Spine sign"
     - **A.** I, II, and III only
     - **B.** I, II, and IV only
     - **C.** I, III, and IV only
     - **D.** II, III, and IV only
8. Pneumatoceles are occasionally seen as a complication of which of the following infections?
   - **A.** Mycoplasmal
   - **B.** Viral
   - **C.** Streptococcal
   - **D.** Staphylococcal
9. Which of the following is a hallmark of cystic fibrosis and is *not* also seen with asthma?
   - **A.** Hyperinflation
   - **B.** Atelectasis
   - **C.** Bronchiectasis
   - **D.** Airway disease
10. CT of the chest in a pediatric trauma patient are not routinely obtained because of _____.
    - **A.** The high radiation dose
    - **B.** The time necessary to complete the scan
    - **C.** A contraindication to the use of intravenous contrast agents
    - **D.** The additional costs associated with CT

REFERENCES

1. Image Gently. *The Alliance for Radiation Safety in Pediatric Imaging*. Available at http://www.imagegently.org/. Accessed December 29, 2016.
2. Kowalczyk N. *Radiographic pathology for technologists*. 7th ed. St. Louis: Mosby/Elsevier; 2017.
3. American College of Radiology Appropriateness criteria. *Pediatric Imaging*. http://www.acr.org/Quality-Safety/Appropriateness-Criteria/Diagnostic/Pediatric-Imaging. Accessed January 17, 2013.
4. Mong A, Epelman M, Darge K. Ultrasound of the pediatric chest. *Pediatr Radiol*. 2012;42:1287-1297.
5. Volpicelli G, Elbarbary M, Blaivas M, International Liaison Committee on Lung Ultrasound for the International Consensus Conference on Lung Ultrasound, et al. International evidence-based recommendations for point-of-care lung ultrasound. *Intensive Care Med*. 2012;38:577-591.

6. Menashe SJ, Iyer RS, Parisi MT, et al. Pediatric chest radiographs: common and less common errors. *AJR*. 2016;207:903-911.
7. Concepcion NDP, Laya BF, Lee EY. Current updates in catheters, tubes, and drains in the pediatric chest: a practical evaluation approach. *Eur J Radiol*. 2016. http://dx.doi.org/10.1016/j.ejrad.2016.06.015.
8. Harris EA, Arheart KL, Penning DH. Endotracheal tube malposition within the pediatric population: a common event despite clinical evidence of correct placement. *Can J Anaesth*. 2008;55(10):685-690.
9. Hegde SV, Hui PK, Lee EY. Tracheobronchial foreign bodies in children: image assessment. *Semin Ultrasound CT MR*. 2015;36(1):8-20.http://dx.doi.org/10.1053/j.sult.2014.10.001.
10. Pinto A, Lanza C, Pinto F, Grassi R, Romano L, Brunese L, Giovagnoni A. Role of plain radiography in the assessment of ingested foreign bodies in pediatric patients. *Semin Ultrasound CT MR*. 2014. http://dx.doi.org/10.1053/j.sult.2014.10.0018.
11. McCance KL, Heuther SE, Brashers VL, et al. *Pathophysiology: the biologic basis for disease in adults and children*. 6th ed. St. Louis: Mosby/Elsevier; 2010.
12. Kirks DR. *Practical pediatric imaging: Diagnostic radiology of infants and children*. 3rd ed. Philadelphia: Lippincott-Raven; 1998.
13. Borowitz D, Parad RB, Sharp JK, et al. Cystic Fibrosis Foundation practice guidelines for the management of infants with cystuc fibrosis transmembrane conductance regulator-related metabolic syndrome during the first two years of life and beyond. *J Pediatr*. 2009;155(suppl 6):S106-116.
14. Kuhn JP, Slovis JP, Haller JO, et al, eds. *Caffey's pediatric diagnostic imaging*. 10th ed. Mosby: Philadelphia; 2004.

Pediatric Flexible Bronchoscopy

7

Hussam Sameer Inany

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. Identify common indications for different types of flexible bronchoscopy in infants and children and the differences between rigid and flexible bronchoscopy.
2. Prepare equipment and the patient for a flexible bronchoscopy procedure.
3. Monitor a patient during a flexible bronchoscopy, including what complications to watch for during and after the procedure.
4. Clean and disinfect bronchoscopes after procedures.

Key Terms

bronchiectasis
bronchoalveolar lavage (BAL)
bronchomalacia
conscious sedation
endobronchial ultrasound
flexible fiberoptic bronchoscopy
high-level disinfection
laryngeal web
laryngomalacia
papillomatosis
rigid bronchoscopy
stridor
tracheomalacia
transbronchial biopsy
vocal cord dysfunction

Flexible fiberoptic bronchoscopy was initially performed in adults because of the relatively large size of the fiberscopes. It was first described in young children in 1978.[1] Pediatric flexible bronchoscopy is now performed by many medical specialists, including pediatric pulmonologists, otolaryngologists, surgeons, anesthesiologists, and pediatric intensivists. It is done in a variety of settings, including bronchoscopy suites, operating suites, intensive care units, and procedure rooms. Flexible bronchoscopes help in evaluating the anatomy and the function of the upper and lower airways. With its assistance in performing specialized procedures such as **bronchoalveolar lavage (BAL)** and **transbronchial biopsy,** flexible bronchoscopy has been a major tool in the assessment and treatment of children with respiratory diseases.

INDICATIONS

Flexible bronchoscopy is indicated when the information needed for management cannot be obtained by noninvasive methods or for diagnostic and therapeutic purposes (Box 7-1). As with any invasive procedure, the potential benefits to be gained in any given patient must be weighed against the risks of the procedure, even the most minor risk.

DIAGNOSTIC BRONCHOSCOPY

For diagnostic purposes, persistent or recurrent respiratory symptoms are the most common indication for flexible bronchoscopy. These symptoms may include stridor, an abnormal voice, wheeze, cough, and recurrent or persistent abnormalities on chest radiography.

Box 7-1 Indications for Flexible Bronchoscopy

DIAGNOSTIC

Airway Anatomy Evaluation
- Fistulas
- Hemangiomas or tumors
- Stenoses or strictures
- Tracheal bronchus
- Tracheostomy evaluation
- Vascular rings
- Congenital anomalies

Biopsy
- Evaluation for rejection posttransplant
- Infections
- Interstitial lung disease
- Lymphadenopathy
- Masses

Cytopathology
- Lipid-laden macrophages
- Hemosiderin-stained macrophages
- Malignant cells

Microbiology
- Bacteria
- Fungi
- *Pneumocystis*
- *Mycobacterium tuberculosis*
- Viruses

Foreign Body Aspiration

Functional Airway Evaluation
- Laryngomalacia, tracheomalacia, bronchomalacia
- Vocal cord dysfunction or paralysis
- Persistent hoarseness

Inhalation Injury
- Hemoptysis
- Recurrent pneumonia

THERAPEUTIC
- Airway dilation
- Atelectasis
- Endotracheal intubation
- Foreign body aspiration
- Instillation of medication
- Laser therapy

Stridor

Stridor is a high-pitched wheeze produced by turbulent airflow through a partially obstructed airway. It can be inspiratory, expiratory, or biphasic. Inspiratory stridor is most commonly a result of an extrathoracic obstruction. Expiratory stridor or mixed expiratory and inspiratory stridor is typically a result of intrathoracic obstruction. Because stridor always has an anatomic basis, visual inspection of the airway is usually required for definitive diagnosis. It is the most common indication for diagnostic flexible bronchoscopy in infants. The possible causes of recurrent or persistent stridor include laryngeal pathology, subglottic stenosis, mass or tumor, extrinsic compression of the tracheobronchial tree, and vocal cord paralysis. **Vocal cord dysfunction** (VCD), an uncontrolled adduction of the vocal cords, is seen in older children and adolescents.

Stridor often varies in intensity depending on the extent of a child's activity or agitation, which increases the child's minute ventilation. This increase in airflow results in louder stridor. Thus stridor is a dynamic process in children, and flexible bronchoscopy is ideally suited for its evaluation. Because flexible bronchoscopy can be performed on a sedated but spontaneously breathing patient, the dynamics of the airways are preserved without disruption by general anesthesia, positive-pressure ventilation, or the oral approach of **rigid bronchoscopy.** Of all indications of diagnostic pediatric flexible bronchoscopy, stridor receives the highest diagnostic yield for the procedure, identifying specific lesions in more than 80% of patients.[2,3]

The most common cause of inspiratory stridor in neonates is **laryngomalacia,** the inward collapse of the softer-than-normal cartilage of the upper airway over the airway opening during inspiration. It is a congenital condition that tends to disappear by 12 to 18 months. The condition occurs in three patterns:
- The prolapse of one or both arytenoids into the supraglottic space during inspiration
- The lateral infolding across the airway of a soft epiglottis that is more omega-shaped than crescent-shaped in a young infant
- The anteroposterior bending of a soft epiglottis across the supraglottic space

Other laryngeal lesions that can produce stridor include unilateral or bilateral vocal cord paralysis from congenital lesions, birth trauma, or recurrent laryngeal nerve injury after thoracic surgery; laryngeal **papillomatosis;** and **laryngeal webs.** Inspiratory or biphasic stridor may also arise from subglottic lesions, such as congenital or acquired subglottic stenosis, subglottic edema resulting from infection or chronic aspiration, subglottic hemangiomas, or as a complication from prolonged intubation.

Tracheomalacia, caused by a congenital or acquired weakness in tracheal cartilaginous support, may cause inspiratory stridor but is more often associated with biphasic or expiratory stridor. Tracheomalacia may be seen in up to one-third of patients with laryngomalacia. It is also present when a tracheoesophageal fistula (TEF) or vascular ring deforms the tracheal cartilage. It can be acquired as a complication of TEF surgical repair. If the weakness in support extends into the mainstem bronchi, the condition is termed **bronchomalacia.**

Additional causes of expiratory stridor include extrinsic tracheal or bronchial obstruction from vascular

rings or slings, anomalous arteries, congenital heart disease, hilar adenopathy, and mediastinal masses.

Wheeze

Recurrent wheezing, a high-pitched, whistling sound, is another common respiratory symptom in the pediatric population. Wheezing usually results from a more distal site of airway obstruction than does stridor. The most common cause of recurrent wheezing in children is asthma, and most patients with asthma do not require bronchoscopy as part of their evaluation. Exceptions include asthmatics with recurrent or persistent atelectasis (lung collapse) or when associated with signs and symptoms of chronic aspiration. A flexible bronchoscopic evaluation is often indicated to investigate other causes of wheezing, particularly when the wheezing is unilateral, is present at birth or at a young age, or is refractory to asthma medications. Other causes of wheezing include anatomic abnormalities of the airway (e.g., bronchomalacia, stenosis, and extrinsic compression of the left mainstem bronchus from a dilated heart), anomalies of the great vessels (vascular ring), recurrent aspiration, and foreign body aspiration.

Cough

Bronchoscopy is indicated in cases of chronic refractory cough, particularly in the presence of **bronchiectasis**—that is, chronic irreversible dilation of the airway that is mostly secondary chronic inflammation or infection in an area of lung. There is little role for bronchoscopy in evaluating the cough that accompanies common childhood conditions such as upper and uncomplicated lower respiratory tract infections, sinusitis, postnasal drip syndrome, and exposure to environmental irritants. On the other hand, bronchoscopy should be considered to evaluate the possibilities of gastroesophageal reflux or aspiration, anatomic abnormalities of airways or large vessels, and any occult endobronchial lesions or foreign bodies, as well as to obtain culture from BAL specimens in children who are not responding to antibiotic therapy (e.g., cases of protracted bacterial bronchitis).

Radiographic Abnormalities

Flexible bronchoscopy is indicated in the evaluation of a number of radiographic abnormalities in children, including recurrent or persistent atelectasis or infiltrate, bronchiectasis, localized pulmonary consolidation or hyperinflation, recurrent pneumonia, and focal atelectasis. Often, airway anatomic anomalies, mucous plugs, or unsuspected foreign body aspiration may be found. Children with lobar atelectasis or consolidation who have failed medical management may benefit from direct instillation of mucolytic agents and removal of mucous plugs via flexible bronchoscopy. Biopsies may also be obtained using flexible bronchoscopes that include mucosal brush biopsies for the evaluation of ciliary motion and ultrastructure, transbronchial biopsies to evaluate for the presence of rejection or infection in lung transplant patients, and biopsies obtained with ultrasound or computed tomography (CT)–guided transthoracic fine needle aspiration (FNA) for mediastinal masses and lymphadenopathy evaluation.

Foreign Body Aspiration

When the presence of a foreign body is confirmed or highly suspected either by radiographic evaluation or by history, the preferred approach is to identify and remove the foreign body by rigid bronchoscopy, because it allows better ventilation of the patient under general anesthesia and facilitates safer delivery of large foreign bodies through the subglottic area and the larynx. If a foreign body is discovered and removed using a rigid bronchoscope, a flexible bronchoscope can be used to evaluate the rest of the airways to rule out the presence of a residual foreign body. A flexible bronchoscope can also be used to rule out the presence of a foreign body in the lower airways of children in whom the diagnosis is suspected and the evaluation using rigid bronchoscopy was negative, because rigid bronchoscopy is mainly used to rule out the presence of foreign bodies in the trachea and mainstem bronchi.

Hemoptysis

Hemoptysis is an uncommon symptom in the pediatric population. It mostly results from infections, a problem with related artificial airway, tracheostomies, primary alveolar hemorrhage, or congenital vascular anomalies.[4]

Flexible bronchoscopy may be indicated in pediatric patients with hemoptysis for airway inspection and localization of their bleeding site, especially in the absence of a predisposing cause or clear explanation for hemoptysis (e.g., infection, underlying lung disease or bronchiectasis). It can be useful for therapeutic purposes as well, for removal of blood clots and placement of single-lumen or double-lumen endotracheal tubes and balloon catheters to tamponade (i.e., to exert direct pressure on) a bleeding site in the airway. In situations with massive hemoptysis or brisk bleeding, however, the flexible bronchoscope is usually inadequate because of its limited visualization and suction capabilities compared with the rigid bronchoscope.

Hyperlucency

Flexible bronchoscopy is useful in evaluating hyperlucencies noted in chest radiograph in the absence of an identified cause. Hyperlucency can be a result of air trapping in the setting of intrinsic obstruction (e.g., foreign body, bronchomalacia, granulation tissue) or extrinsic compression related to lymphadenopathies, aberrant blood vessels, or mediastinal masses.[4]

Inhalation Injury

In patients with acute inhalation of a toxic or heated gas, flexible bronchoscopic evaluation of the upper and lower airways can be helpful in evaluating the extent of injury and determining the therapy and level of respiratory support needed. The decision for elective intubation with the assistance of bronchoscopy may be made if significant laryngeal edema is visualized.

ENDOBRONCHIAL ULTRASOUND

The use of an adult **endobrachial ultrasound** (EBUS) scope for performing EBUS transbronchial needle aspiration (TBNA) in children was first reported in 2009.[5]

A wide variety of diseases in children can present with peripheral pulmonary nodules that require histologic diagnosis, such as infectious or inflammatory primary and secondary malignancies and posttransplant lymphoproliferative disease.

Thoracoscopy, open thoracotomy, and percutaneous biopsy were previously required to obtain histologic specimens in patients with such findings. They are associated with a significant morbidity rate during and after the procedure. EBUS could provide a safe alternative to open lung biopsy or percutaneous interventional radiologic techniques.

Two types of EBUS exist: radial probe EBUS and the linear (convex) probe EBUS. The radial probe EBUS was the first to be used. It is performed by passing a miniature ultrasound probe inside a guide sheath through the working channel of the flexible bronchoscope into an area of the airway identified using images obtained before the procedure. The characteristic "snowstorm" appearance represents tissue displacing normal lung when the probe is either within or adjacent to the peripheral lesion and can be used to guide sampling.[6,7] The probe is then removed and biopsy forceps or a brush are passed through the guide sheath to collect specimens.

The linear probe EBUS (Figure 7-1) is more recent and allows real-time ultrasound guidance. A dedicated bronchoscope with a linear ultrasound transducer allows real-time endobronchial ultrasound-guided transbronchial needle aspirates (EBUS-TBNA) to be performed. The probe is provided with a balloon that can be inflated with saline to improve the image by securing good contact with the airways. Doppler mode can be used to confirm blood flow in suspected vascular structures. After identifying the lesion, the sample is then obtained by passing the needle through the working channel of the bronchoscope.[6,7]

THERAPEUTIC BRONCHOSCOPY

The flexible bronchoscope is an excellent therapeutic tool. It is useful in placing an endotracheal tube in difficult intubation cases (e.g., patients with craniofacial abnormalities). Flexible bronchoscopy is also used for direct instillation of medications such as *N*-acetylcysteine (Mucomyst), dilute sodium bicarbonate, or recombinant human deoxyribonuclease I (DNase) into a specific area of the airway to help dislodge retained secretions or viscous mucous plugs before bronchoscopic suctioning. The flexible bronchoscope has also been used to administer surfactant in patients with acute respiratory distress syndrome. Laser surgery of airway lesions can be done through a flexible bronchoscope, but a rigid scope allows for mechanical and laser resection and for better control of bleeding complications.

FIGURE 7-1 Linear probe endobronchial ultrasound (EBUS).

FLEXIBLE NASOPHARYNGOSCOPY

The flexible bronchoscope may also be used for examination of the nasopharynx. However, the flexible nasopharyngoscope is more convenient for this purpose. The procedure is performed on an awake patient with only local anesthesia. In a tertiary center it is customary for our ear, nose, and throat (ENT) colleagues to perform this examination. This type of examination might be performed in the pulmonary function laboratory by a pulmonologist in the context of a VCD evaluation. This technique is useful to examine the upper airway for foreign bodies, polypoid disease, mass lesions, adenoidal anatomy, and septal anatomy and to

obtain a dynamic view of palatal, laryngeal, and vocal cord function. Examination of the airway below the vocal cords is reserved for the flexible and rigid bronchoscopes.

CONTRAINDICATIONS

Flexible bronchoscopy has been shown to be a safe procedure, even when performed on ill pediatric patients. However, certain conditions can place a patient at risk for complications (Box 7-2). Contraindications to flexible bronchoscopy are mainly relative, with some absolute contraindications including absence of informed consent, inadequate facility, inexperienced provider, hemodynamic instability, uncorrected coagulopathy, life-threatening arrhythmias, and severe refractory hypoxemia.[4] If it is determined by a trained specialist that the possible benefit of bronchoscopy outweighs the risks, and appropriate equipment and personnel are available, then the procedure may be performed.

Flexible bronchoscopy can cause hypoxemia, most often as a result of occlusion of the airway by the bronchoscope during the procedure, and hypoventilation or apnea from sedation. Pulse oximetry and cardiac and respiratory tracings should be continuously monitored during and after the procedure. Supplemental oxygen should be provided to maintain normal oxygen saturation. If the patient is already hypoxemic, flexible bronchoscopy can further worsen the hypoxemia and place the patient at serious risk. Flexible bronchoscopy through a laryngeal mask airway (LMA) may improve the safety of the procedure. Patients with impending respiratory failure may be electively intubated before the bronchoscopy, in anticipation of worsening ventilation and oxygenation during and after the procedure.

Box 7-2 Contraindications to Flexible Bronchoscopy

ABSOLUTE CONTRAINDICATIONS
- Absence of informed consent
- Cardiovascular instability
- Inability to oxygenate the patient adequately
- Inadequate facilities and personnel
- Uncontrolled coagulopathy or bleeding
- When risks outweigh benefits

RELATIVE CONTRAINDICATIONS
- Severe bleeding diatheses or coagulopathy
- Hypercapnia with acidosis
- Hypoxemia
- Severe pulmonary hypertension
- Severe upper airway obstruction
- Superior vena cava obstruction
- Uncooperative patient
- Uncontrolled asthma
- Uremia

Elective flexible bronchoscopy should not be performed in a patient who has cardiovascular instability, uncontrolled asthma, coagulopathy, pulmonary hypertension, severe upper airway obstruction, or superior vena cava obstruction until these conditions are stabilized. It should be performed selectively and with great caution in patients with acute laryngotracheitis because of the risks of sudden laryngospasm during the procedure and additional postprocedural airway edema that may severely compromise an already swollen airway. The bronchoscope should never be inserted forcefully past any area of airway narrowing, to avoid further injury and compromise to that site. As noted earlier, the strong suspicion of foreign body aspiration is a relative contraindication to flexible bronchoscopy and an indication for rigid bronchoscopy.

EQUIPMENT

The equipment required to perform flexible bronchoscopy are: Flexible bronchoscope and an image processor with a light source

FLEXIBLE BRONCHOSCOPE

The flexible bronchoscope (Figure 7-2) parts are (1) the control handle, (2) a flexible shaft, and (3) the distal tip.

Control Handle

The control handle (Figure 7-3) directs the insertion and movement of the scope. The control handle contains an angulation lever to flex and extend the distal tip. The larger scopes (>2.2 mm outer diameter [OD]) have a suction port with or without a button that activates suction through the suction channel.

FIGURE 7-2 Flexible bronchoscope.

FIGURE 7-3 **A,** Control handle with the angulation lever. The working channel is visible on the right side of the photograph. **B,** The control handle with the suction adapter connected to the suction tube. The working channel is on the right side of the photograph.

The control handle also contains an opening port to which syringes attach for airway lavage, and instruments (forceps, brush) may be passed through the port for the collection of airway specimens. A suction adapter extends from the control handle of the bronchoscope and attaches to tubing connected to the suction source.

Flexible Shaft and Distal Tip

The flexible shaft contains lighting cables, imaging cables, and the working channel. The distal tip (Figure 7-4) is the part of the bronchoscope that contains the camera, opening of the suction and instrument channel, and the light guide. The instruments most often used in pediatric patients range in OD from 2.2-mm scopes for neonates, to 2.8- to 3.7-mm scopes for older children, and 4.7- to 6.3-mm scopes for adolescents.

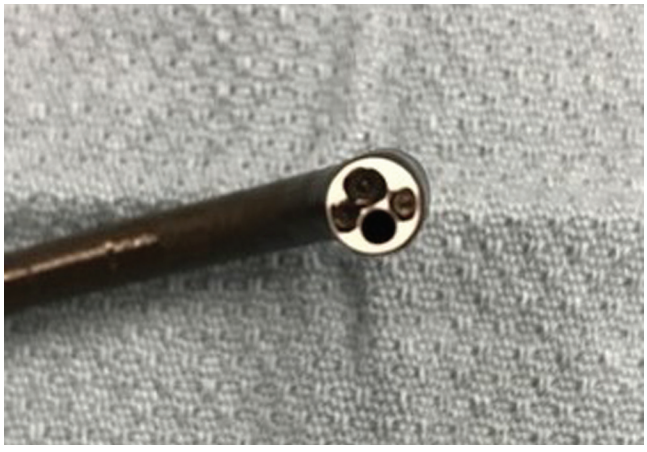


FIGURE 7-4 Distal tip of a 5.0-mm outer diameter bronchoscope with two light bundles, a camera (11 o'clock), and a working and suction port opening (5 o'clock).

The tubes of the thinner bronchoscopes, 2.2 mm or smaller in diameter, contain only light and image bundles. They have been nicknamed "spaghetti scopes," and their use is limited to visualization of an airway via insertion down an endotracheal tube.

Larger, flexible bronchoscopes have two control cables aligned 180 degrees from each other that connect a hinged bending section at the distal tip of the tube to a control lever at the head of the scope. These cables allow the operator to flex and extend the distal tip of the bronchoscope to direct the passage of the scope through the airways. The 2.2-mm scopes have this directable capability, but they lack the suction channel. The larger scopes contain suction channels, varying in diameter from 1.2 mm in the 2.8- to 3.7-mm scopes to 3.2 mm in the 6.3-mm scopes. These suction channels allow for the suction of airway secretions, the instillation of lavage fluids or medications into the airway, and the passage of brushes and biopsy forceps for obtaining airway cytology and pathology specimens. The channel, direction cables, and fiberoptic bundles are enmeshed in a woven metal sheath and then enclosed in a nonlatex flexible plastic membrane.

Light Source and Image Processors

The light source of the flexible bronchoscope transmits the light from the working tip to the image processor that can be used to adjust the intensity, color, and brightness of the light and the acquired images. The image

FIGURE 7-5 Bronchoscope cart showing (from top to bottom): Monitor, light source and image processor, and a dedicated computer with high-capacity digital storage.

processor (Figure 7-5) can also store images and videos for future review.

Images are transmitted in one of two ways, the fiberoptic transmission or digital video transmission:

- Fiberoptic transmission was the first method used for image transmission; images are transmitted using fiberoptic bundles that consist of thousands of tiny glass fibers that are coated with a highly reflective glass material. These fibers transmit light and images by internal reflections at the core–coating interface. Images are then viewed using an eyepiece located on the control handle. The eyepiece could be connected to a video monitor via an image processor. This arrangement of highly reflective, minute glass fibers accounts for the bronchoscope's flexibility and high image quality. However, it also imparts substantial fragility to the instrument, which makes it prone to damage with continuous use.
- Digital video transmission using charge-coupled devices (CCDs): Efforts to miniaturize CCDs have led to the development of bronchoscopes with tiny CCDs in their tips that record an image and then transport it electronically to a video processor for presentation on monitors. The CCD bronchoscopes provide larger and clearer images, free of the dots characteristic of fiberoptic images.

PREPARATION

To perform an efficient and safe procedure the practitioner needs to fully prepare the bronchoscopy area, the equipment, medications, the patient, and the personnel who will participate in the procedure.

EQUIPMENT AND SUPPLIES

The proper selection and preparation of equipment are important to ensure a safe and effective procedure.

The light source, video recorder, and monitor are usually maintained on a portable bronchoscope cart. Equipment, such as 1% to 2% lidocaine spray, 2% lidocaine jelly, syringes containing aliquots of 1% to 2% lidocaine, a Lukens trap, 10-mL normal saline aliquots for lavage, and clean gauzes, may be placed on top of the cart for easy access (Figure 7-6). A cardiac monitor, pulse oximeter, noninvasive blood pressure monitor, and emergency resuscitation cart should also be placed at the bedside. Appropriately sized resuscitation bag and mask, laryngoscopes and endotracheal tubes, and resuscitation medications must be readily available. Wall suction and oxygen should be connected and turned on for prompt access if needed. Two sources of wall suction should be used: one connected to the bronchoscope to clear the field of view and to obtain specimens; and the other connected to a suction catheter or Yankauer suction tip for use if the patient has excessive oropharyngeal secretions or vomits during the procedure. On certain occasions, special equipment or medications may be needed, such as a swivel adapter for an endotracheal tube, positive end-expiratory pressure (PEEP) valves, tracheostomy tubes, wire brushes for cytology, transbronchial needle catheters, sodium bicarbonate, *N*-acetylcysteine, and DNase (Box 7-3).

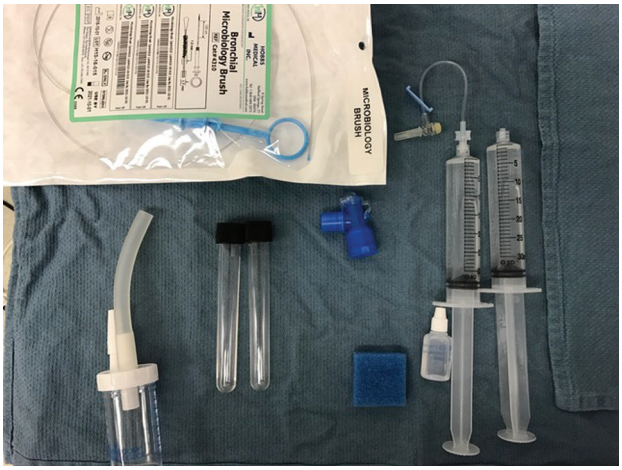


FIGURE 7-6 Basic supplies of flexible bronchoscopy, from left to right: Lukens trap, sample collecting tubes, swivel adapter, lubrication jelly, two 10-mL aliquots of normal saline for bronchoalveolar lavage, and a cytology brush (top). These items are placed on a clean drape on top of a portable bronchoscopy cart.

Box 7-3 Equipment and Supplies for Pediatric Flexible Bronchoscopy

BASIC SUPPLIES
- Slip-tip syringes
- Swivel adapters
- Lubricant
- Specimen traps
- Gauze sponges, alcohol wipes, cotton-tipped applicators
- Suction tubing
- Bite blocks
- Institution-specific documentation forms

BRONCHOSCOPE AND VIDEO EQUIPMENT
- Appropriately sized flexible bronchoscopes
- Light source
- Image processor
- Monitor
- Video recording and still image capture capability
- Dedicated computer with high-capacity storage

PROTECTIVE EQUIPMENT
- Face masks and eye protection
- Gloves
- Gowns with water barrier
- Enzymatic cleaning solution
- Biohazard bags

FLUIDS AND MEDICATIONS
- Normal saline solution
- 1% and 2% injectable lidocaine solution
- 2% lidocaine jelly to apply to the nares

SPECIALIZED SUPPLIES
- Transbronchial aspiration needles
- Biopsy forceps
- Fixative-filled specimen containers
- Grasping forceps
- Retrieval baskets
- Cytology brushes

During the procedure, all pediatric patients require some type of sedation. The most common approach is **conscious sedation** following the guidelines of the American Academy of Pediatrics (1992). For administration of conscious sedation, the presence of a trained clinician to attend to the sedation alone is required. Intravenous drugs are preferable to intramuscular medications because of their quicker onset, shorter duration, and titratable dosage for optimal effects. Although various sedative agents are available, the combination of a benzodiazepine (e.g., midazolam) and a narcotic (e.g., fentanyl or morphine) is widely accepted. In addition to sedative effects, the narcotic provides analgesic and antitussive effects, and the benzodiazepine offers anxiolytic effects and anterograde amnesia. The most common side effect of this combination is respiratory depression. On occasion, benzodiazepines can induce cardiovascular depression, and narcotics can elicit muscular rigidity and impaired liver and kidney functions. Fortunately, if these complications occur, specific reversal agents, naloxone (0.01 mg/kg per dose) and flumazenil (0.2 mg/kg per dose), can be given to restore the patient's respiratory status. These antagonists, along with atropine and epinephrine for adverse cardiac events, should be immediately available.

Additional medications that should be available include aerosolized albuterol to treat any bronchospasm that may develop, aerosolized epinephrine for airway edema, and diphenhydramine and a corticosteroid to treat any potential anaphylactic reaction to the sedating medications. Albuterol can be also used preoperatively in patients with a history of airway hyperresponsiveness. The presence of an anesthesiologist to manage the sedation and monitoring of the patient is increasingly common.

PATIENT

Patient preparation includes a thorough history and physical examination before the procedure. Any radiographic studies should be reviewed. Information regarding the child's current health status and drug allergies must be obtained. Elective bronchoscopic procedures should be postponed if the patient has a reversible condition or acute illness that may increase the risk for complications from the sedation or the procedure itself. After a thorough description of the procedure to the parents and to the patient, if the child is able to understand, written informed consent must be obtained. One of the major risks of flexible bronchoscopy is aspiration of gastric contents. Infants younger than 6 months should not take anything by mouth for 3 to 4 hours before the procedure, older infants and toddlers for 4 to 6 hours, and older children 8 hours, to ensure an empty stomach.

Flexible laryngoscopy may be performed in infants and cooperative older children with only topical anesthesia because it causes no more trauma than nasopharyngeal suctioning and can be equally brief when done by an experienced operator. When the bronchoscope is to be passed below the glottis, intravenous access is recommended.

For psychological support and patient comfort, parents should be allowed to stay with the patient as long as possible before starting the procedure. However, they should not overstimulate the patient, especially when conscious sedation is used. The importance of a calm, nonstimulating atmosphere in the bronchoscopy area cannot be overstated. This may be achieved by low-level lighting, calm and quiet actions by the bronchoscopist and support personnel, and a smooth prebronchoscopy routine. Premedication with a benzodiazepine 30 to 60 minutes before the procedure can help the patient relax before starting the procedure.

PERSONNEL

Typically the flexible bronchoscopy team includes a bronchoscopist, a nurse, a respiratory therapist, and the clinician providing conscious sedation. All team members should be informed of the patient's diagnosis, indication for bronchoscopy, allergies, and biological risks to the patient and team members. In addition, the team should be fully informed of the planned procedures and any difficulties that may arise. Everyone should wear a clean protective gown, gloves, mask, and eye protection. All body fluids, including bronchoalveolar lavage specimens, should be handled carefully using universal precautions.

Personnel safety is increased by identifying patients with potentially transmissible pathogens, such as hepatitis viruses, human immunodeficiency virus, and *Mycobacterium tuberculosis.* Approved high-efficiency particulate air (HEPA) filter masks should be worn for all procedures involving patients with suspected *M. tuberculosis* infection, and the procedure should be performed in a room that meets ventilation requirements for tuberculosis. Patients with, or at risk of having, tuberculosis should be kept in a respiratory isolation room before and after the procedure.

PROCEDURE

Most pediatric flexible bronchoscopies are performed with the patient in a supine position on a bed. The height of the bed should be adjusted to the bronchoscopist's comfort level. When the patient and bronchoscopy team are ready and all preparations are completed, a "time-out" procedure is performed according to institutional policy, and the selected sedation is initiated. Appropriate sedation will decrease the patient's anxiety, discomfort, and unwanted physiological effects. Nevertheless, many younger patients may need a gentle restraining system even when sedated.

CONSCIOUS SEDATION

Several different conscious sedation regimens have been used safely and successfully for pediatric flexible bronchoscopy. As noted earlier, one of the most widely accepted is a combination of a benzodiazepine (e.g., midazolam) and a narcotic (e.g., fentanyl or meperidine) given intravenously. The usual pediatric dose of intravenous midazolam ranges from 0.05 to 0.1 mg/kg to a maximal total dose of 0.4 to 0.6 mg/kg (or 6-10 mg). Typically, sedation is begun with a small dose (0.05-0.1 mg/kg) and is then titrated upward every 5 minutes to achieve the optimal sedative effect. The same approach is also used for intravenous fentanyl, 1 to 2 μg/kg to a maximal total dose of 5 to 10 μg/kg, starting with a 1-μg/kg dose and titrating upward every 5 minutes. Some bronchoscopists prefer a stronger sedative, such as intravenous ketamine (1 mg/kg per dose) or intravenous propofol (1-2 mg/kg per dose).[8]

Other combinations of drugs are given intramuscularly and include meperidine, promethazine, and chlorpromazine and the combination of droperidol, promethazine, and chlorpromazine. The disadvantages of intramuscular sedation include the inability to titrate the optimal dose of the medications and the lack of intravenous access in case of an emergency. However, the intramuscular approach is sometimes justified for short procedures in stable children with difficult intravenous access. Intranasal midazolam has also been shown to induce adequate sedation for pediatric patients undergoing endoscopic procedures or imaging studies.[9] The usual dose of intranasal midazolam ranges from 0.2 to 0.5 mg/kg. Regardless of the method, optimal sedation is achieved when the child is sleepy and has minimal reaction to noxious stimuli, while still maintaining adequate ventilation and protective airway reflexes. In patients who are at increased risk for cardiopulmonary compromise during conscious sedation, general anesthesia may be preferred.

TOPICAL ANESTHESIA

Conscious sedation is augmented by application of the local anesthetic agent, 1% to 2% lidocaine, to the nasal cavity, posterior pharynx, vocal cords, and tracheobronchial tree. Another technique is to pretreat the subject with a lidocaine aerosol (4-8 mg/kg) given by nebulizer.[10] Lidocaine 2% jelly may also be applied to the nares with a cotton-tipped applicator or small syringe. With small infants, care should be taken that the total lidocaine dose does not exceed the maximal therapeutic range of 3 to 4 mg/kg. Toxic lidocaine levels have been reported with topical airway administration.

PATIENT MONITORING

Continuous cardiac, respiratory, and oximetry monitoring must be performed during and after the procedure. During the procedure the patient should be closely monitored for cardiac and respiratory rates and tracings, blood pressure, oxygen saturation, clinical airway obstruction, chest wall movement, peripheral perfusion, and cyanosis. Ideally, oxygen saturation should be maintained above 95% at all times, with supplemental oxygen delivered to the patient if necessary.

TECHNIQUE

When the bronchoscope is balanced on the left hand, the left thumb controls the angulation lever on the control head and the right thumb and index finger direct the insertion tube at the naris (for right-handed operators). Routes for bronchoscopic approaches include nasal, oral, and endotracheal tube; tracheostomy tube; and LMA.

The most common route for nonintubated pediatric patients is the transnasal approach. The flexible bronchoscope is lubricated with lidocaine jelly or another sterile water–based lubricant and then inserted through a nostril into the nasopharyngeal area. A topical decongestant (e.g., phenylephrine) may be administered to the nasal mucosa first to facilitate passage of the scope past edematous tissue and to reduce the risk of bleeding. The nasopharyngeal and laryngeal anatomy is visualized. The vocal cords are assessed for movement and then anesthetized with lidocaine sprayed through a suction channel of the bronchoscope. Adequate laryngeal anesthesia is critical to prevent sudden laryngospasm. The bronchoscope is then passed through the vocal cords into the tracheobronchial tree. Another dose of 1% to 2% lidocaine is usually applied to the carina to minimize the cough reflex. The tracheobronchial anatomy is then examined.

If BAL is performed, the bronchoscopist wedges the bronchoscope in the selected segmental or subsegmental bronchi, and normal saline is instilled in three to five aliquots of up to 1 mL/kg per aliquot. The saline is then suctioned back through the suction channel. Typically, one-third to one-half of the instilled volume is recovered with suctioning. A specimen is usually collected in a Lukens trap and sent for microbiology or pathology studies. Ideally, if a specimen is collected for microbiological evaluation, suction should not be applied until the bronchoscope is inside the trachea to minimize contamination of the channel with nasopharyngeal secretions. In some cases, a protected catheter may be introduced through the working channel and used to obtain a clean specimen when a larger bronchoscope is in use. In special cases, consultation with the microbiologist or pathologist beforehand ensures that the specimen is large enough for the requested study and is handled and sent appropriately.

During the bronchoscopy the respiratory therapist is often responsible for connecting and disconnecting suction, attaching normal saline syringes and traps for lavage, and giving certain transbronchoscopic medications. The therapist and assisting nurse may divide responsibility for monitoring the patient's oxygenation and respiratory status, stabilizing the patient's head and upper airway, and comforting the patient. Because the bronchoscopist is focused on the procedure, the therapist and nurse are responsible for detecting and promptly notifying the bronchoscopist of any untoward patient occurrence. In most instances, the licensed independent practitioner providing conscious sedation will provide this function. The respiratory therapist is also responsible for assisting in emergency respiratory management, such as maintaining patency of the patient's airway, suctioning oropharyngeal secretions, handling emergency equipment, and giving certain respiratory medications.

A PEEP-Keep is used when performing flexible bronchoscopy in a patient through an endotracheal tube or LMA. In a patient who is being mechanically ventilated, the risk of further compromise to the patient's respiratory condition is higher with a partially occluded endotracheal tube. Special considerations should be made for maximizing the patient's ventilation and oxygenation and compensating for air leaks and increased resistance that may occur. In this situation the respiratory therapist or anesthesiologist is responsible for ventilator adjustment and stabilization of the endotracheal tube. It is often necessary to remove the patient from the ventilator to provide ventilation by bag–valve mask (Ambu bag) during the procedure.

POSTPROCEDURAL MONITORING AND COMPLICATIONS

Monitoring of the patient must continue after the procedure until the patient has fully awakened or has returned to preprocedural baseline status. Children, particularly anxious toddlers, often require large doses of medications, with the level of sedation increasing after the procedure, when the agents are still active and the child is no longer stimulated by the procedure. It is essential to continue to monitor the adequacy of the patient's oxygenation, ventilation, and airway patency until the sedation has completely resolved. Breath sounds should be monitored for the development of any stridor or wheezing after the procedure. To prevent aspiration, oral fluids are withheld until the patient is fully awake and the topical laryngeal anesthesia has worn off, usually about 1 hour after administering the topical anesthetic.

In general, flexible bronchoscopy is a safe and well-tolerated procedure in pediatric patients, especially when it is performed by an experienced bronchoscopy team that employs careful monitoring and takes appropriate precautions. The most common complications include transient cough, fever, hypoxemia, mild epistaxis, and bronchospasm during the procedure.[11] Cough is almost universally seen during and after the procedure, but it is usually self-limited and resolves within 24 hours. Minor epistaxis is common and does not require therapy. Respiratory depression may occur and is usually associated with oversedation and sometimes requires reversal agents. Any bronchospasm is relieved promptly in most patients by bronchodilator aerosol treatments.

A less common but potentially more serious complication is laryngospasm. This problem can be avoided by application of topical lidocaine to the vocal cords. If laryngospasm occurs, the bronchoscope must be

withdrawn immediately and airway resuscitation initiated. These measures include jaw thrust, suction of secretions, and mask ventilation. Rarely, laryngospasm may become life threatening and require paralysis and endotracheal intubation.

More serious complications, including arrhythmias, pulmonary hemorrhage, and pneumothorax, are seldom encountered during pediatric flexible bronchoscopy. Death as a direct result of the procedure is extremely rare.

EQUIPMENT MAINTENANCE

Because the bronchoscope and its accessories are extremely fragile and expensive, special attention must be taken during cleaning and maintenance procedures. Proper care can increase the life span of the equipment, decrease repair and replacement costs, and reduce the potential risk of cross-contamination. Handling requires the avoidance of any excessive angulation or twisting of the scope, actions that can damage the quartz fiber bundles. Inadequate disinfection of a bronchoscope can result in serious adverse outcomes to a patient. The organisms most often responsible for cross-contamination between bronchoscopies are *Mycobacterium* and *Pseudomonas* spp.

The flexible bronchoscope should be cleaned immediately after each procedure. Soak the instrument in enzymatic detergent for at least 5 to 10 minutes. Dried secretions or blood will prevent penetration of the disinfecting agent. Therefore the exterior surface should be wiped or gently scrubbed with a soft cloth or brush. The suction port should be irrigated and flushed with detergent solution and then scrubbed with a short, thick brush. The suction channel should be scrubbed with a long, thin brush, and afterward the brush should be examined for retained blood or mucus. It may be necessary to run the brush through the channel a number of times until it is clear of debris. If the suction valve is not disposable, it should be disassembled and flushed thoroughly with a cleaning solution. Because flexible bronchoscopy is not a sterile procedure, cleaning a bronchoscope does not require routine sterilization, and high-level disinfection has been considered satisfactory. **High-level disinfection** is a cleaning method that inactivates all viruses, fungi, and vegetative microorganisms but not necessarily all bacterial spores. The most common agent used is 2% alkaline glutaraldehyde. Immersion in glutaraldehyde for 20 minutes can destroy virtually all pathogens surviving on a well-cleaned bronchoscope.[12]

Because of increasing concern about more virulent and resistant microorganisms, many centers are adopting routine sterilization of their bronchoscopes. Two highly effective methods against all types of microorganisms are ethylene oxide gas sterilization and peracetic acid submersion. Ethylene oxide is noncorrosive and able to penetrate all portions of the bronchoscope without requiring high pressures. However, a venting cap must be placed to equalize the pressure between the interior and the exterior of the bronchoscope. The major disadvantage of ethylene oxide sterilization is that it is time-consuming, taking at least 12 to 16 hours to complete the process. An alternative method is the STERIS system (Figure 7-7), an automated, microprocessor-controlled device using a sterilant concentrate, peracetic acid, as the active biocidal agent. This chemical sterilization process requires only 25 minutes. Once the disinfection or sterilization process is completed, the bronchoscope is rinsed with tap water and may be wiped with alcohol before storage in a dry, clean cabinet.

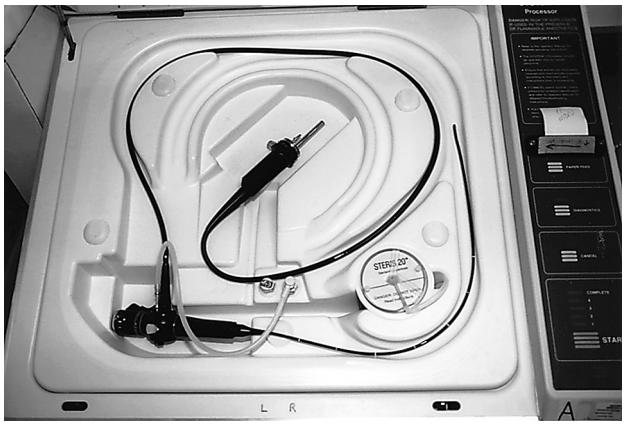


FIGURE 7-7 Correct placement of flexible bronchoscope in a STERIS cleaning apparatus, used for chemical sterilization of the instrument.

COMPARISON WITH RIGID BRONCHOSCOPY

Rigid bronchoscopy is most often performed in the operating room by surgeons or otolaryngologists, with general anesthesia administered to the patient by an anesthesiologist. The rigid bronchoscope has some advantages over flexible bronchoscopy, including its relatively large internal diameter, improved anatomic definition (e.g., posterior aspect of the larynx and cervical trachea), the ability to provide ventilation during the procedure, and the ability to use larger instruments. It is particularly useful in removal of a foreign body or when laser therapy is required. Relative disadvantages of rigid bronchoscopy include the inability to allow inspection of distal airways, the inability to assess the dynamic and natural state of the airways, and the complications associated with general anesthesia. Thus the risks and benefits of each procedure must be carefully considered for each patient before choosing the bronchoscopic method. The two procedures may be coordinated and performed sequentially in the operating room for different diagnostic and therapeutic purposes in select patients.

Case Study

You are called by the intensive care team to evaluate a 12-year-old boy who is currently intubated for management of acute respiratory distress syndrome (ARDS). He has no underlying chronic medical condition and has been healthy until 1 week ago when he presented with fever, cough, and shortness of breath. He was found to have left lower lobe pneumonia with mild pleural effusion. He was admitted to the regular inpatient floor for intravenous antibiotic management. His hospital course was complicated by ARDS, for which he required a transfer to the intensive care unit (ICU), where he was intubated and started on appropriate ventilator settings. He started to show signs of improvement, and the team was planning to extubate him later today, but he suddenly developed increase FiO_2 and PEEP requirements. You examine the patient and note asymmetric chest rise and decreased air entry in the right side.

What would be your next step of action?

Key Points

- Flexible bronchoscopy allows for the examination of the lower airway and collection of diagnostic specimens, including cultures and biopsy material. Therapeutic intervention may also be possible. Rigid bronchoscopy is indicated when the information obtained will be of higher quality or when the safety of the procedure is enhanced.
- The performance of safe and efficient bronchoscopy requires adequate preparation. All equipment should be readily available on a cart. All medications should be drawn up beforehand. The light sources and video equipment should be tested. The patient should be prepared; a child life service is very helpful in this regard. The consent must be signed and placed in the chart. The child should have nothing by mouth, following institutional guidelines for conscious sedation or general anesthesia. A time-out procedure should always be performed.
- Close monitoring of the patient is critical for safe performance of bronchoscopy. In most cases the heart rate, respiratory rate, and saturation will be continuously monitored. Blood pressure will be measured frequently according to directives related to conscious sedation policies. Frequent inspection and auscultation of breathing should be performed. Ideally, saturation should be maintained above 95%, and supplemental oxygen should be used when necessary. During conscious sedation a licensed independent practitioner should be available to monitor the patient. Common complications include cough, fever, and transient hypoxia. Complications should be anticipated, and sufficient personnel and resources to manage them must be available.
- The safe use of the equipment requires reliable and consistent cleaning between procedures. The bronchoscope must be soaked in enzymatic solution sufficiently long enough to loosen biological material. The bronchoscope should be scrubbed with detergent, and the suction and working channels should be meticulously cleaned with a scrub brush. High-level disinfection or gas sterilization is then performed. An institutional cleaning protocol should be used to ensure consistency of performance.

Assessment Questions

1. Flexible bronchoscopy is commonly performed in all the following settings *except:*
   - **A.** Operating rooms
   - **B.** Bronchoscopy suites
   - **C.** Pulmonary clinic rooms
   - **D.** Intensive care units
   - **E.** Procedure rooms
2. The most common diagnostic indication for flexible bronchoscopy in infants is:
   - **A.** Stridor
   - **B.** Wheezing
   - **C.** Hoarse voice
   - **D.** Persistent atelectasis
   - **E.** Difficult intubation
3. Regarding endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA), all of the following are true *except:*
   - **A.** It has a lower complication rate compared with thoracotomy and thoracoscopy.
   - **B.** It is contraindicated in children.
   - **C.** The linear type provides real-time ultrasound guidance for TBNA.
   - **D.** It is safe to perform in children with mediastinal lymphadenopathy.
4. Airway dynamics can be disrupted by:
   - **A.** General anesthesia
   - **B.** Conscious sedation
   - **C.** Topical lidocaine
   - **D.** Intranasal midazolam
   - **E.** Sleep
5. Flexible bronchoscopy is indicated in the evaluation of wheezing in all the following settings *except:*
   - **A.** Wheezing that is unilateral
   - **B.** Wheezing that has been present since birth
   - **C.** Wheezing that is refractory to asthma therapy
   - **D.** Wheezing that is triggered by viral infections
   - **E.** Wheezing associated with persistent atelectasis
6. Bronchoalveolar lavage may be performed to look for:
   - **A.** Infection
   - **B.** Malignancy
   - **C.** Bleeding
   - **D.** Aspiration
   - **E.** All of the above

7. Which of the following is an absolute contraindication for flexible bronchoscopy?
   - **A.** The diagnosis could be obtained by open lung biopsy.
   - **B.** The patient is hypoxemic.
   - **C.** Absence of informed consent.
   - **D.** The patient is febrile with acute pneumonia.
   - **E.** History of controlled asthma.
8. A 3-year-old child is intubated with a 4.5-mm endotracheal tube and is mechanically ventilated for severe pneumonia. The respiratory therapist is asked to set up a bronchoscope for bronchoalveolar lavage to obtain microbiology specimens. What is the most appropriate scope for this procedure?
   - **A.** 1.8-mm nondirectable "spaghetti" bronchoscope
   - **B.** 2.2-mm directable flexible bronchoscope without a suction channel
   - **C.** 2.7-mm directable flexible bronchoscope with a suction channel
   - **D.** 4.5-mm directable flexible bronchoscope with a large suction channel
   - **E.** 4.0-mm rigid bronchoscope
9. Topical anesthesia of the airway may be achieved by:
   - **A.** Intranasal administration of midazolam
   - **B.** Intravenous administration of fentanyl
   - **C.** Intravenous administration of midazolam
   - **D.** Airway instillation or nebulization of lidocaine
   - **E.** Airway instillation or nebulization of a topical corticosteroid
10. During a bronchoscopy, the respiratory therapist may do each of the following *except:*
    - **A.** Connect and disconnect suction and specimen traps
    - **B.** Administer supplemental oxygen as needed
    - **C.** Administer saline lavages or transbronchoscopic medications
    - **D.** Administer conscious sedation medications
    - **E.** Assist in emergency airway management
11. The most common complication after flexible bronchoscopy is:
    - **A.** Cough
    - **B.** Wheezing
    - **C.** Hemoptysis
    - **D.** Fever
    - **E.** Pneumothorax
12. Acceptable cleaning and decontamination of a flexible bronchoscope include all the following *except*:
    - **A.** Soaking the scope in an enzymatic detergent solution
    - **B.** Immersion in 70% ethanol solution
    - **C.** Immersion in 2% alkaline glutaraldehyde solution
    - **D.** Ethylene oxide gas sterilization
    - **E.** Immersion in peracetic acid

REFERENCES

1. Faro A, Wood RE, Schechter MS, et al. Official American Thoracic Society technical standards: flexible airway endoscopy in children. *Am J Respir Crit Care Med*. 2015;191(9):1066-1080.
2. Barbato A, Magarotto M, Crivellaro M, et al. Use of the paediatric bronchoscope, flexible and rigid, in 51 European centres. *Eur Respir J*. 1997;10(8):1761-1766.
3. Godfrey S, Avital A, Maayan C, Rotschild M, Springer C. Yield from flexible bronchoscopy in children. *Pediatr Pulmonol*. 1997;23(4):261-269.
4. Pérez-Frías J, Moreno Galdó A, Pérez Ruiz E, et al. [Pediatric bronchoscopy guidelines]. *Arch Bronconeumol*. 2011;47(7):350-360.
5. Dhooria S, Madan K, Pattabhiraman V, et al. A multicenter study on the utility and safety of EBUS-TBNA and EUS-B-FNA in children. *Pediatr Pulmonol*. 2016;51(10):1031-1039.
6. Chen A, Chenna P, Loiselle A, Massoni J, Mayse M, Misselhorn D. et al. Radial probe endobronchial ultrasound for peripheral pulmonary lesions. A 5-year institutional experience. *Ann Am Thorac Soc*. 2014;11(4):578-582.
7. Steinfort DP, Wurzel D, Irving LB, Ranganathan SC. Endobronchial ultrasound in pediatric pulmonology. *Pediatr Pulmonol*. 2009;44(4):303-308.
8. Midulla F, de Blic J, Barbato A, et al. Flexible endoscopy of paediatric airways. *Eur Respir J*. 2003;22(4):698-708.
9. Fishbein M, Lugo RA, Woodland J, Lininger B, Linscheid T. Evaluation of intranasal midazolam in children undergoing esophagogastroduodenoscopy. *J Pediatr Gastroenterol Nutr*. 1997;25(3):261-266.
10. Gjonaj ST, Lowenthal DB, Dozor AJ. Nebulized lidocaine administered to infants and children undergoing flexible bronchoscopy. *Chest*. 1997;112(6):1665-1669.
11. de Blic J, Marchac V, Scheinmann P. Complications of flexible bronchoscopy in children: prospective study of 1,328 procedures. *Eur Respir J*. 2002;20(5):1271-1276.
12. Woodcock A, Campbell I, Collins JV, et al. Bronchoscopy and infection control. *Lancet*. 1989;2(8657):270-271.

8 Invasive Blood Gas Analysis and Cardiovascular Monitoring

Brian K. Walsh

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. Describe indications for obtaining blood gas samples.
2. Identify common anatomic sampling sites used to obtain blood gases.
3. Describe potential patient and caregiver complications associated with blood gas sampling.
4. Interpret a complete hemodynamic profile of a patient.
5. Describe common techniques used for monitoring cardiac output and index in children.
6. Discuss various measurements that can be used to determine the adequacy of cellular oxygenation.
7. Identify variables that can shift the oxygen dissociation curve.

Key Terms

arterial blood gas
capillary blood gas
carboxyhemoglobin
cardiac index
cardiac output
central venous catheter
central venous oxygen saturation
central venous pressure
cutdown method
fetal hemoglobin
high position
low position
mean arterial pressure
methemoglobin
modified Allen test
percutaneous method
peripheral artery catheter
pulse pressure
right atrial pressure
serum lactate
umbilical artery catheter
venous blood gas

Blood gases are considered the most effective test for evaluating the efficiency of gas exchange and cardiopulmonary interaction. Evaluating an infant or child with respiratory impairment requires the analysis of blood gases in umbilical, arterial, capillary, or mixed venous blood samples. To interpret these blood gas values correctly, the clinician must understand acid–base balance and gas exchange and be able to recognize normal and abnormal blood gas values. The techniques of blood gas sampling can affect the results. This chapter reviews the procedures, indications, complications, and contraindications for each technique. It also reviews various clinical techniques that are used to monitor and evaluate cardiac performance, response to therapeutic interventions, and the severity and progression of disease processes in pediatrics. It is beyond

the scope of this chapter to describe noninvasive methods to measure gas exchange. Chapter 9 provides a complete overview of these concepts.

BLOOD GAS SAMPLING

Blood gas sampling may occur from arterial, venous, or capillary sites. Blood gas analysis (BGA) is indicated when an accurate measurement of acid–base balance or pulmonary gas exchange is required.[1] This analysis may be needed for a variety of reasons (Box 8-1).[2] Figure 8-1 shows the various anatomic sites that provide access for percutaneous arterial puncture and catheterization; Figures 8-2 and 8-3 show recommended sites for capillary puncture. **Venous blood gas** sampling can occur at any site approved for venipuncture for routine purposes.

PAIN CONTROL

Blood gas sampling can be a painful procedure, but the resulting information is often a vital part of patient management. Because painful procedures do not always evoke vigorous pain responses in critically ill newborns, many believe that such newborns are not being affected by pain.[3] However, infants probably have a higher sensitivity to painful procedures than older age groups.[4,5] For infants older than 4 months and for children, anesthetic cream or a lidocaine injection may be used to control the pain felt during a blood gas procedure.[6] For nonintubated infants and premature newborns, a pacifier dipped in 24% sucrose is effective in helping ameliorate the effects of pain. If the newborn is intubated, the sucrose can be administered as drops on the tongue or palate from an oral medication syringe.[7] Depending on the type and duration of procedure, more potent short-acting analgesic or anesthetic agents may be appropriate.[8]

Box 8-1 Indications for Blood Gas Analysis

- To evaluate ventilation ($Paco_2$, $Pvco_2$, $Pcco_2$)
- To evaluate acid–base balance (pH, $Paco_2$, $Pvco_2$, $Pcco_2$)
- To evaluate oxygenation (Pao_2, oxyhemoglobin)
- To evaluate the oxygen-carrying capacity (Pao_2, oxyhemoglobin, hemoglobin, dyshemoglobin)
- To evaluate intrapulmonary shunt
- To quantify response to therapy
- Supplemental oxygen
- Mechanical ventilation
- To assist in diagnosis
- To monitor the severity or progress of a disease
- To assess early goal-directed therapy (EGDT) in patients with sepsis, septic shock, and after major surgery ($Scvo_2$)
- To assess inadequacy of circulatory response

$Paco_2$, Partial pressure of carbon dioxide in arterial blood; *Pao_2*, partial pressure of oxygen in arterial blood; $Scvo_2$, **central venous oxygen saturation**.

ARTERIAL SAMPLING SITES

Figure 8-1 illustrates potential sites for arterial puncture or catheterization in infants and children. Arterial sampling sites provide the most accurate blood gas results. The brachial and femoral sites are usually avoided because both feed large distal networks and neither has collateral circulation. Also, the brachial pulse is difficult to palpate in infants and small children because of the naturally large fat pad located in that area of the arm. Injury to the brachial nerve can also result in serious complications. Only a highly skilled clinician should perform a brachial artery puncture if necessary.

In a child, the femoral artery is reserved for an emergency, and then only as a last resort. In neonates and infants, the femoral artery lies close to the femoral vein, nerve, and hip joint, and because of their proximity, damage inflicted on any one of these structures by femoral puncture is likely to cause severe complications and is thus not indicated for this population.[9]

The preferred site in both neonatal and pediatric populations is the radial artery. The radial artery

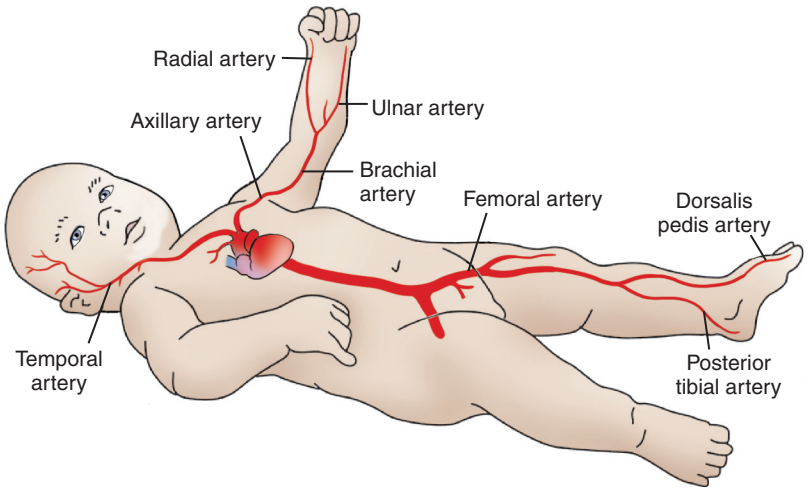


FIGURE 8-1 Arterial sites that may be used for peripheral artery puncture in infants and children.

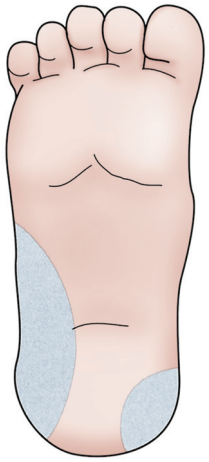


FIGURE 8-2 Recommended puncture sites *(shaded areas)* in an infant's heel to obtain capillary blood for analysis.

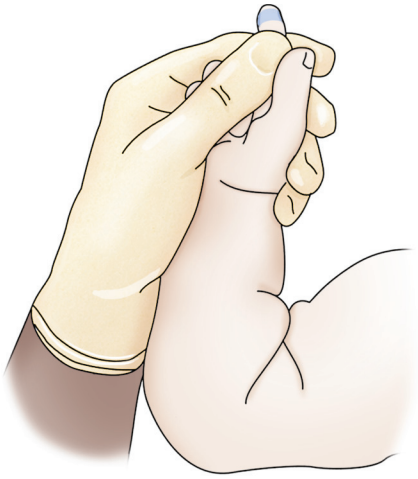


FIGURE 8-3 Technique for grasping the finger for a capillary puncture, with recommended site for puncture indicated *(shaded area)*.

provides good access as well as collateral circulation to the hand by the ulnar artery. There are usually no nerves or veins directly adjacent to the radial artery, and the patient's wrist is easier to manipulate than are other body parts. The bone and firm ligaments of the wrist make it easy to palpate, stabilize, and compress the radial artery.[1,7] A **modified Allen test** (described in the next section) is performed to ensure collateral circulation around the radial artery and to prevent complications. The ulnar artery should be avoided because it runs adjacent to the ulnar nerve.

The dorsalis pedis or posterior tibial artery is considered if the radial artery shows signs of poor collateral circulation. In addition, the temporal artery provides an alternative site for premature or newborn infants. Access is generally good, because two branches are close to the scalp. In most premature and neonatal patients, the temporal artery branches are larger than the radial artery.

MODIFIED ALLEN TEST

The modified Allen test is used to verify the presence of collateral circulation to the hand and should be performed to confirm whether poor circulation exists before puncturing the radial, posterior tibial, or dorsalis pedis artery. To assess blood flow to the hand, the practitioner should hold the child's wrist with both hands, thumbs on top. The practitioner asks the child to make a tight fist and then occludes the radial and ulnar arteries by pressing down on them with the thumbs, one on each artery. Keeping both arteries occluded, the practitioner asks the child to unclench the fist and notes whether the palm is blanched, which indicates impaired blood flow, then removes the pressure from the ulnar artery. The palm will become pink within 5 seconds if the ulnar artery is patent and able to provide collateral circulation.[7]

The passive method for performing the modified Allen test, used on an infant or child who cannot follow commands, is performed by gently squeezing or elevating the hand while occluding both arteries. Once the ulnar artery is released, the results are interpreted as previously described.[1] The Allen test can also be used to verify collateral circulation when using one of the arteries of the foot as a puncture site, by elevating the foot and compressing the dorsalis pedis and posterior tibial arteries. Collateral circulation is confirmed by releasing pressure from the artery that will not be punctured and assessing the nail beds and sole of the foot for return of blood flow.[1,7]

ARTERIAL PUNCTURE

When infrequent sampling is required, **arterial blood gas** (ABG) samples are obtained by arterial puncture. This procedure involves percutaneously puncturing one of the aforementioned peripheral artery sites. Obtaining a blood gas sample from an infant or child is generally more difficult than in an adult and requires more patience, skill, and time. However, an experienced clinician using proper technique can quickly obtain a sample that yields accurate results. Two individuals are helpful when performing an arterial puncture on a child who is too young to understand the need for the test but strong enough to react to the procedure. On a small infant or neonate, a transilluminating light placed behind the wrist may help visualize the location of the radial artery.[1,7]

PROCEDURE

Performing a successful arterial puncture requires knowledge of the anatomy involved and proficient technical skills. The practitioner should collect the equipment required for the arterial puncture (Box 8-2) and use the following sequence of technical steps as a guideline for performing the puncture[1,7]:

1. Wash hands and adhere to universal precautions for bloodborne pathogens, using properly fitting

Box 8-2 Equipment for Arterial Puncture and Blood Gas Collection

- 1-mL preheparinized* tuberculin syringe
- 25-gauge needle *or* preheparinized* 25-gauge butterfly needle infusion kit
- Correctly fitting examination gloves
- Povidone-iodine and alcohol wipes
- Sterile gauze
- Needle-capping and protection device
- Eye and splash shield
- Patient label

*Use dry heparin or expel liquid heparin from the syringe and needle hub or butterfly set before starting the procedure.

examination gloves, along with eye and splash protection.[2,9-11]

2. Palpate the pulse at various sites (see Figure 8-1) to determine the best site for testing.
3. Perform the modified Allen test if appropriate for the artery being sampled.
4. Use an assistant to help restrain the child and immobilize the limb if required.
5. Scrub the puncture site with an approved antiseptic swab and allow to air dry, or use a sterile gauze pad. Do not blow on the site to dry it.
6. Palpate the artery again, and position the index and middle finger of the nondominant hand to stabilize the artery.
7. Maintain a clean field around the syringe and syringe kit while opening it. Prepare the kit for use, and heparinize the syringe if required. Remember to expel the heparin completely from the barrel of the syringe and hub of the needle.
8. Insert the needle of the syringe or butterfly catheter into the artery at a 35- to 45-degree angle with the bevel up, and advance it gently. Enter the artery from the direction opposite, or against, the blood flow. A flash in the hub of the syringe or butterfly catheter verifies that the needle penetrated the artery and is located in the lumen. In a small pediatric patient it is quite easy to pass through the artery with the needle. If a good pulse is palpated and no blood return occurs after the needle is inserted, pull the needle back incrementally and continue to watch for a flash of blood. If resistance is met when inserting the needle, slowly withdraw it immediately and change direction, because it has most likely touched the bone.
9. Obtain the required amount of blood. Because the arterial pressure is usually high enough, manual aspiration is not required. If manual aspiration is required, however, the barrel of the syringe is withdrawn slowly. When using a butterfly catheter, attach the syringe to the catheter and slowly aspirate the correct amount of blood into the syringe. Maintain the sample amount as close to the technically feasible minimal volume as possible.[2,7]
10. After obtaining the sample, withdraw the needle and immediately apply firm pressure to the puncture site with a sterile gauze pad for at least 5 minutes. Apply pressure for a longer period if the patient has a coagulopathy or is receiving anticoagulation therapy (e.g., heparin). Avoid using pressure dressings. Patients should not apply the pressure because they may not press hard or long enough.
11. While holding the site, gently remove air bubbles from the sample. If using a butterfly catheter, remove it from the syringe.
12. Continue compressing the site, and seal the syringe with a one-handed safety cover device to prevent exposure of the sample to air. Gently roll the syringe between the hands or fingers to mix the heparin with the specimen.[3]
13. Immediately apply the proper patient label to the specimen according to institutional policy.
14. For accurate results, analyze the sample immediately, or analyze room temperature samples within 10 to 15 minutes after they are drawn. Samples placed on ice should be analyzed within 1 hour.[12]

CONTRAINDICATIONS

The major contraindication to an arterial puncture is lack of collateral circulation. Punctures should not be performed at sites where the extremity has previously blanched, which may result from arterial obstruction or spasm. Punctures should not be performed through a site distal to or through a surgical shunt, as in a dialysis patient. If a limb is infected or shows evidence of peripheral vascular disease, an alternative site should be selected.[10]

COMPLICATIONS

Hematoma formation is the most common complication during arterial puncture and is seen more often in brachial than in radial artery punctures. Complications can be minimized by immediately applying adequate pressure to the puncture site after the needle is withdrawn. As with any invasive procedure, infection is a possible complication but is relatively low with aseptic technique. Scarring, laceration of the artery, and hematoma formation are more likely to occur with repeated puncture of an artery.[8] Alternating puncture sites decreases this risk. Other complications associated with arterial punctures in infants and children include nerve damage, bleeding, obstruction of the artery by clots or spasms, trauma to the artery, and pain.

Because the median nerve is close to the brachial artery, the nerve may be punctured as well during the procedure, which will cause intense pain down the arm. Because the posterior tibial artery and nerve are also close to one another, special care should also be taken to prevent nerve damage during puncture of

this artery. Although the femoral artery is much easier to puncture, complications in infants tend to occur more often and include thrombosis, nerve damage, and necrosis of the head of the femoral bone.[7]

Although gloves are worn and universal precautions applied during all arterial punctures, needle sticks remain a risk to the clinician and are the most common source of transmission of bloodborne pathogens to health care workers.[2,8,9,13] Most of these complications can be prevented by having only thoroughly trained and highly skilled clinicians perform a puncture.

Clinical Highlight

Arterial complications are more severe than most capillary and venous complications. Special care should be taken to rule out contraindications to arterial puncture. Collateral circulation should also be verified via an active or passive modified Allen test before arterial puncture.

CAPILLARY BLOOD GAS SAMPLES

Capillary blood gas (CBG) sampling provides a common alternative to ABG analysis in infants or children. Punctures for capillary samples are less invasive than arterial punctures, are easier and quicker to perform, and can be used when there is no arterial catheter for drawing ABG samples.[13,14] Drawing a CBG sample is usually less painful, but local anesthetic application helps alleviate pain associated with the procedure.[6,7,15]

In general, a CBG sample correlates best with arterial pH and carbon dioxide tension ($Paco_2$) values. Correlation of capillary samples with arterial samples varies depending on the parameters measured.[10,16,17] When a capillary sample site is adequately "arterialized" and puncture and sampling procedures are performed correctly, the pH and carbon dioxide partial pressure (Pco_2) of capillary samples can accurately reflect those of arterial samples. Often, capillary Po_2 is lower than arterial values; however, given a clinically acceptable difference between capillary Po_2 and Pao_2, the capillary Po_2 may trend with increases and decreases in arterial values.[11,16] Although some studies have shown a significant correlation between capillary Po_2 and Pao_2, the use of capillary Po_2 to determine oxygenation is currently not recommended.[2] The accuracy of capillary blood gas values is severely attenuated by the presence of hypotension, hypothermia, hypovolemia, and lack of perfusion.[12] Conversely, correlation of capillary and arterial blood gas values improves with hypoxemia, as venous and arterial Po_2 converge. Special consideration should be given to patients with circulatory defects. Decreased venous return, secondary to cor pulmonale or decreased **cardiac output,** leads to venous congestion and peripheral pooling, which may result in an increase in Pco_2. Conversely, increased blood flow may result in decreased capillary Pco_2.[13]

Although capillary punctures are less invasive, it is necessary to obtain an arterial sample at some point to ensure correlation and accuracy regardless of the specific marker being evaluated. Using noninvasive monitors such as pulse oximeters or transcutaneous oxygen and carbon dioxide monitors to evaluate oxygenation and ventilation when arterial samples are not obtained is an effective way to eliminate the need for frequent CBGs.[12] However, many factors that lead to inaccurate CBG sampling may also affect the accuracy of monitoring (see Chapter 9).[1]

PUNCTURE SITES

The least hazardous puncture site for infants is the posterolateral foot, just anterior to the heel (see Figure 8-2).[1,11] The posterior heel curvature and back of the heel must be avoided, because the lancet could puncture the bone and result in calcaneous osteomyelitis. A capillary puncture should not be performed on the medial aspect of the heel, which is the location of the posterior tibial artery. For children and some infants, the palmar or fleshy surface of the distal aspects of the fingers (middle or ring) and toes is ideal (see Figure 8-3).[10,11,13] The earlobes are a secondary site for puncture in children. In general, punctures should not be performed on the fingers and toes of neonates because of the higher risk of nerve damage in this area.[11,13] Previous puncture sites or inflamed areas with an apparent or possible infection should not be used. As previously discussed, extremities with localized swelling or edema should be avoided because of the effect of extracellular or interstitial fluid on sample accuracy. Cyanotic areas should also be avoided.[13]

PROCEDURE

Successful capillary puncture is not complicated, but it does require proficient technical skill. The practitioner should collect the equipment required (Box 8-3) and use the following sequence of steps as a guide to collect a CBG sample[1,7,11]:

1. Select a puncture site and warm the area for 5 to 10 minutes. Use a warm (greater than 37°C but less than 42 to 45°C) wet cloth or disposable warming pack, and apply it with caution.[1,7]

Box 8-3 Equipment for Capillary Puncture and Blood Gas Collection

- Warming device or warm damp cloth
- Lancet and mechanical puncture device
- Lancet disposal system
- Correctly fitting examination gloves
- Alcohol wipes
- Sterile gauze
- Adhesive bandage
- Eye and splash shield
- Preheparinized capillary tubes
- Metal "flea," magnet, and capillary tube caps (if required)
- Patient label

2. Give a 12% to 24% sucrose solution pacifier 2 minutes before the procedure, or apply an anesthetic cream or subcutaneous injection for pain control.[3,5-7]
3. Wash hands and adhere to universal precautions for bloodborne pathogens, using properly fitting examination gloves, along with splash protection.[8,9]
4. Remove the warming device. Clean the site with an antiseptic and dry with a sterile gauze pad; alcohol will hemolyze the blood.
5. Immobilize the area by properly grasping the hand or foot (see Figures 8-3 and 8-4), and stabilize the area by anchoring the hand or foot on a hard surface. Use an assistant to help restrain a child, and immobilize the limb if required. Restrain infants by swaddling them in a blanket.[7]
6. Finger or toe stick: Hold the digit (patient's finger or toe) with the thumb and forefinger, supporting the digit behind or close to the nail (see Figure 8-3). Keep fingertips well away from the puncture site.
7. Heel stick: Consider using venipuncture or a digit first, because either may be less painful and require less resampling.[3-7] Hold the heel gently but firmly. Wrap the forefinger around the infant's upper heel and ankle while holding the arch of the foot with the thumb (see Figure 8-4).
8. Position the lancet.
   a. For a finger or toe stick, hold the lancet at a 10- to 20-degree angle to the longitudinal axis of the phalangeal bone. Do not direct it into the bone.
   b. For a heel stick, hold the lancet between the thumb and index finger of the opposite hand, perpendicular to the puncture site.
9. Poke the point of the lancet into the skin with one continuous, deliberate motion. Correct depth depends on the infant, but 1 to 2 mm is generally sufficient to produce a free-flowing drop of blood.[7,16,17] Use a mechanical puncture when available, because most produce consistent results with less need for resampling.[7,15] Avoid superficial punctures and the need to repeat the puncture. Do not slice, dig, or make multiple punctures.[1,6,7,16] Ease thumb pressure after the lancet is removed.
10. Wipe away the first drop of blood, which may be contaminated with intracellular, interstitial, or lymphatic fluids, with a dry sterile gauze pad.
11. Apply moderate pressure to the heel or digit, without massaging or squeezing, until a free-flowing drop of blood appears. Squeezing or "milking" the sample may cause red blood cell hemolysis, especially in newborns, because their hematocrit levels are higher and their red blood cells more fragile. Squeezing also results in bruising and contamination of the specimen with lymphatic and venous drainage.
12. Collect the blood by placing the tip of the capillary tube into the blood droplet without touching the puncture wound. Hold the capillary tube angled horizontally, or slightly downward, with the colored ring away from the infant. Keep the tube in contact with the blood droplet until the required amount of blood fills the tube, usually 40 to 125 μL.[7] Maintaining contact with the droplet limits unnecessary exposure to air and reduces the incidence of air bubbles in the sample. Do not scrape blood that has smeared onto the skin surface into the capillary tube. Scraping from the skin surface increases exposure to air and alters the partial pressure of the gases being measured.[1,7,9]
13. Apply pressure to the puncture site with a sterile gauze pad until the bleeding stops. Use an adhesive bandage only on children old enough not to place it in their mouth and possibly aspirate it.
14. Label the tube with the proper patient information.
15. If the sample cannot be analyzed immediately after collection, insert a metal mixing bead (or "flea") into the capillary tube and seal it. Mix the sample by running a magnet gently back and forth along the tube, and place the sample on ice; this decreases the incidence of sample clotting. Remove the metal flea before analyzing the blood.

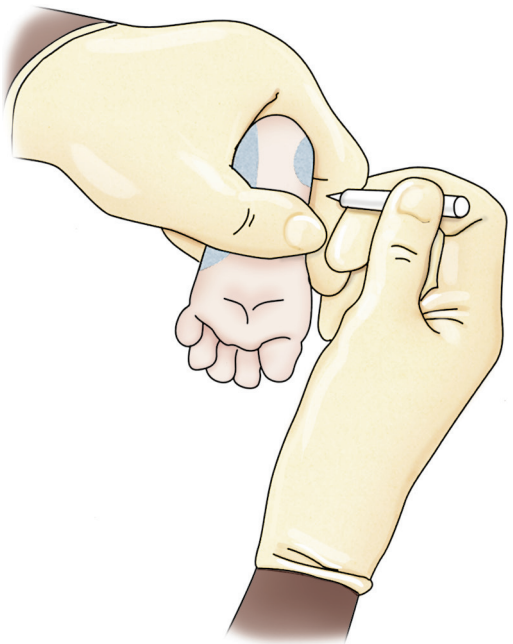


FIGURE 8-4 Technique for stabilizing the heel for a capillary puncture.

CONTRAINDICATIONS

CBG sampling should not be performed when accurate assessment of oxygenation or ABG values is necessary. CBGs should not be used for routine blood gas monitoring when less painful or noninvasive measurements provide results that are more accurate.

Capillary puncture is contraindicated in neonates younger than 24 hours. A newborn has a low systemic output, and vasoconstriction tends to be maximal during this stage secondary to a decrease in environmental temperature and an increase in circulating catecholamines.[11,16,18,19] CBG sampling is not recommended for patients with decreased peripheral blood flow, especially

in the case of hypotension.[11,16,20] CBG sampling may be difficult to perform on a patient with polycythemia (hematocrit greater than 65%) because of the short clotting time. Do not use areas that are edematous, inflamed, or infected, or other areas previously mentioned. Avoid heel samples from ambulatory children who have formed calluses on the soles of their feet.[7,21]

COMPLICATIONS

Serious complications may result in medical management if capillary results do not accurately reflect the patient's condition. Consider potential errors in correlation with arterial values before deciding on a clinical course of action based on CBG values.[9,11,20]

Although capillary puncture is a relatively safe procedure, complications have been observed. Burns have been reported secondary to heel warming, but using a prepackaged warming kit that does not require an external heat source minimizes this problem. Other complications include infection, scarring, calcaneous osteomyelitis, calcifications, nerve damage, arterial laceration, bruising, cellulitis, hematoma, and bleeding.[1,10,11] Some of these complications may seem benign at first but lead to developmental delays in such milestones as grasping and walking.

Clinical Highlight

Capillary blood gas samples are more vulnerable to inaccuracies caused by sampling technique and site selection than those for arterial blood gases and venous blood gases. Special care must be taken during capillary blood gas sampling and analysis.

ARTERIAL CATHETERS

For frequent blood gas sampling, an **umbilical artery catheter** (UAC) is used for critically ill newborns, and a **peripheral artery catheter** or arterial line is used for critically ill older infants or children (Figure 8-5).

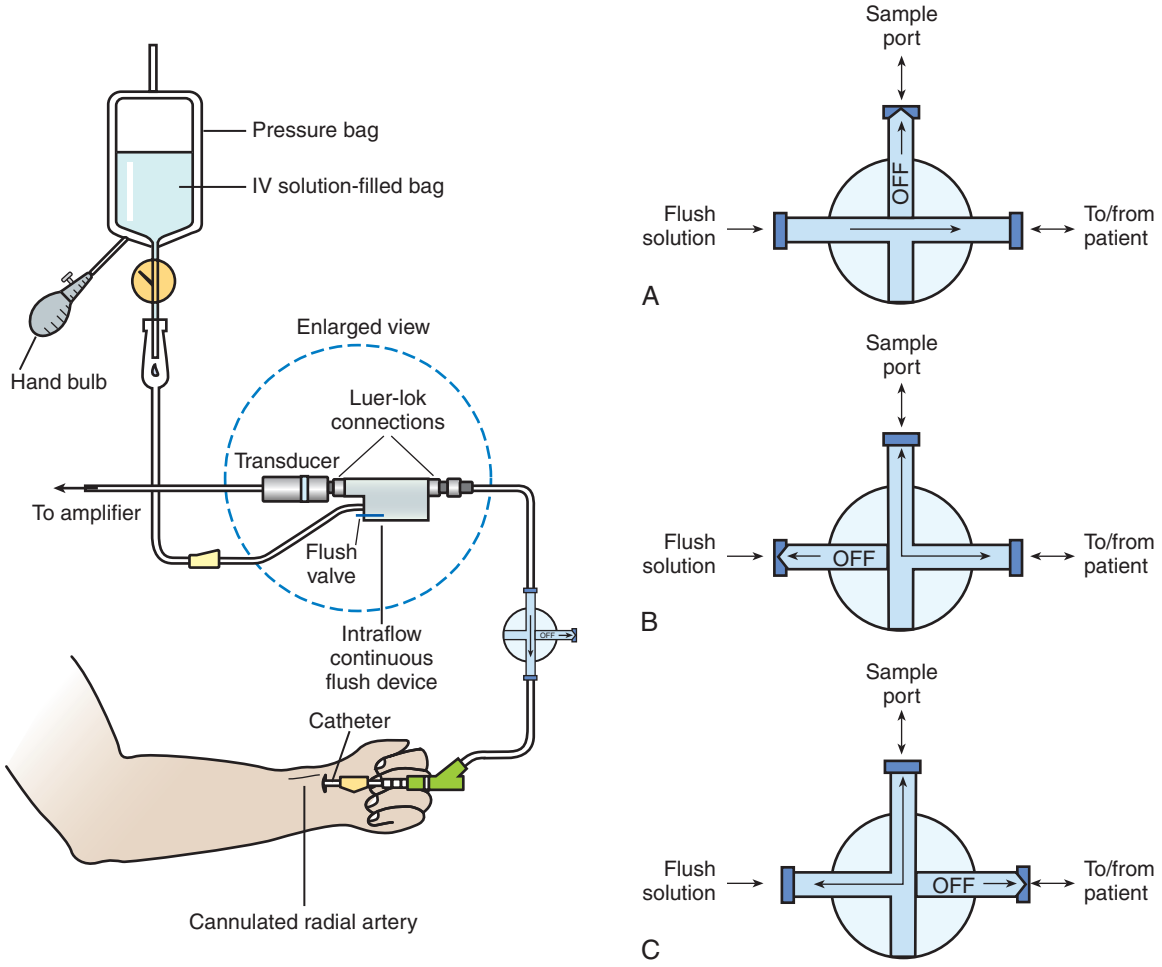


FIGURE 8-5 An indwelling arterial line and continuous infusion and flush system used to monitor blood pressure and obtain blood gas samples. Enlarged view shows a three-way stopcock system. **A,** Normal position with the stopcock off to the sampling port allows continuous monitoring of blood pressure and flushing of the line if using a (pigtail) flush system. **B,** Position to draw blood or inject flush solution to the patient with the stopcock turned off to flush solution. **C,** Position to flush the sample port with the stopcock off to the patient. All ports are closed at all intermediary positions.

Arterial catheters provide access for arterial blood pressure analysis and ABG sampling. UACs and arterial catheters also allow blood pressure monitoring in patients who are hemodynamically unstable.

UMBILICAL ARTERY CATHETERIZATION

In infants, the umbilicus typically provides ready access to two arteries. Facing the child, the two umbilical arteries are located at about the 5 and 7 o'clock positions. Prompt catheterization is essential in neonates, because these vessels will undergo arterial spasm in the presence of increased arterial oxygen, making cannulation difficult if not impossible.[7]

It should be noted that some congenital anomalies may be associated with an umbilicus with a single artery.

Two positions are typically used to place the tip of the UAC. In the **high position** the catheter overlies the sixth through eighth thoracic vertebrae (T6 to T8); this position avoids major tributaries of the aorta because it is below the ductus arteriosus and above the celiac access. The **low position** is usually at the third to fourth lumbar (L3 to L4) space, between the renal artery and aortic intersection and above the takeoff of the inferior mesenteric artery. The UAC is placed to avoid the large tributaries supplied by these vessels to minimize trauma and hemodynamic disturbances of vital organs.[22]

The choice of high or low catheter placement is empiric. Hospitals tend to favor one site or the other; both are associated with their own set of complications related to hypoglycemia, hypotension, vasospasm, and embolic disturbances of organs distal to the catheter tip. A meta-analysis and literature reviews demonstrate a small advantage when using the high position over the low position.[23]

The starting point for how far a catheter should be inserted is determined by first measuring the distance from the umbilicus to the shoulder. This measurement is then looked up on a *nomogram* (a diagram allowing computation of a function) to determine the correct catheter insertion distance.[24-28]

Using sterile technique, the practitioner inserts the catheter into one of the arteries. The artery that is less tortuous upon initial insertion will be easier to cannulate. The tip is directed toward the ipsilateral groin. The catheter is advanced with a gentle downward pressure, using a rotating motion to allow the catheter to seek the arterial lumen. It is advanced to a distance one-third the infant's body length plus 1 cm for the high position. Patency is confirmed by the ease of blood flow. The UAC is connected to a prepared fluid pressure–transducing system (see Figure 8-5).[7,18]

The catheter is secured by suturing it into the umbilical artery and taping it to the abdomen. Chest and abdominal radiographs help confirm placement. A UAC may remain in place for several days to weeks as indicated by patient need.[1,18,24]

PERIPHERAL ARTERY CATHETERIZATION

The clinician must rely on peripheral arterial catheterization for pediatric patients. An arterial line is also used for blood gas monitoring in infants or newborns without umbilical artery access.

Arterial line placement is accomplished by using either a **percutaneous method** (through the skin) or a cutdown method (a small surgical stoma that allows direct visualization and cannulation of the isolated vessels). As previously noted, the most commonly used site is the radial artery; the posterior tibial and dorsalis pedis arteries are occasionally used. Other monitoring sites, such as the brachial artery, superficial temporal artery, and femoral artery, are rarely used because of the increased risk of complications. Arterial catheter sizes range from 22 to 24 gauge for neonates and from 20 to 22 gauge for pediatric patients.[24]

Before placing an arterial catheter, the modified Allen test previously described can be performed to observe collateral blood flow to the hand or foot being punctured.[17] When performing a radial artery puncture in small children and infants, the use of a transilluminating light or ultrasound to locate the radial artery is helpful.[28]

PROCEDURE FOR SAMPLING

The following procedure can be used as a guideline for drawing a blood sample from an arterial or umbilical artery catheter.[1,28] Both catheters are connected to a heparinized normal saline continuous infusion and flush source and blood pressure–monitoring transducer (see Figure 8-5).

1. Wash hands and adhere to universal precautions for bloodborne pathogens, using properly fitting examination gloves, along with eye and splash protection.[8,9]
2. Uncap the locking port of the three-way stopcock. Apply appropriate antibacterial solution to the stopcock port or rubber infusion port, depending on institutional procedures, and allow to dry.[1] Because multiple syringes are required, maintain a clean field around the site and a place to set the syringes that are not in use.
3. Attach a 3-mL syringe to the stopcock, or attach a syringe with a 25-gauge needle to the infusion port (see Figure 8-5, *A*).
4. Turn the stopcock off to the continuous infusion and flush line, aspirate 1.25 to 2 mL of blood diluted with the infusion fluid, and remove the syringe. Do not discard this sample, and keep the tip sterile, because it must be reinfused after the blood sample is acquired.
5. Close the stopcock by making a one-quarter turn between the syringe and the line to the continuous infusion and flush line (see Figure 8-5, *B*).
6. Attach a sterile preheparinized syringe to the port. Switch the stopcock back one-quarter turn toward the continuous infusion and flush line to the off position.

7. Aspirate 0.25 to 1 mL of blood into the sampling syringe, depending on the volume required by the blood gas analyzer.
8. Close the stopcock by making a one-quarter turn back toward the syringe, and remove the sample (see Figure 8-5, *A*).
9. Reattach the syringe with the aspirated infusion volume, and switch the stopcock toward the infusion line (see Figure 8-5, *B*) to the off position and toward the sampling syringe to the on position. Slowly reinfuse the solution from the syringe.
10. Repeat the procedure for turning the stopcock off to the continuous infusion and flush line, remove the syringe, and attach a syringe prefilled with flush solution.
11. Open the stopcock back to the flush syringe, and infuse 0.5 to 1.5 mL of solution to flush blood from the line. Turn the stopcock off to the sampling port, and remove the flush syringe. Return the stopcock cap to its position.
12. If using a flush device (pigtail) instead of a flush syringe, turn the stopcock off to the patient (see Figure 8-5, *C*) and open to the continuous infusion and flush line, then flush solution through the sample port and turn stopcock off to the sample port to flush blood through the line to the patient.
13. Record the amount of blood sampled and flush solution infused to keep accurate input and output records.
14. Immediately apply the proper patient label to the specimen according to institutional policy.
15. For accurate results, analyze the sample immediately, or analyze room-temperature samples within 10 to 15 minutes after they are drawn. Samples placed on ice should be analyzed within 1 hour.[10]

When infusing or reinfusing solution into the umbilical or arterial line, tapping the syringe while holding it upward releases bubbles to the surface, where they can be expelled before attaching the syringe to the stopcock. When infusing, keeping the syringe in a perpendicular position will allow air bubbles to rise toward the plunger. If bubbles form, tapping them will allow them to rise toward the plunger. The practitioner should then continue infusing the solution but not infuse air bubbles into the arterial line.

COMPLICATIONS

As with any invasive method of monitoring, peripheral artery catheterization carries an increased risk of infection.[24,25] The risk is greater when a catheter has been in place for longer than 72 hours. Some complications associated with the use of arterial catheters are related to thrombotic phenomena, either at the site of the catheter tip or distal to catheter placement.

The risk of thrombosis tends to depend on the size of the catheter and the duration of placement. Children younger than 5 years are at greater risk. Once significant perfusion or thrombotic problems are identified, the catheter should be removed as soon as possible and the affected extremity managed to improve perfusion.

The circulating blood volume in a neonate is approximately 85 to 90 mL/kg; it is 70 to 75 mL/kg in children.[26] Therefore it is important to record and limit the amount of blood drawn from these patients. Hemorrhage may occur during insertion, from frequent or excessive blood sampling, and if the catheter tubing is inadvertently disconnected. Blood transfusions are given to replace the blood volume lost as a result of these factors. Pallor, decreased pulses, and poor capillary refill are all signs of ischemia. Injection of even a small amount of air into the arterial system can result in rapid and devastating air embolism to the brain.

UAC complications may also include intraventricular hemorrhage, altered mesenteric blood flow, and necrotizing enterocolitis.[24,29] These and other complications, such as misplacement into the iliac artery or infarction of various organ systems, including the kidney, liver, and spinal cord,[30,31] may result in life-threatening or prolonged severe disability.

MEASUREMENTS

The placement of arterial catheters allows direct measurement of arterial blood pressure values: the systolic and diastolic pressures. Monitoring arterial pressure waveforms helps determine the patency of the arterial line and the quality of the pulse pressure, as well as calculate the **mean arterial pressure** (MAP). The arterial line monitor calculates MAP internally. However, the following formula can be used to obtain an indirect measurement of MAP with a sphygmomanometer:

$$\text{MAP} = \frac{[(2 = \text{diastolic}) + \text{systolic}]}{3}$$

MAP is often used as an indication of left ventricular afterload, thus representing the resistance against which the left ventricle must pump. The **pulse pressure** is the difference between the systolic and the diastolic blood pressure. A decreasing pulse pressure may indicate hypovolemia, and an increasing pulse pressure may indicate a restoration of normal volume status.

CENTRAL VENOUS CATHETERS

Indications for a **central venous catheter** are as follows:

- Cardiovascular instability
- Intravascular volume disturbances (e.g., extreme dehydration, hemorrhage, increased intracranial pressure, renal failure, and diabetic ketoacidosis)
- Administration of drugs, fluids, or nutritional support to the central circulation

- The need for **central venous pressure** (CVP) monitoring[32]
- Central venous catheterization is also indicated when other peripheral access sites have been exhausted. Placing a CVP line allows measurement of **right atrial pressure** (RAP) to assist in the following:
  - Managing fluid volume
  - Infusing fluid volumes larger than a peripheral intravenous catheter can accommodate
  - Administering total parenteral nutrition and providing a secure long-term venous site in a chronically ill child[33-35]

MONITORING SITES

Techniques for central line placement in infants and children vary according to the patient's age and condition. *Monitoring sites* for central venous catheterization are locations where a peripheral vein can be cannulated by either the percutaneous or the cutdown method and the catheter can be advanced to a central location in the vena cava. The percutaneous technique is relatively safe and easy, with many potential sites.

The **cutdown method,** or surgical cannulation, reduces the risk of trauma to the vein and adjacent tissue. Cutdown also provides additional sites for patients with poor peripheral perfusion or lack of percutaneous sites. Cutdown locations include the internal and external jugular veins, common facial vein, brachial vessels, saphenous vein, and femoral veins. The cutdown technique requires experience to prevent surgical complications such as bleeding, inadvertent interruption of arterial flow, and dissection through vital structures such as muscles and nerves.

Common vessels used for percutaneous approaches are the external and internal jugular veins (the right is preferred over the left vein), subclavian vein, brachial veins, and saphenous vessels.[36-37]

The umbilicus offers a unique site in the newborn, because the umbilical vein is available for placement of a central catheter.[34]

PROCEDURE

Placement of the catheter is performed under sterile conditions with the child sedated and in accordance with the recommendations for pain control.[6] The site is usually anesthetized with lidocaine before the catheter is placed in the vein. The catheter is advanced until an RAP waveform appears on the monitor. A flush line and pressure transducer are connected as with any indwelling catheter used for pressure monitoring. Catheter placement is confirmed with a chest radiograph.

COMPLICATIONS

The major complication of venous catheter use in general is catheter-related *sepsis*, especially when the catheter is in place longer than 72 hours.[33] Fungal sepsis is especially significant in the neonatal population.[38-39] In older children the additional complication of *pulmonary embolism* is significant.[39] Embolism appears to be a largely unrecognized clinical entity in neonates.

The percutaneous approach may be difficult in patients with poor peripheral perfusion and in those with chronic disease who require many venous catheters. The cutdown method requires a higher degree of skill and training than the percutaneous approach to prevent complications. Cardiac arrhythmias may occur if the catheter tip slips into the right ventricle. Inadvertent placement of the catheter tip in the left atrium is possible if the patient has a patent foramen ovale or atrial septal defect. Perforation of the trachea is rare but has occurred with insertion into the jugular vein. Saphenous and femoral vein sites tend to be at higher risk for thrombosis. Air embolus may occur during insertion and when tubing is disconnected.[40]

Catheterization should be discontinued at the first sign of inflammation or when the patient's condition no longer requires its use. Percutaneous sites should be rotated on a regular basis. Any vein may be safely reused after 4 to 7 days.

MEASUREMENTS

The placement of a central venous catheter allows measurement of the RAP, which represents the filling pressure of the right atrium. Systemic venous return, intravascular volume, tricuspid valve performance, myocardial function, and right ventricular pressure all affect the RAP. Normal values for RAP range from 2 to 7 cm H_2O but must be interpreted cautiously, because filling pressures vary with changes in thoracic and intrapleural pressure, such as during mechanical ventilation. The value of the RAP measurement is useful in monitoring trends and after changes in therapy.

Central venous oxygen saturation can be used to provide information about the peripheral extraction, delivery, and consumption of oxygen. Central venous oxygen saturation can be sampled from a truly "central" location ($Scvo_2$) or from a mixed venous source (Svo_2). Venous oximetry aids in the monitoring and implementation of early goal-directed therapies (EGDT) for patients with septic shock; it may also help reduce morbidity and mortality of patients undergoing major or traumatic surgery.[41-44] Blood samples taken from the right atrium may be similar to mixed venous samples; however, the "gold standard" for measuring mixed venous oxygenation is obtained by using a pulmonary artery catheter. This approach demands caution, because catheter tip placement may be influenced by venous return from one portion of the body rather than the whole body. Of note, the presence of a high gradient between central venous Pco_2 ($Pcvo_2$) and arterial Pco_2 can be indicative of poor circulatory response in the settings of severe hemorrhagic shock, poor cardiac output, cardiopulmonary resuscitation, and postcardiopulmonary bypass.[45-49]

Clinical Highlight

Central line infections are a major concern when sampling from this type of line. Practitioners must take extra precautions and sample as infrequently as possible.

Decreased CVP values usually indicate hypovolemia. Reduced CVP values occur during fluid imbalance, hemorrhage, extreme vasodilation, and shock. Increased CVP values may result from the following:

- Hypervolemia, as with sudden fluid shifts or volume overload
- Interference with the right ventricle's ability to pump blood, such as tricuspid valve regurgitation or stenosis, right ventricular failure or infarction, increased pulmonary vascular resistance, or cardiac tamponade
- Increased systemic vasoconstriction
- Left ventricular failure[36]

NONINVASIVE MEASUREMENT OF CARDIAC OUTPUT AND PERFUSION

Because of the inherent risks and limitations associated with pulmonary artery catheters, trends favoring noninvasive techniques to accurately measure cardiac output and tissue perfusion have resulted in new technologies.

A noninvasive cardiac output monitor that uses partial rebreathing of CO_2 to determine cardiac output via the Fick principle can now be used in mechanically ventilated children. A study has shown that this method correlates well with simultaneous cardiac output measurements obtained from a pulmonary artery catheter in patients with a body surface area of at least 0.6 m^2 and a tidal volume of at least 300 mL.[50] This limitation in tidal volume will keep most from using this method; however, the traditional Fick method is often used in the cardiac catheter lab.

$$\text{cardiac output} = \text{oxygen consumption} / \text{arteriovenous oxygen difference}$$

Or, often abbreviated:

$$CO = VO_2 / Ca - Cv$$

The values derived from these methods are not interchangeable, and measurements from a pulmonary arterial catheter may be more sensitive. Nonetheless, the noninvasive method may be suitable for detecting large changes in cardiac output.[51] By determining the cardiac output, CVP, and arterial blood pressure, one can achieve a complete hemodynamic profile of a patient (Table 8-1).

Signal extraction pulse oximetry, which uses signal extraction software to analyze the plethysmographic waveform to determine pulsatile strength, is now being used to provide continuous noninvasive measurements of peripheral perfusion.[52] The perfusion index (PI) is the ratio of the pulsatile blood flow to the nonpulsatile or static blood in peripheral tissue.[53] The PI has been used as an objective parameter to evaluate perfusion and determine severity of illness in critically ill neonates.[54] The pulse variability index (PVI) continuously detects the cyclic changes of the perfusion index signal caused by variations in the intrathoracic pressure during a complete respiratory cycle. The PVI value has been shown to reliably predict fluid responsiveness in mechanically ventilated patients.[55]

Table 8-1 Normal Ranges of Derived Hemodynamic Parameters

PARAMETER	FORMULA	RANGE
Cardiac index	CO/BSA	3-4.5 L/minute/m^2
Stroke volume	CO/HR	50-80 mL/beat
Stroke volume index	SV/BSA	30-65 mL/beat/m^2
Systemic vascular resistance	MAP – LAP/CO	11-18 mm Hg/L/min
Pulmonary vascular resistance	PAP – PCWP/CO	1.5-3 mm Hg/L/min
Shunt fraction	$(Cco_2 - Cao_2)/(Cco_2 - Co_2)$	Less than 5%

PATIENT INFORMATION

It is important to monitor and record several parameters when taking a blood gas sample. Documenting the specific puncture or sample site and whether it is arterial, venous, mixed venous, or capillary is essential. The caregiver should also record the date and time at which the sample was taken, along with the patient's respiratory variables. Important respiratory variables include respiratory frequency, temperature, fraction of inspired oxygen (Fio_2), and specific oxygen device used. If the patient is mechanically ventilated, the record should include the type of ventilator, mode of ventilation, tidal volume, peak inflation pressure, positive end-expiratory pressure (PEEP), and other relevant settings. The patient's position (e.g., upright in an infant seat), activity level (e.g., whether crying or breath holding), clinical appearance, and other signs of respiratory distress are noted. Any adverse reactions, along with the corrective action taken, must also be documented.

FREQUENCY

The clinical status of the patient, rather than an arbitrarily set time or frequency, should dictate the need

for arterial and capillary punctures.[2,11,13] It is also important to understand that an infant, especially a premature neonate, has a much smaller quantity of blood. Frequent blood sampling results in hypovolemia and anemia in these patients. During mechanical ventilation, a 10-minute delay should be allowed after changing the Fio_2 in a patient without chronic pulmonary disease before taking an ABG sample.[56] Samples should not be drawn until 20 to 30 minutes after changing the Fio_2 of a spontaneously breathing patient without chronic pulmonary disease. Patients with chronic pulmonary disease should not have samples drawn for at least 30 minutes after an Fio_2 change.[2,13]

BLOOD GAS INTERPRETATION

Although a thorough discussion of blood gas interpretation is beyond the scope of this chapter, using the blood gas result requires some explanation of acid–base balance and gas exchange. *Gas exchange* refers to the exchange of oxygen and carbon dioxide between air and blood and then between blood and tissue. Proper gas exchange depends on many factors, such as blood flow, cardiac output, metabolic rate, diffusion, shunting, and gas concentration of the inspired air. An abnormality in any of these factors will result in a change in blood gas values and possibly an increase in the work of the cardiopulmonary system. Usually, only three values are measured during blood gas analysis: pH, Pco_2, and Po_2. Bicarbonate (HCO_3^-) and oxygen saturation are also usually calculated using the Henderson–Hasselbach equation, temperature, blood pH, and the oxyhemoglobin dissociation curve. On occasion, other non–blood gas values may be measured simultaneously, depending on the analyzer in use at the time.

Typically, interpretation of blood gas values involves acid–base interpretation, to evaluate the pH and Pco_2 values, and evaluation of oxygenation, or Po_2, separately. Normal Pao_2 and $Paco_2$ values reflect normal gas exchange, whereas an abnormality in gas exchange results in abnormal values. Normal values can vary considerably, based on patient age. Some mechanical ventilator methods that use a lung-protective strategy have redefined normal ranges in acid–base status, especially in premature infants. Recognizing normal and abnormal values helps practitioners understand more completely, and interpret, blood gas values (Table 8-2).

ACID–BASE BALANCE

Assessing acid–base balance is accomplished by evaluating the pH, $Paco_2$, and HCO_3^- values for acidosis or alkalosis and the degree of compensation present (Table 8-3). $Paco_2$ is directly proportional to the adequacy of alveolar ventilation. Thus acid–base abnormalities are classified as primarily respiratory or metabolic. The amount to which the pH is balanced by the metabolic or respiratory processes determines the degree of compensation. Boxes 8-4 to 8-7 list common causes of metabolic acidosis and alkalosis and respiratory acidosis and alkalosis.

OXYGENATION

The arterial partial pressure of oxygen (Pao_2) reflects exchange of oxygen, or oxygenation. Oxygen moves into the airway and the alveolus, at which point a pressure gradient causes it to diffuse across the alveolar–capillary membrane into the pulmonary capillary blood. It is then carried in the blood to the tissues in two forms: (1) dissolved in plasma and (2) bound to hemoglobin. Although the amount of oxygen dissolved in plasma is small, it is critical because it determines the pressure gradients among the inspired air, the blood, and the tissues. Hemoglobin carries most of the oxygen as oxyhemoglobin.

The amount of oxygen bound to hemoglobin is expressed as *arterial oxygen saturation* (Sao_2) or % O_2 Hb saturation. The oxyhemoglobin dissociation curve illustrates the relationship between Pao_2 and Sao_2 regarding the loading and unloading of oxygen by the hemoglobin molecule (Figure 8-6). The sigmoid shape of the curve shows that the hemoglobin loads

Table 8-2 Approximate Normal Range of Arterial Blood Gas Values

	ELBW (<1000 g) PREMATURE INFANT	VLBW (<1500 g) PREMATURE INFANT TO LATE-TERM INFANT	TERM INFANT TO TODDLER	CHILD TO ADULT
Parameter	(<28 weeks of GA)	(28-40 weeks of GA)	(Up to 2 years)	(>2 years)
pH	≥7.25 (≥7.20)*	≥7.25 (≥7.20)*	7.3-7.4	7.35-7.45
Arterial carbon dioxide tension ($Paco_2$, mm Hg)	45-55 (60)	45-55 (60)	30-40	35-45
Arterial oxygen tension (Pao_2, mm Hg)	45-65	50-70	80-100	80-100
Bicarbonate (Hco_3^2) (mEq/L)	15-18	18-20	20-22	22-24

ELBW, Extremely low birth weight; *GA,* gestational age; *VLBW,* very low birth weight.
*Values in parentheses may be accepted for certain lung protection ventilator strategies.

and unloads oxygen differently at various Pao_2. The Pao_2 at which the Sao_2 is 50% saturated is known as the P_{50} value. Under normal conditions, the P_{50} is approximately 26.5 mm Hg; however, this value can change depending on conditions that cause shifts in

Table 8-3 Laboratory Values for Acid–Base Disturbances

DISEASE	pH	$Paco_2$	Hco_3^2
Metabolic acidosis			
Uncompensated	↓	N	↓
Partially compensated	↓	↓	↓
Compensated	N	↓	↓
Metabolic alkalosis			
Uncompensated	↑	N	↑
Partially compensated	↑	↑	↑
Compensated	N	↑	↑
Respiratory acidosis			
Uncompensated	↓	↑	N
Partially compensated	↓	↑	↑
Compensated	N	↑	↑
Respiratory alkalosis			
Uncompensated	↑	↑	N
Partially compensated	↑	↓	↓
Uncompensated	N	↓	↓
Mixed acidosis	↓	↑	↓
Mixed alkalosis	↑	↓	↑

HCO_3^-, Bicarbonate; *N*, normal; *$Paco_2$*, arterial carbon dioxide tension.
*Compensation of metabolic alkalosis by hypoventilation is limited by the physiologic response to hypoxic hypoxia caused by the elevated $Paco_2$.

Box 8-4 Causes of Metabolic Acidosis

Diarrhea
Small bowel, biliary, or pancreatic tube or fistula drainage
Parenteral nutrition
Ingestion of chloride-containing compounds
- Calcium chloride
- Magnesium chloride
- Ammonium chloride
- Hydrochloric acid

Renal tubular acidosis
Renal failure
Carbonic anhydrase deficiency
Lactic acidosis
- Tissue hypoxia
- Sepsis
- Neonatal cold stress

Ketoacidosis
- Diabetes mellitus
- Starvation

Ingestion of toxins
- Salicylate poisoning
- Methanol poisoning
- Ethylene glycol poisoning
- Prolonged use of paraldehyde

Inborn errors of metabolism

Box 8-5 Causes of Metabolic Alkalosis

Vomiting
Nasogastric suctioning
Congenital chloride-wasting diarrhea
Dehydration
Drugs
- Diuretics
- Steroids
- Sodium bicarbonate

Cushing syndrome
Bartter syndrome
Hypokalemia
Hypochloremia
Chewing tobacco
Massive blood transfusion
Infants with cystic fibrosis fed regular formula or breast milk (low in sodium)

Box 8-6 Causes of Respiratory Acidosis

HYPOVENTILATION CAUSED BY LUNG DISEASE
Upper airway obstruction
- Laryngotracheobronchitis (croup)
- Epiglottitis
- Foreign body

Small airway obstruction
- Asthma
- Bronchiolitis

Chronic obstructive pulmonary disease
- Cystic fibrosis
- Bronchopulmonary dysplasia
- Bronchiectasis

Pneumonia
Pulmonary edema
Respiratory distress syndrome
Aspiration
- Meconium
- Foreign body

Pulmonary hypoplasia

IMPAIRED LUNG MOTION
Pleural effusion
Pneumothorax
Thoracic cage abnormalities
- Flail chest
- Scoliosis
- Osteogenesis imperfecta
- Thoracic dystrophy

APNEA
Neuromuscular Disorders
Brainstem/spinal cord injury or tumor
Paralysis of diaphragm
Medications
Muscular dystrophy
Guillain-Barré syndrome
Myasthenia gravis
Poliomyelitis

OTHER
Botulism
Extreme obesity

Box 8-7 Causes of Respiratory Alkalosis

Hyperventilation caused by:
Anxiety
Fever
Sepsis
Hypoxemia
  Pneumonia
  Atelectasis
  Pulmonary emboli
  Congestive heart failure
  Asthma
Central nervous system disorders
  Head injury
  Brain tumor
  Infection
  Cerebrovascular accident
  High altitude
Liver failure
Reye syndrome
Hyperthyroidism
Salicylate poisoning
Improperly set mechanical ventilation

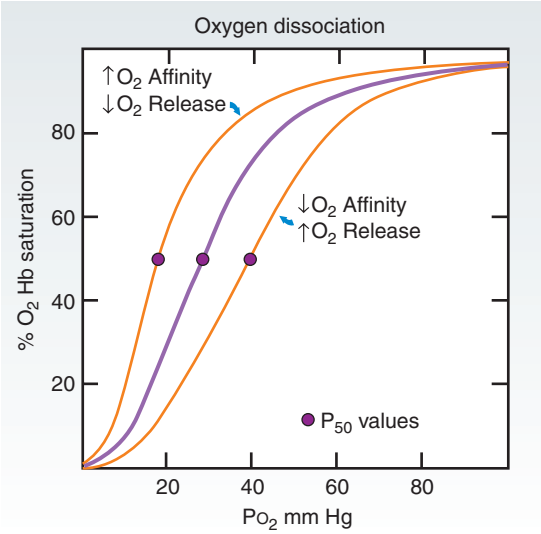


FIGURE 8-6 Oxyhemoglobin dissociation curve, illustrating the P_{50} value (P_{O_2} at 50% saturation) with the effects of right and left shifts of the curve. As the curve shifts to the right, the oxygen affinity of hemoglobin decreases, more oxygen is released at a given P_{O_2}, and the P_{50} value increases. When the curve shifts to the left, there is increased oxygen affinity, less oxygen is released at a given P_{O_2}, and the P_{50} value decreases.

Table 8-4 Factors That May Shift the Oxyhemoglobin Dissociation Curve

INCREASED AFFINITY (SHIFT TO LEFT)	DECREASED AFFINITY (SHIFT TO RIGHT)
Increased pH	Decreased pH
Decreased P_{CO_2}	Increased P_{CO_2}
Decreased temperature	Increased temperature
Decreased 2,3-DPG	Increased 2,3-DPG
Fetal hemoglobin	
Carboxyhemoglobin	
Methemoglobin	

2,3-DPG, 2,3-diphosphoglycerate; *P_{CO_2}*, partial pressure (tension) of carbon dioxide.

the oxyhemoglobin dissociation curve. The oxyhemoglobin dissociation curve is affected by several factors and may shift left or right (Table 8-4). A shift to the *right* results in a decrease in oxygen affinity, decrease in oxyhemoglobin, and increase the unloading of oxygen at the cellular level. A shift to the *left* increases oxygen affinity, increases oxyhemoglobin, and decreases the unloading of oxygen at the cellular level.

The oxygen content of the blood, expressed as a percentage, is the sum of the oxygen dissolved in the plasma and the oxygen in combination with hemoglobin (Hb, g/dL). Oxygen content accurately reflects the amount of oxygen in the blood, as follows:

$$O_2 \text{ content} = (Hb \times 1.34 \times Sao_2) + (Pao_2 \times 0.003)$$

Oxygen delivery, expressed as milliliters per minute, is the product of the O_2 content of the arterial blood and the cardiac output (Figure 8-7). Oxygen delivery reflects the total oxygen available at the cellular level in 1 minute as follows:

$$O_2 \text{ delivery} = O_2 \text{ content} \times \text{cardiac output} \times 10$$

Normal oxygen delivery ranges from 133 to 200 mL/minute in newborns, 200 to 400 mL/minute during infancy, and 460 to 1200 mL/minute during childhood.[29]

Determining **serum lactate** in a blood sample provides important information about oxygenation. Lactic acid is commonly the byproduct of anaerobic metabolism,

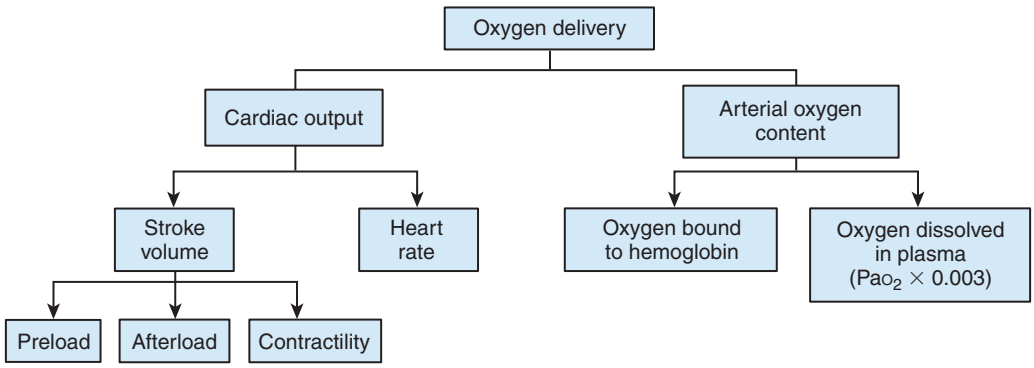


FIGURE 8-7 Components of oxygen delivery.

which results from hypoxia at the cellular level. Higher lactate levels are indicative of decreased O_2 delivery. Normal values for serum lactate typically range from 0.7 to 1.3 mmol/L.[57] A serum lactate concentration of 4.8 mmol/L or greater has been associated with increases in morbidity and mortality in children.[58]

ABNORMAL HEMOGLOBIN

Abnormal hemoglobin may also have an effect on the capacity of hemoglobin to combine with oxygen. The following hemoglobins are sometimes encountered in the infant and pediatric population: **Fetal hemoglobin** accounts for approximately 85% of the hemoglobin in the full-term infant. It causes a shift to the left of the oxyhemoglobin dissociation curve and consequently an increased affinity of hemoglobin for oxygen. In utero, this compensates for the low fetal Pao_2 and causes more oxygen to be picked up in the placenta. At about 6 months to 1 year of age, all fetal hemoglobin should be converted to normal hemoglobin.

Methemoglobin forms when hemoglobin is oxidized to the ferric state. It causes the oxyhemoglobin dissociation curve to shift to the left, resulting in a decrease in hemoglobin's ability to combine with oxygen. Nitrate-containing molecules in medications and therapeutic gases may cause methemoglobinemia.

Carboxyhemoglobin forms when carbon monoxide combines with hemoglobin, which reduces the amount of oxygen that can attach to the hemoglobin. In carbon monoxide poisoning the patient has reduced oxygen content even though the Pao_2 may be normal (see Chapter 31). A left-shifted oxyhemoglobin dissociation curve compounds the tissue hypoxia further.

Key Points

- Blood gas samples should be used to evaluate the efficiency of gas exchange, acid–base homeostasis, and cardiopulmonary interaction.
- Blood gas samples may be obtained from arterial, capillary, or venous sources. When selecting an arterial sampling site, those with adequate collateral circulation are preferred. The posterolateral foot is the least hazardous site for capillary puncture. For frequent sampling, indwelling catheters may be placed in either peripherally or centrally located vessels.
- Patient or caregiver complications may arise from blood gas sampling. Patient complications commonly include minor hematomas but may be as severe as neurovascular injury or infection. Caregiver complications are commonly related to inadvertent needle sticks. Universal precautions should always be applied during blood gas sampling and analysis.
- Indwelling catheters can provide valuable hemodynamic data. Arterial catheters can be used to monitor mean arterial pressure; central venous catheters can be used to evaluate RAP, CVP, and $Scvo_2$.
- Commonly, cardiac output can be determined noninvasively using rebreathing techniques and the Fick principle.
- Cellular oxygenation can be evaluated arterially (Pao_2, Sao_2), in conjunction with cardiac output measurements (total oxygen delivery), or via venous values ($Scvo_2$, Svo_2). Serum lactate is also an indicator of cellular oxygenation, because lactic acid is a common by-product of anaerobic metabolism.
- Functional understanding of the oxyhemoglobin dissociation curve is necessary to evaluate oxygenation, because this curve illustrates the oxygen affinity of hemoglobin at various Pao_2s. A shift of the curve to the right indicates an increase in this affinity; a shift to the left indicates a decrease in this affinity.

Assessment Questions

See Evolve Resources for answers.

1. The most accurate way to detect changes in oxygenation in the blood is by obtaining the following:
   A. Capillary blood gas
   B. Mixed venous blood gas
   C. Arterial blood gas
   D. Pulse oximetry
2. What method for obtaining blood gases should be tried initially in a neonate?
   A. Capillary blood gas determination
   B. Pulmonary artery catheterization
   C. Umbilical artery catheterization
   D. Femoral artery puncture
3. The high placement of an umbilical artery catheter should be visually confirmed at which anatomic landmark using radiography?
   A. T6-T8
   B. T3-T4
   C. L1-L2
   D. T1-T3
4. The cardiac index is calculated by which equation?
   A. $Cao_2/Spo_2 \times 100$
   B. Stroke volume/cardiac output
   C. $Cao_2 \times CO$
   D. Cardiac output/BSA
5. Common factors that can reduce pulmonary vascular resistance include:
   A. Hypoxemia and acidosis
   B. High mean airway pressure
   C. Fluid resuscitation
   D. Nitric oxide
6. Complications associated with indwelling vascular catheters include:
   A. Infection
   B. Air embolism
   C. Periventricular leukomalacia
   D. Both A and B

7. Oxygen delivery is composed of all of the following, *except:*
   - **A.** Cardiac index
   - **B.** Cardiac output
   - **C.** Hemoglobin
   - **D.** CaO_2
   - **E.** A and C
   - **F.** A, C, and D

8. Venous oximetry is helpful in reducing morbidity and mortality in the setting(s) of:
   - **A.** Septic shock
   - **B.** Major surgery
   - **C.** Inhalation injury
   - **D.** A and B

REFERENCES

1. Czervinske MP. Arterial blood gas analysis and other cardiopulmonary monitoring. In: Koff PB, Neu J, eds. *Neonatal and Pediatric Emergency Care*. St. Louis: Mosby; 1988.
2. AARC clinical practice guideline. In-vitro pH and blood gas analysis and hemoximetry. American Association for Respiratory Care. *Respir Care*. 2001;46:498.
3. Johnston CC, Stevens BJ, Franck LS, Jack A, Stremler R, Platt R. Factors explaining lack of response to heel stick in preterm newborns. *J Obstet Gynecol Neonatal Nurs*. 1999;28(6):587-594.
4. Anand KJ. Clinical importance of pain and stress in preterm neonates. *Biol Neonate*. 1998;73(1):1-9.
5. Johnston CC, Stevens BJ, Yang F, Horton L. Differential response to pain by very premature neonates. *Pain*. 1995;61(3):471-479.
6. Stevens B, Yamada J, Ohlsson A. Sucrose for analgesia in newborn infants undergoing painful procedures. *Cochrane Database Syst Rev*. 2004;(3):CD001069. https://www.ncbi.nlm.nih.gov/pubmed/15266438
7. Lefrak L, Burch K, Caravantes R, et al. Sucrose analgesia: identifying potentially better practices. *Pediatrics*. 2006;118(suppl 2):S197-S202.
8. Anand KJ. Consensus statement for the prevention and management of pain in the newborn. *Arch Pediatr Adolesc Med*. 2001;155(2):173-180.
9. National Committee for Clinical Laboratory Standards (Clinical and Laboratory Standards Institute). *Procedures for the Collection of Arterial Blood Specimens*. 4th ed. NCCLS document no. H11-A3, Wayne, PA: Clinical and Laboratory Standards Institute; 2004.
10. Centers for Disease Control. Update: universal precautions for prevention of transmission of human immunodeficiency virus, hepatitis B virus, and other bloodborne pathogens in health-care settings. *MMWR Morb Mortal Wkly Rep*. 1998;37(24):377-382, 387-388.
11. Occupational Safety and Health Administration. *Final Rule: Occupational Exposure to Bloodborne Pathogens*. Washinton, DC: OSHA; 2008.
12. Escalante-Kanashiro R, Tantaleán-Da-Fieno J. Capillary blood gases in a pediatric intensive care unit. *Crit Care Med*. 2000;28(1):224-226.
13. American Association for Respiratory Care. AARC clinical practice guideline. Capillary blood gas sampling for neonatal and pediatric patients. *Respir Care*. 1994;39(12):1180-1183.
14. McLain BI, Evans J, Dear PR. Comparison of capillary and arterial blood gas measurements in neonates. *Arch Dis Child*. 1988;63(7 Spec No):743-747.
15. Johnson KJ, Cress GA, Connolly NW, Burmeister LF, Widness JA. Neonatal laboratory blood sampling: comparison of results from arterial catheters with those from an automated capillary device. *Neonatal Netw*. 2000;19(1):27-34.
16. Courtney SE, Weber KR, Breakie LA, et al. Capillary blood gases in the neonate. A reassessment and review of the literature. *Am J Dis Child*. 1990;144(2):168-172.
17. Yildizdas D, Yapicioglu H, Yilmaz HL, Sertdemir Y. Correlation of simultaneously obtained capillary, venous, and arterial blood gases of patients in a paediatric intensive care unit. *Arch Dis Child*. 2004;89(2):176-180.
18. Koch G. Comparison of carbon dioxide tension, PH and standard bicarbonate in capillary blood and in arterial blood with special respect to relations in patients with impaired cardiovascular and pulmonary function and during exercise. *Scand J Clin Lab Invest*. 1965;17:223-229.
19. Cousineau J, Anctil S, Carceller A, Gonthier M, Delvin EE. Neonate capillary blood gas reference values. *Clin Biochem*. 2005;38(10):905-907.
20. Ueta I, Jacobs BR. Capillary and arterial blood gases in hemorrhagic shock: a comparative study. *Pediatr Crit Care Med*. 2002;3(4):375-377.
21. Sell EJ, Hansen RC, Struck-Pierce S. Calcified nodules on the heel: a complication of neonatal intensive care. *J Pediatr*. 1980;96(3 Pt 1):473-475.
22. Symansky MR, Fox HA. Umbilical vessel catheterization: indications, management, and evaluation of the technique. *J Pediatr*. 1972;80(5):820-826.
23. Barrington KJ. Umbilical artery catheters in the newborn: effects of position of the catheter tip. *Cochrane Database Syst Rev*. 2000;(2):CD000505. https://www.ncbi.nlm.nih.gov/pubmed/10796375.
24. Cole FS, Todres ID, Shannon DC. Technique for percutaneous cannulation of the radial artery in the newborn infant. *J Pediatr*. 1978;92(1):105-107.
25. Eshali H, Ringertz S, Nyström S, Faxelius G. Septicaemia with coagulase negative staphylococci in a neonatal intensive care unit. Risk factors for infection, and antimicrobial susceptibility of the bacterial strains. *Acta Paediatr Scand Suppl*. 1989;360:127-134.
26. Hazinski MF. Hemodynamic monitoring of children. In: Daily EK, Schroeder JS, eds. *Techniques in Bedside Hemodynamic Monitoring*. 5th ed. St. Louis: Mosby; 1994:275-341.
27. MacDonald MG. Umbilical artery catheterization. In: Avery GB, Fletcher MA, MacDonald MG, eds. *Neonatology: Pathophysiology and Management of the Newborn*. Philadelphia: Lippincott Williams & Wilkins; 1999:1338.
28. Tibby SM, Murdoch IA. Monitoring cardiac function in intensive care. *Arch Dis Child*. 2003;88(1):46-52.
29. Lott JW, Conner GK, Phillips JB. Umbilical artery catheter blood sampling alters cerebral blood flow velocity in preterm infants. *J Perinatol*. 1996;16(5):341-345.
30. Brown MS, Phibbs RH. Spinal cord injury in newborns from use of umbilical artery catheters: report of two cases and a review of the literature. *J Perinatol*. 1988;8(2):105-110.

31. Cumming WA, Burchfield DJ. Accidental catheterization of internal iliac artery branches: a serious complication of umbilical artery catheterization. *J Perinatol*. 1994;14(4):304-309.
32. Duck S. Neonatal intravenous therapy. *J Intraven Nurs*. 1997;20(3):121-128.
33. Widness JA, Kulhavy JC, Johnson KJ, et al. Clinical performance of an in-line point-of-care monitor in neonates. *Pediatrics*. 2000;106(3):497-504.
34. Hamilton H, Fermo K. Assessment of patients requiring i.v. therapy via a central venous route. *Br J Nurs*. 1998;7(8):451-454, 456-460.
35. Chiang VW, Baskin MN. Uses and complications of central venous catheters inserted in a pediatric emergency department. *Pediatr Emerg Care*. 2000;16(4):230-232.
36. Jordan W. Arterial catheters. In: Blumer JL, ed. *A Practical Guide to Pediatric Intensive care*. St. Louis: Mosby; 1990:825.
37. MacDonald MG. Umbilical vein catheterization. In: Avery GB, Fletcher MA, MacDonald MG, eds. *Neonatology: Pathophysiology and Management of the Newborn*. Philadelphia: Lippincott Williams & Wilkins; 1999:148.
38. Trotter CW. Percutaneous central venous catheter-related sepsis in the neonate: an analysis of the literature from 1990 to 1994. *Neonatal Netw*. 1996;15(3):15-28.
39. Green C, Yohannan MD. Umbilical arterial and venous catheters: placement, use, and complications. *Neonatal Netw*. 1998;17(6):23-28.
40. Wynsma LA. Negative outcomes of intravascular therapy in infants and children. *AACN Clin Issues*. 1998;9(1):49-63.
41. Blasco V, Leone M, Textoris J, Visintini P, Albanèse J, Martin C. [Venous oximetry: physiology and therapeutic implications]. *Ann Fr Anesth Reanim*. 2008;27(1):74-82.
42. Christensen M. Mixed venous oxygen saturation monitoring revisited: thoughts for critical care nursing practice. *Aust Crit Care*. 2012;25(2):78-90.
43. Marx G, Reinhart K. Venous oximetry. *Curr Opin Crit Care*. 2006;12(3):263-268.
44. Walkey AJ, Farber HW, O'Donnell C, Cabral H, Eagan JS, Philippides GJ. The accuracy of the central venous blood gas for acid-base monitoring. *J Intensive Care Med*. 2010;25(2):104-110.
45. Futier E, Robin E, Jabaudon M, et al. Central venous O_2 saturation and venous-to-arterial CO_2 difference as complementary tools for goal-directed therapy during high-risk surgery. *Crit Care*. 2010;14(5):R193.
46. Idris AH, Staples ED, O'Brien DJ, et al. Effect of ventilation on acid-base balance and oxygenation in low blood-flow states. *Crit Care Med*. 1994;22(11):1827-1834.
47. Steedman DJ, Robertson CE. Acid base changes in arterial and central venous blood during cardiopulmonary resuscitation. *Arch Emerg Med*. 1992;9(2):169-176.
48. Utoh J, Moriyama S, Goto H, et al. [Arterial-venous carbon dioxide tension difference after hypothermic cardiopulmonary bypass]. *Nihon Kyobu Geka Gakkai Zasshi*. 1997;45(5):679-681.
49. Weil MH, Tang W, Noc M. Acid-base balance during cardiopulmonary resuscitation. *Crit Care Med*. 1993;21(suppl 9):S323-S324.
50. Levy RJ, Chiavacci RM, Nicolson SC, et al. An evaluation of a noninvasive cardiac output measurement using partial carbon dioxide rebreathing in children. *Anesth Analg*. 2004;99(6):1642-1647.
51. Koppl J. Hemodynamic monitoring using a PiCCO in a ten month old infant suffering from serious burn injury. *Bratisl Lek Listy*. 2000;108:359.
52. Masimo Corporation. *Clinical Applications of Perfusion Index*. Available at http://www.masimo.de/pdf/whitepaper/LAB3410D.pdf. Retrieved May 2017.
53. Kotake Y, Yamada T, Nagata H, Suzuki T, Takeda J. Can mixed venous hemoglobin oxygen saturation be estimated using a NICO monitor? *Anesth Analg*. 2009;109(1):119-123.
54. De Felice C, Latini G, Vacca P, Kopotic RJ. The pulse oximeter perfusion index as a predictor for high illness severity in neonates. *Eur J Pediatr*. 2002;161(10):561-562.
55. Cannesson M, Slieker J, Desebbe O, et al. The ability of a novel algorithm for automatic estimation of the respiratory variations in arterial pulse pressure to monitor fluid responsiveness in the operating room. *Anesth Analg*. 2008;106(4):1195-1200.
56. Hess D, Good C, Didyoung R, et al. The validity of assessing arterial blood gases 10 minutes after an FIO2 change in mechanically ventilated patients without chronic pulmonary disease. *Respir Care*. 1985;30:1037.
57. Vincent JL. Lactate and biochemical indexes of oxygenation. In: Tobin MJ, ed. *Principles and Practices of Intensive Care Monitoring*. New York: McGraw-Hill; 1998:369-375.
58. Basaran M, Sever K, Kafali E, et al. Serum lactate level has prognostic significance after pediatric cardiac surgery. *J Cardiothorac Vasc Anesth*. 2006;20(1):43-47.

Noninvasive Monitoring In Neonatal And Pediatric Care

9

Craig D. Smallwood

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. Describe the fundamental monitoring methods used to assess heart rate, respiratory rate, and blood pressure.
2. Recognize the principles of operation of pulse oximetry.
3. Describe proper placement of a pulse oximeter probe.
4. Describe the difference between end-tidal CO_2 monitoring and volumetric capnography.
5. Explain the physiologic phenomenon responsible for a gradient between end-tidal and arterial CO_2 measurements.
6. Interpret specific abnormalities associated with capnograms.
7. Explain the importance of proper transcutaneous site selection and application.
8. List two problems associated with transcutaneous monitoring.
9. State the objective of indirect calorimetry.
10. Identify limitations of indirect calorimetry.
11. Describe the general function of near-infrared spectroscopy and most common use in infants.

Key Terms

alveolar volume
calorimetry
capnography
carbon dioxide production (Vco_2)
carboxyhemoglobin
CO_2 elimination
dead-space volume
deoxyhemoglobin
direct calorimetry
electrocardiography
end-tidal CO_2
energy expenditure
indirect calorimetry
infrared spectrometry
mainstream capnography
near-infrared spectroscopy (NIRS)
oxygen consumption (Vo_2)
oxyhemoglobin
postductal oxygen saturation
preductal oxygen saturation
$P_{TC}o_2$
$P_{TC}co_2$
pulse oximetry
regional oxygen saturation in the brain ($bRSO_2$)
resting energy expenditure
sidestream capnography
signal extraction technology (SET)
transcutaneous monitor
volumetric capnography

Monitoring of neonatal and pediatric patients is essential during each phase of the disease process (from the outpatient clinic to emergency room to the intensive care unit). Close monitoring of physiologic function can provide clinicians with information that helps guide decision making. Appropriate monitoring (including proper application, use, and interpretation of data) can delineate the need for clinical interventions and the effect of those interventions over time. Respiratory-related illness is a leading reason for hospital admission in pediatrics and is therefore critical. Technologies have evolved over the last few

decades to enhance the accuracy of measurements, eliminate the propensity for human error and bias, and readily display information dynamically and as a trend. These efforts have led to a number of specific devices that the respiratory therapist must learn to master to provide the best care possible, which can prove to be lifesaving.[1]

FUNDAMENTAL MONITORING

Heart rate, respiratory rate (RR), and blood pressure are three of the four vital signs that can be noninvasively monitored and are readily available in a variety of clinical settings. Because these were discussed in Chapter 4, here we give only a brief summary of essentials for patients who are continuously monitored, such as in the intensive care unit.

ELECTROCARDIOGRAPHY

Electrocardiography (ECG) is used to measure and display the heart rate and rhythm by measuring body surface electrical potentials generated by the heart. It is easy to perform, noninvasive, and has been used for many years. Typically, ECG monitoring uses a set of three electrodes, which are placed on the upper left (LA), upper right (RA), and lower left (LL) portions of patient's thorax. Most lead manufacturers color code the leads to assist with appropriate placement: LA is black, RA is white, LL is red. A simple mnemonic to ensure proper placement of the electrodes is *White on the right, smoke over fire. White* refers to the white lead, *smoke* refers to the black lead, and *fire* refers to the red lead. Electrodes are available in different sizes to be applied according to patient size. The electrodes are typically plugged into the bedside monitor so that data (heart rate and waveform) can be displayed at the bedside and transmitted to a central telemetry console for remote monitoring. Continuous monitoring and interpretation of the ECG can ensure adequate heart rate and detect potentially life-threatening changes in rate and rhythm (such as severe bradycardia or ventricular fibrillation). A normal ECG waveform will have several distinct features, including depolarization and repolarization of the atria and ventricles. The most prominent feature is the QRS complex, which results from ventricular contraction. However, limitations of the technology, included inaccurate measurements caused by motion artifact, for instance, should be considered when interpreting results. Additionally, infant electrocardiographs present extra challenges caused by rapidly changing hemodynamics. A full-term infant will have a different ECG than a premature baby (34 weeks of gestation or less). In addition, the ECG of a normal infant will undergo changes during the baby's first few weeks of life. Not until a child is approximately 3 years of age will the ECG start to resemble that of an adult, although still with considerable differences.[2]

IMPEDANCE RESPIRATORY RATE

Using the same electrodes as those employed during ECG monitoring, RR and impedance tracing can be measured and displayed on a bedside monitor and telemetry console for continuous monitoring and assessment. The monitor works by introducing a small alternating current into the patient, which is not felt by the patient and is monitored by one of the other electrodes. Because body tissue and air impede the flow of electricity, it is possible to detect RR based on changes in impedance. It is important to note that impedance RR monitors do not measure respirations (gas exchange) but simply chest excursions. In some cases, children may exhibit ineffective breathing movements (in which case the thorax could change shape) without actually inhaling or exhaling a breath. Although rare, in this case the impedance monitor would not provide an accurate reflection of RR. A more accurate monitor of respiration is **end-tidal CO_2,** which is discussed later. However, for most patients, impedance RR equals the number of respirations; therefore it is widely monitored and used throughout the hospital.

NONINVASIVE BLOOD PRESSURE

Blood pressure (BP) is another of the four vital signs and is an essential metric of physiologic health in the intensive care unit. Although not a direct measure of cardiac output, BP may be used, with caution, as a surrogate for cardiac output (along with proper assessment of heart rate, perfusion, etc.). It is therefore a physiologic variable, and increases and decreases in BP can be life threatening, requiring immediate intervention. Additionally, in mechanically ventilated children, increases in intrathoracic pressure (by increasing positive end-expiratory pressure, for example) can reduce venous return, resulting in decreased BP. Close BP monitoring is therefore necessary for mechanically ventilated children, particularly the most severely ill. Although BP can be determined by using an indwelling arterial catheter, the procedure is invasive and increases the risk for infection. Noninvasive BP monitoring can provide periodic monitoring for patients who do not require such intensive monitoring. Generally, a noninvasive BP is determined by using a cuff affixed to an upper extremity. In larger patients, generally the cuff is placed around the bicep, but for small children or infants a cuff can be placed around a leg. Although this measure can be determined manually, most intensive care units have an automated system that is integrated into the bedside monitor. Unlike manual determination of systolic and diastolic blood pressure by auscultation of Korotkoff sounds, an automated system uses a sensitive transducer to measure simultaneously the total pressure in the cuff as well as oscillations that result from the pulsating blood vessel. The systolic and diastolic blood pressures are recognized by the changes

in oscillation intensity. Often, monitors can calculate BP at clinician-determined intervals (anywhere from minutes to hours) and display the results as needed. Care should be taken to ensure proper placement of the cuff or results will not reflect the patient's true BP. As mentioned previously, noninvasive BP by cuff cannot be monitored continuously and may not be sufficient for some acutely ill children. In mechanically ventilated children, increases in intrathoracic pressure (by increasing positive end-expiratory pressure, for example) can reduce venous return, resulting in decreased BP.

PULSE OXIMETRY

Oxygenation monitoring is essential in neonatal and pediatric patients, particularly those who are critically ill, such as during supported ventilation. Hypoxemia, reduced blood oxygen content, can lead to tissue and end organ damage, brain and developmental delays, and death. Conversely, hyperoxemia, elevated blood oxygen content, can cause retinopathy of prematurity in neonates, and long-term exposure to elevated concentrations of oxygen can cause chronic changes in pulmonary tissue or even fibrosis. Skilled caregivers cannot always detect hypoxemia by visual assessment when oxygen saturation levels drop below 80%. **Pulse oximetry** provides a means of monitoring oxygenation level trends over time or in response to therapeutic interventions. Pulse oximetry is simple to use, is accurate (when applied correctly), and poses minimal discomfort to the patient. Despite limited scientific evidence showing improved outcomes with pulse oximetry, it is widely used to continuously monitor patients throughout the hospital, in clinic, and at home.[3]

PRINCIPLES OF OPERATION

Oxygen is carried in the blood in two forms: bound and dissolved. Approximately 98% of the oxygen found in arterial blood is bound to hemoglobin, whereas the remaining 2% is dissolved in the plasma.[3] The hemoglobin binds with oxygen in the pulmonary circulation and is then released at the tissue level for use. The saturated concentration of oxygen in the artery (Sao_2) is related to that which is dissolved in the plasma (Pao_2). This relationship and its modified response to pH, CO_2, and other factors is described by the **oxyhemoglobin** dissociation curve. Pulse oximeters measure the relative concentration of oxyhemoglobin to total hemoglobin in pulsatile arterial blood (Spo_2).[3]

A pulse oximeter sensor has two light-emitting diodes (LEDs) that function as light sources and a photodiode that measures the amount of light from the LEDs (Figure 9-1). One LED emits red light, and the other diode emits infrared light. The sensor is placed over a translucent part of the body (finger, toe, earlobe, etc.). As the light from the diodes passes through the blood and tissue, some of the light from both the red and the infrared diodes is absorbed by oxyhemoglobin. The photodiode then measures the amount of light that passes through the body without being absorbed. Because oxyhemoglobin (hemoglobin bound with oxygen) and **deoxyhemoglobin** (hemoglobin not bound with oxygen) absorb significantly different amounts of light, the proportion of oxyhemoglobin (expressed as a percentage) is determined (Figure 9-2). To measure arterial blood, the sensor detects pulsatile blood as it enters the tissue.

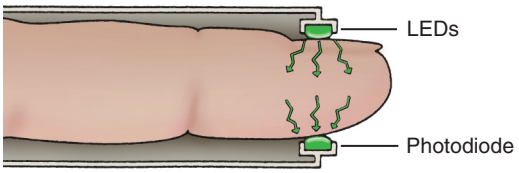


FIGURE 9-1 Proper alignment of light-emitting diodes (LEDs) opposite the photodiode in a sensor applied to a patient's finger. (From *Pulse oximetry*, note 7. Image used with permission from Nellcor Puritan Bennett, LCC, Boulder, CO, part of Covidien.)

APPLICATION

Pulse oximeters do not require calibration at the bedside because they are precalibrated during the manufacturing process and the calibration is built in to the device's algorithm. The wavelength of the sensor diodes is checked and then coded into a calibration resistor. The instrument decodes the resistor each time it is turned on, at periodic intervals during use, or when a new sensor is used.

Various sensors are available for different clinical settings. The disposable bandage type for wrapping around a finger or toe is used most often for neonates and larger children (Figure 9-3). Application of the sensor is crucial to the quality of readings from the pulse oximeter. The sensor should be placed over a vascular area with the diodes and the photodiode directly opposite each other and in good contact with the skin. The sensors should be placed firmly to avoid falling off or motion artifact, but care should be taken to avoid overtightening and compromising local circulation.[4] The sensor sites should be changed routinely and the monitoring sites assessed for tissue injury. Finger and ear clips are also available for larger patients. Care must be taken with the clip type of sensors, because the clinician has limited control of the spring tension and the pressure created on the extremity.

The gold standard for blood oxygen measurement is the arterial blood gas. However, this requires an arterial sample be obtained using a needle and syringe or indwelling catheter. Needle sticks can be traumatic for some children, and the pain associated with it can increase agitation, thus increasing respiratory and heart rates, which may unintentionally affect gas exchange, rendering the arterial blood gas biased

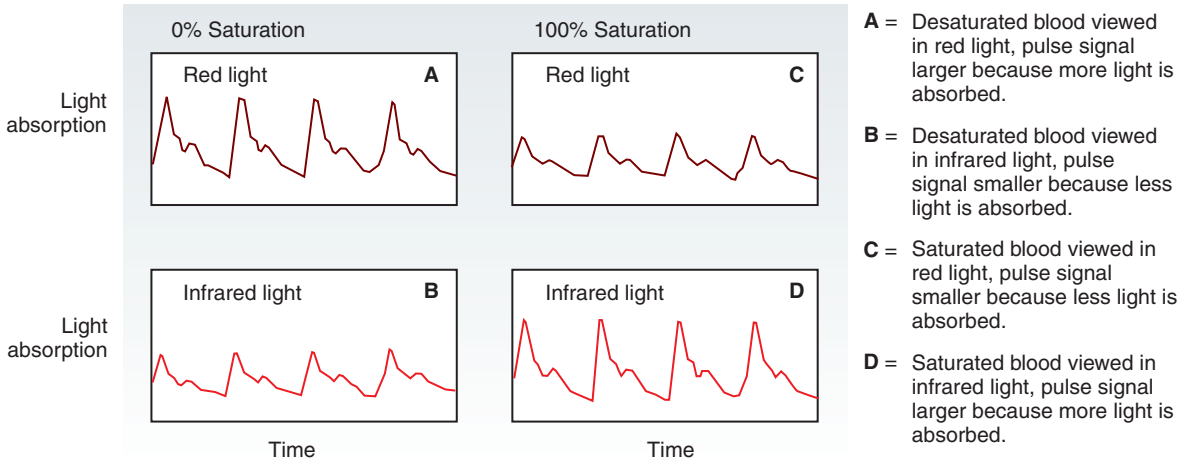


FIGURE 9-2 Differences in light absorption between deoxygenated hemoglobin (0% saturation) and oxygenated hemoglobin (100% saturation) during pulsatile signals. (From *Clinical reference card*, no 1. Hayward, CA, Nellcor, 1988.)

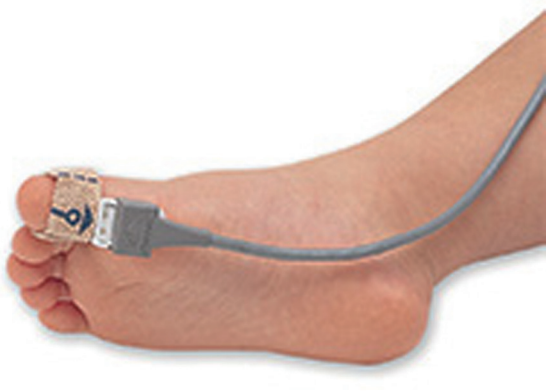


FIGURE 9-3 Pulse oximeter probe attached to a child's toe. (©2018 Medtronic. All rights reserved. Used with the permission of Medtronic.)

and limited in usefulness. Conversely, pulse oximetry is noninvasive, comfortable, and therefore routinely used to assess oxygenation in the neonatal and pediatric population.[4]

In the premature infant, site selection is crucial. In cardiac circulation, the ductus arteriosus provides a communication between the aorta and the pulmonary artery during fetal circulation. The failure of the duct to close after birth results in a left-to-right shunt, referred to as a *patent ductus arteriosus (PDA).* Three arterial vessels take off from the aorta. The first diverts blood to the right arm and head, before the PDA (preductal). The remaining vessels occur postductal and therefore contain some proportion of deoxygenated blood resulting from shunting of deoxygenated pulmonary blood into the arterial circulation. **Preductal oxygen saturation** reflects an infant's blood state before the ductus arteriosus and before it has a chance to be mixed with deoxygenated blood. A **postductal oxygen saturation** is a measurement taken after the ductus arteriosus and has been mixed with deoxygenated blood from the pulmonary circulation. Therefore sensor placement on the right arm or head will reflect preductal values and on the left arm and the lower parts of the body will reflect postductal oxygen saturation values. In some premature infants, preductal and postductal oxygen saturations are simultaneously monitored. The difference between preductal and postductal oxygen saturation can reflect the degree of shunting, response to related therapies, and need for intervention. This phenomenon can be observed using a transcutaneous monitor as well, which is discussed later in this chapter.

LIMITATIONS

Pulse oximetry was originally developed by anesthesiologists for use in the operating room. Unlike the operating room, however, patients can be awake, alert, and active. This introduces motion artifacts that adversely, albeit temporarily, affect the accuracy of pulse oximetry.[5] Artifact typically manifests in two ways. First, the device may continue to read Spo_2 but underestimate the true concentration of oxyhemoglobin, potentially setting off a lower alarm limit. Second, if the artifact obscures the pulse, the "loss of pulse" alarm could be triggered, indicating the device is not able to pick up any information. Furthermore, electrical noise and changes in ambient light (e.g., fluorescent) can produce artifacts that affect pulse oximeters; however, with improved technology, this is less of a problem than in the past. Accuracy of arterial oxygen saturation measurement is reduced at levels below 80%. However, the clinical relevance of this is limited, because saturations less than 80% indicate a medical emergency for most children. When using a finger probe, some nail polishes can negatively affect Spo_2 accuracy, causing displayed values to be falsely low. Acrylic nails do not appear to interfere with pulse oximetry readings.[3] It is important to note that impaired peripheral perfusion (perfusion to where the

sensor is placed) can affect the Spo_2. Conditions such as low cardiac output, vasoconstriction, vasoactive therapy, and hypothermia can adversely affect the accuracy of pulse oximetry, and therefore care should be taken in these circumstances when interpreting results.[4]

Some studies have questioned the correlation of pulse oximeters and arterial blood gases in the neonate.[6] Neonatal patients with hyperbilirubinemia or anemia and those receiving hyperalimentation, total parenteral nutrition (TPN), or inotropic infusions may not yield ideal correlation with arterial blood gases. The sensitivity of pulse oximetry to detect the presence and degree of hyperoxia may be limited in the neonatal patient. If the oximeter is reading an Spo_2 of 100%, the arterial oxygen tension (Pao_2) could be between 90 and 250 mm Hg. However, many neonatal intensive care units target an Spo_2 below a certain threshold to reduce the risk of retinopathy of prematurity in premature babies. Proper site selection, understanding the principles of operation, and routinely assessing the patient to correlate the Spo_2 with other physiologic data should help minimize these limitations and ensure that the pulse oximeter remains a valuable clinical tool.[3-7]

Another important limitation concerns other gases that can be combined with hemoglobin, such as carbon monoxide (yielding **carboxyhemoglobin**). Most pulse oximeters cannot differentiate between oxyhemoglobin and carboxyhemoglobin. Therefore, in subjects with suspected carbon monoxide inhalation, a pulse oximeter will yield a percentage of hemoglobin with bound gases, not specifically those bound with oxygen. Caution should be exercised when interpreting pulse oximetry data in patients with suspected inhalation injury.

Recent technologic advancements in pulse oximetry, such as **signal extraction technology (SET),** and noninvasive hemoglobin and oxygen content measurements, may prove to benefit patients with enhanced monitoring. SET pulse oximetry combines the traditional method based on red and infrared pulse oximeter signals with advanced techniques, allowing signal "noise" produced by venous blood movement during motion to be filtered out, producing more accurate measurements of the arterial oxygenation of patients who are moving or with poor tissue perfusion. Noninvasive hemoglobin and oxygen content can be measured using dedicated pulse oximetry devices and specialized sensors. Some studies have shown that this provides an accurate measurement of hemoglobin in most subjects.[9] However, more research is needed to assess the accuracy and agreement of measurements in critically ill infants and children, particularly because these patients may have reduced peripheral perfusion that could adversely affect hemoglobin measurements during pulse oximetry.

CAPNOGRAPHY

Capnography is the measurement and representation of exhaled carbon dioxide. Capnography uses a noninvasive airway adapter or specialized nasal cannula as well as a dedicated monitoring device to measure the exhaled partial pressure of CO_2 (Pco_2) and the total volume of exhaled CO_2 per unit of time. This technique is especially useful during mechanical ventilation because it can provide clinicians with important information about ventilation (such as changes in hemodynamics, confirmation of endotracheal tube placement, and response to changes in therapy, as well as others).[10] **End-tidal CO_2** refers to the partial pressure of CO_2 and the end of an exhalation ($Petco_2$) and is commonly displayed in the unit mm Hg. **Volumetric capnography** refers to the simultaneous measurement of gas flow and CO_2 concentrations such that volumetric CO_2 values can be numerically and graphically displayed. Volumetric carbon dioxide elimination (Vco_2) is typically measured in milliliters per minute (mL/minute).

PRINCIPLES OF OPERATION

The most common methods used to continuously measure carbon dioxide concentration in an exhaled gas employ **infrared spectroscopy** and mass spectrometry. Infrared spectrometry is based on the fact that infrared light is strongly absorbed by carbon dioxide. Mass spectrometry uses an electronic beam that ionizes gases. The resulting particles are then deflected, emitting a specific wavelength by which the concentration of the gas can be determined. Infrared spectrometry allows for real-time, continuous measurement and display of Pco_2 with a delay time of about 0.25 second. Mass spectrometry is also accurate but has a delay time of 0.1 to 80 seconds. In addition, it is expensive, is not as portable, and is therefore rarely used at the bedside.[11]

Gases from an exhaled breath can reach the sample chamber in one of two ways. **Mainstream capnography** is used primarily during mechanical ventilation, with placement at the proximal end of an endotracheal tube (Figure 9-4). This method uses infrared spectrometers. **Sidestream capnography** analyzers continuously aspirate a sample of gas through a small tube to the analyzer and can be used during mechanical ventilation and spontaneous breathing. Bedside sidestream monitors also primarily use infrared spectroscopy, although some do use mass spectrometry. However, the narrow tubing can become occluded with mucus or water, causing inaccuracies. In addition, infants with small tidal volumes can contaminate the sample line with fresh gases. It is important to choose the correct adapter given a patient's size and gas flows. An infant CO_2 adapter has a small internal diameter and therefore small dead space (which reduces the amount of added mechanical dead space) but increases the airway resistance. If an infant CO_2 adapter is used on a larger

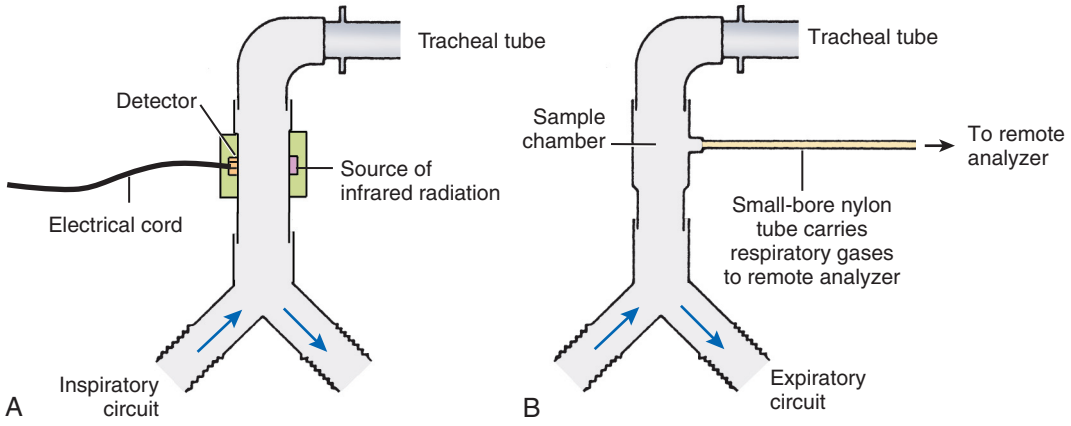


FIGURE 9-4 Location of mainstream airway adapter **(A)** and sidestream adapter **(B)** in patient's airway.

child, airway resistance is elevated, which could cause significant discomfort for the patient and limit ventilation. On the other hand, if an adult sensor is placed on a small infant, the proportion of added mechanical dead space to the breathing circuit could cause rebreathing of CO_2, impeding appropriate ventilation. It is therefore important to follow manufacturer's recommendations for sensor selection.

$Petco_2$ can be used as a surrogate for the arterial partial pressure of CO_2 ($Paco_2$) within physiologic limits. Normally, $Petco_2$ is 2 to 5 mm Hg below $Paco_2$. The reason for this is the proportion of dead-space ventilation. At the alveolar level, $Paco_2$ will equal the partial pressure of CO_2 in the alveolar gas ($PAco_2$) as diffusion occurs across the alveolar capillary membrane. Each breath contains a portion that is not involved in gas exchange, referred to as the **dead-space volume** (such as that in the endotracheal tube and conducting airways). **Alveolar volume** is that which is involved in gas exchange as it comes into direct contact with capillaries for O_2 and CO_2 exchange. In healthy infants and children, dead space accounts for around 30% to 40% of ventilation. This means that for a tidal volume of 100 mL, one would expect 30 mL to not be involved in gas exchange and therefore not contain CO_2. Let us assume that $Paco_2$ and consequently $Paco_2$ contain 40 mm Hg. In this example, 70 mL contains 40 mm Hg of CO_2 and 30 mL contains 0 mm Hg. As these gases are mixed and exhaled, the alveolar gas is "diluted" by dead space and the $Petco_2$ concentration may be around 35 mm Hg. It is essential that the clinician has a firm understanding of this physiologic phenomenon, because changes in dead space will affect the gradient between $Petco_2$ and $Paco_2$; increased dead space will increase the gradient, and reduced dead space will reduce the gradient. $Petco_2$ monitoring has also been used to help ensure the adequacy of chest compressions during cardiopulmonary resuscitation and to confirm proper placement of endotracheal tubes after intubation.

If $Petco_2$ is thought of as the concentration of CO_2 in an exhaled breath, Vco_2 is thought of as the flow of CO_2 out of the patient (**CO_2 elimination**). Some CO_2 monitors, and often those that are integrated into the mechanical ventilator, provide simultaneous Pco_2 and flow data. A plot of Pco_2 and volume can therefore be plotted. The Pco_2–volume plot enables the estimation of airway dead-space volume, alveolar volume, CO_2 elimination, and alveolar minute ventilation (Figure 9-5). CO_2 elimination is normally 2 to 3 mL/kg/minute in adults. However, typical values seen in children are greater when normalized to body weight. Newborn infants can range approximately 5 to 7 mL/kg/minute, and older children anywhere from 3 to 5 mL/kg/minute.[12] Monitoring CO_2 elimination may help guide decision making and response to ventilator titration in mechanically ventilated children.[10]

LIMITATIONS

Although both methods for Pco_2 monitoring require the placement of an airway adapter proximal to the patient's breathing circuit, mainstream capnography adapters tend to be a bit more bulky, because the sensors used to measure Pco_2 are located at the airway. In small infants, the added weight of the mainstream sensor can be a concern. In some cases it may not be used because of this, but in most cases can be used safely with careful attention to sensor placement and endotracheal tube securement. As discussed earlier, inappropriate sensor selection can have a detrimental effect on ventilation with each method. Water condensation and secretions can also build up to the point that they occlude either the sensor window in mainstream analyzers or the samples line in sidestream analyzers. Frequent assessment of the sensor, sensor replacement, and appropriate secretion and humidification management will ensure that Pco_2 is measured continuously without protracted interruptions.

INTERPRETATION OF CAPNOGRAM

Trending $Petco_2$ will give the bedside clinician a good sense of the adequacy of ventilation for the patient. An increase in $ETco_2$ from previous levels might indicate

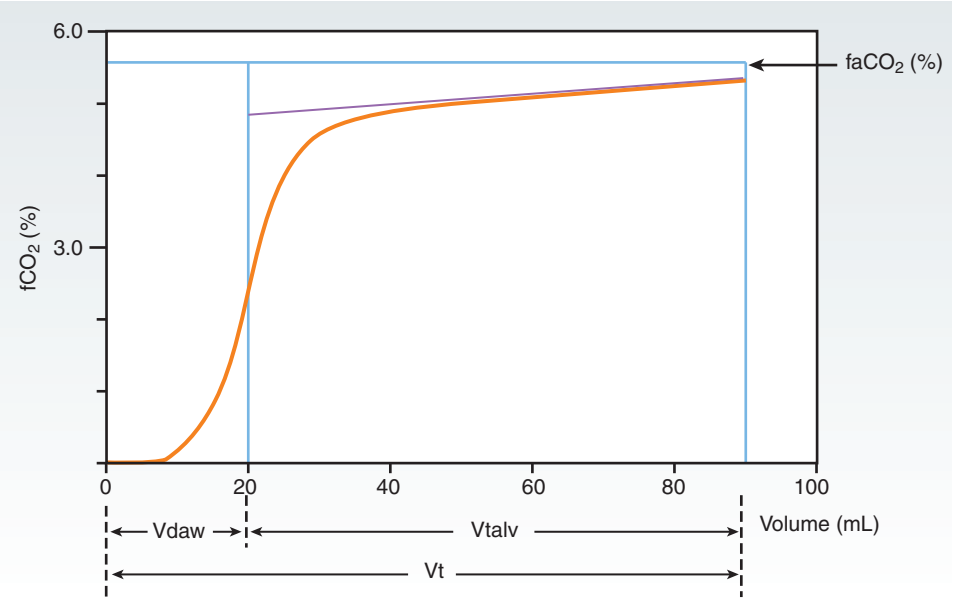


FIGURE 9-5 Volumetric capnography plot of carbon dioxide (CO_2) (expressed as a fraction) and exhaled tidal volume showing airway dead space, alveolar volume, and dead-space volume.

hypoventilation. The possibility of decreased tidal volume or RR should be investigated. A decrease in $ETco_2$ from previous levels might indicate hyperventilation. Interpretation of the capnogram (waveform display of the exhaled carbon dioxide) can also help the clinician detect other ventilatory abnormalities.

The normal capnogram can be divided into four phases (Figure 9-6):

Phase A-B: The inspiratory phase, during which the sensor detects no carbon dioxide

Phase B-C: The initial expiratory phase, during which carbon dioxide rapidly increases as the alveoli begin to empty

Phase C-D: The completion of expiration as the alveoli empties (alveolar plateau) and shows a slight increase in carbon dioxide

Phase D-E: The beginning of inspiration as the waveform returns to zero

DETECTION OF VENTILATION PROBLEMS

The clinician can use the capnogram to detect important ventilation problems in neonatal and pediatric patients.

Endotracheal Tube in Esophagus

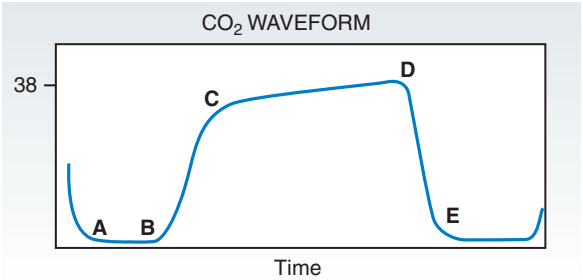
A normal capnogram provides evidence that the endotracheal tube is in the proper position and that alveolar ventilation is occurring. When the endotracheal tube is placed incorrectly in the esophagus, no carbon dioxide will be detected or only small transient capnograms will be present.

Rebreathing

Rebreathing is characterized by an elevation in the A-B phase of the capnogram, with a corresponding increase in $ETco_2$. It indicates the rebreathing of previously exhaled carbon dioxide. Rebreathing can be caused by allowing an insufficient expiratory time or by inadequate inspiratory flow (Figure 9-7).

Obstructed Airway

Obstruction of the expiratory flow of gas will be noted as a change in the slope of the B-C phase of the capnogram. The B-C phase may diminish without a plateau. Obstruction can be caused by a foreign body in the upper airway, increased secretions in the airways, the



A–B: Exhalation of CO_2 free gas from dead space.

B–C: Combination of dead space and alveolar gas.

C–D: Exhalation of mostly alveolar gas (alveolar plateau).

D: "End-tidal" point—CO_2 exhalation at maximum point.

D–E: Inhalation of CO_2 free gas.

FIGURE 9-6 Normal capnogram.

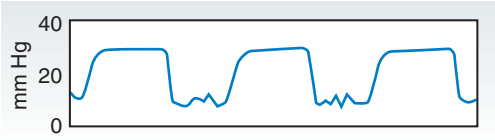


FIGURE 9-7 Effect of rebreathing carbon dioxide on the capnogram. Note that the inspiratory level does not return to zero. (From Stock MC: Non-invasive carbon dioxide monitoring. *Crit Care Clin* 4:511, 1988.)

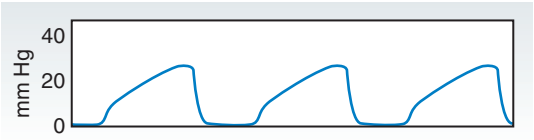


FIGURE 9-8 Capnogram with sloping alveolar plateau representative of airway obstruction. (From Stock MC: Non-invasive carbon dioxide monitoring. *Crit Care Clin* 4:511, 1988.)

patient having bronchospasms, or partial obstruction of the ventilator circuit (Figure 9-8).

Paralyzed Patients

Patients who are paralyzed and receiving mechanical ventilation may develop a cleft in the C-D phase of the capnogram. The cleft may indicate a return in diaphragmatic activity and the need for additional paralytic agents (Figure 9-9).

Pneumothorax

A stair-stepping of the D-E phase of the capnogram, caused by unequal and incomplete emptying of the lungs, and a failure to return to baseline may suggest a pneumothorax (Figure 9-10).

Cardiogenic Oscillations

Cardiogenic oscillations may be seen in patients with long expiratory times and slow respiratory rates. The

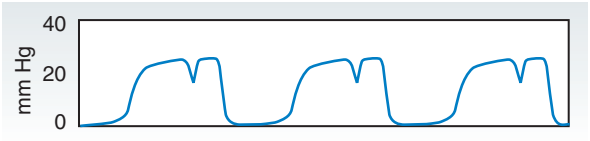


FIGURE 9-9 Curare cleft in the alveolar plateau. (From Stock MC: Non-invasive carbon dioxide monitoring. *Crit Care Clin* 4:511, 1988.)

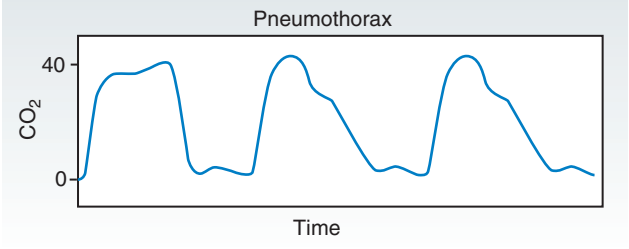


FIGURE 9-10 Stair effect on the descending limb of the capnogram indicating a potential pneumothorax. (From Curley MA, Thompson JE: End tidal CO_2 monitoring in critically ill infants and children. *Pediatr Nurs* 16:397, 1990.)

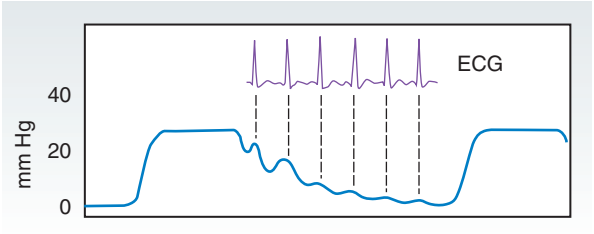


FIGURE 9-11 Cardiogenic oscillations in synchrony with the electrocardiography (ECG) signal. (From Stock MC: Non-invasive carbon dioxide monitoring. *Crit Care Clin* 4:511, 1988.)

oscillations will be seen in the D-E phase of the capnogram and occur as the heart contracts and moves the lungs, causing gas flow (Figure 9-11).

Volumetric Capnography (the Carbon Dioxide–Volume Plot)

The concentration of CO_2 is plotted against exhaled tidal volume to determine relevant ventilation data such as airway dead space, alveolar tidal volume, and extrapolation of CO_2 elimination and alveolar minute ventilation.

TRANSCUTANEOUS MONITORING

In the hands of an experienced and trained clinician, a well-maintained and properly calibrated **transcutaneous monitor** will provide accurate information regarding the pediatric patient's oxygenation status.[13] Transcutaneous measurement of the partial pressure of oxygen **($P_{TC}O_2$)** and carbon dioxide tension **($P_{TC}CO_2$)** provides continuous information about the body's ability to deliver oxygen to the tissues and to remove carbon dioxide. Because the sensor is placed on surface tissue, it is important to note that measurements may not reflect arterial blood gas tensions, but rather that of the underlying tissue. When hemodynamic conditions are stable, transcutaneous measurements correlate well with arterial values, but this correlation does not necessarily mean that the measured values will be identical.

PRINCIPLES OF OPERATION

Transcutaneous measurements of Po_2 and Pco_2 require a heating element, built into the sensor, that elevates the temperature in the underlying tissue. Increasing the skin's temperature increases capillary blood flow to the tissues, making it more permeable to gas diffusion. The tissue under which the sensor is placed will continue to consume oxygen and produces carbon dioxide (according to the metabolic demands). Consequently, measured values obtained with a transcutaneous monitor will differ from arterial values.[14,15] Generally, the Po_2 is slightly lower than in the arteries, and the Pco_2 is slightly higher.

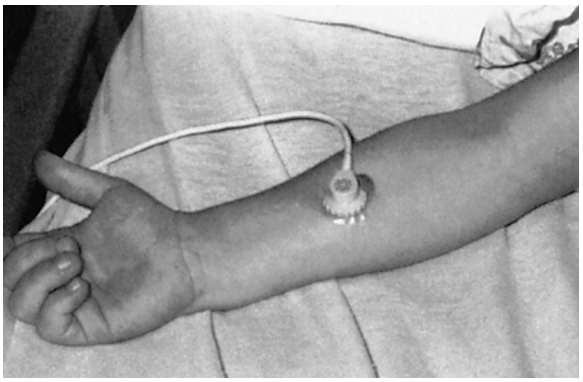


FIGURE 9-12 Transcutaneous oxygen monitor electrode placed on a child's arm. (From Stock MC: Non-invasive carbon dioxide monitoring. *Crit Care Clin* 4:511, 1988.)

APPLICATION

The most critical aspect of transcutaneous monitoring is site selection and the application of the sensor (Figure 9-12). The site should be a highly vascular area such as the earlobe, upper chest, abdomen, or thighs or the lower back if the patient is supine; bony areas and those with limited perfusion, such as over the spine, should be avoided.

Selecting a sensor temperature is important to proper operation.[16] The temperature range is usually 41 to 44°C. Heating of the sensor requires that the site be changed on a routine basis to prevent thermal injuries. The frequency of site changes ranges from 4 to 12 hours (depending on the device and sensor temperature) but can be reduced if necessary.

Meticulously following the manufacturer's membrane-changing procedure and calibration instructions will result in the most accurate readings. Once the machine has been prepared and the site selected, the skin must be cleaned to wipe away dead skin, oils, and medications. The accuracy of the sensor is improved by using 1 or 2 drops of contact gel or even normal saline or sterile water. This liquid-to-liquid medium makes the diffusion of gases more efficient. The sensor is then attached to the skin with a fixation ring (or earlobe clip). This ring must form a good seal between the sensor and skin, eliminating air bubbles.

LIMITATIONS

Transcutaneous monitoring provides a noninvasive, simple means of continuously monitoring ventilation. However, it can be labor intensive, involving sensor preparation, frequent site and membrane changes, and calibration.[15] Additionally, because transcutaneous monitors require the tissue to be heated, a period of time (usually just a few minutes) exists immediately after application during which no values can be measured. Once the tissue has been appropriately heated, values can be displayed. For long-term monitoring this is generally not a concern; however, in emergency situations requiring immediate action, a transcutaneous monitor may not be ideal. A transcutaneous monitor is limited in its usefulness during cardiopulmonary resuscitation and airway obstruction or apnea detection.

Changes in perfusion can adversely affect the accuracy of transcutaneous measurements. The skin reacts to cold, shock, and certain drugs by contracting the superficial blood vessels, opening larger, deeper arterioles to achieve a shunting effect. Capillary blood flow is reduced upon exposure to cold temperatures to reduce the loss of body heat. Shock and certain medications can also divert blood from capillaries to the central circulation. In all cases of reduced capillary perfusion, the capillary blood, which is measured using a transcutaneous monitor, may reflect measurements associated with venous blood, with a considerably lower Po_2 and higher Pco_2 (compared with values obtained with good capillary perfusion).[15] If a patient has poor skin integrity, transcutaneous monitoring may also be contraindicated.

Some sensors combine oxygen saturation (So_2) and transcutaneous carbon dioxide measurements in a single ear sensor. The sensor is heated to 42°C to maximize capillary blood flow. The location of the sensor on the ear may decrease motion artifact, because less head movement occurs in neonates. This type of sensor reduces the number of wires attached to the patient's chest, enabling a clearer view for chest radiographic examinations. When end-tidal CO_2 measurements are not possible or are found to be limited in some way (e.g., in newborns with large air leaks or those requiring high-frequency ventilation), a transcutaneous sensor may be optimal.

CALORIMETRY

Appropriate nutrition in children is associated with reduced risk of hospital mortality.[17] However, ensuring that nutritional requirements are correctly met for critically ill neonatal and pediatric patients can be difficult. By correctly assessing nutritional needs and tracking adequate intake, outcomes may be improved. **Calorimetry** is the measurement of gas exchange and the determination of **energy expenditure** (where energy expenditure is the amount of energy burned by a patient per unit of time, typically expressed in kilocalories per day [kcal/day]). *Gas exchange* refers to the volume of oxygen that is consumed by the patient **(oxygen consumption [V_{O_2}])** and the volume of carbon dioxide that is produced by the patient **(carbon dioxide production [V_{CO_2}]). Resting energy expenditure** (REE) is generally defined as the amount of energy required in a 24-hour period during which the body is performing minimal activity (typically expressed as kcal/day). The determination of a patient's REE, appropriate energy prescription, and intake can reduce the risk of overfeeding and underfeeding. A neonate's energy

Table 9-1 The Schofield Equation

AGE	MALES	FEMALES
<3 years	0.167W + 15.174H − 617.6	16.252W + 10.232H − 413.5
3-10 years	19.59W + 1.303H + 414.9	16.969W + 1.618H + 371.2
10-18 years	16.25W + 1.372H + 515.5	8.365W + 4.65H + 200.0
18-30 years	15.057W − 0.1H + 705.8	13.623W + 2.83H + 98.2

H, Height in cm; *W*, weight in kg.
From Schofield WN: Predicting basal metabolic, new and review of previous work. *Hum Nutr Clin Nutr* 39(C Suppl 1):5–41, 1985.

expenditure, when expressed per unit of body weight, is higher at birth compared with other times in life.[21] Equations are available that relate a child's gender, age, height, and weight into an estimation of energy expenditure. An example that is commonly used in neonates and pediatric patients is the Schofield equation (Table 9-1).[18] However, formulas are known to be inaccurate in many children, particularly those requiring mechanical ventilation.[19] Therefore determination of REE through measurement of Vo_2 and Vco_2 is often required.[20]

Two methods exist for measuring calorimetry: direct and indirect. **Direct calorimetry** extrapolates energy expenditure by measuring heat produced and lost from the body, whereas **indirect calorimetry** combines measurements of Vo_2 and Vco_2 into an equation to calculate energy expenditure. Most energy expenditure reports contain results for Vo_2, Vco_2, REE, and respiratory quotient (which is Vco_2/Vo_2 and can be used to determine substrate utilization). For critically ill, mechanically ventilated patients, Vo_2 will be approximately 4.5 to 6.3 mL/minute/kg for newborns and infants, 2.7 to 4.5 mL/minute/kg for older children, and 1.6 to 2.4 mL/kg/minute for large teenagers and adults.

PRINCIPLES OF OPERATION

Direct calorimeters are bulky, expensive, and not suitable for critically ill infants and children. Indirect calorimeters, on the other hand, can be transported to the patient's bedside. Open- and closed-circuit designs are available on indirect calorimeters. Although closed-circuit indirect calorimeters may sometimes be used, open-circuit devices are much more common. The open-circuit indirect calorimeter measures the volume of consumed oxygen and eliminated carbon dioxide (Vo_2 and Vco_2, respectively). To accomplish this, inspiratory and expiratory gas concentrations are measured with an O_2 sensor (typically a galvanic cell) and CO_2 sensor (typically a nondispersive infrared sensor similar to that used in $ETco_2$ monitors, albeit with greatly improved accuracy) and a highly accurate flow sensor. All sensors must be precisely calibrated before usage. The system can be set up to take measurements during mechanical ventilation and during spontaneous breathing. During mechanical ventilation some systems use a sensor placed at the airway (similar to an end-tidal CO_2 sensor), whereas others require multiple connections: inspiratory gas concentration sample, expiratory gas concentration sample, and flow sensor placed at the ventilator exhaust (Figure 9-13). Alternatively, a spontaneously breathing child requires a canopy placed over the child's head (or on top of the infant if the patient is small enough) connected to the indirect

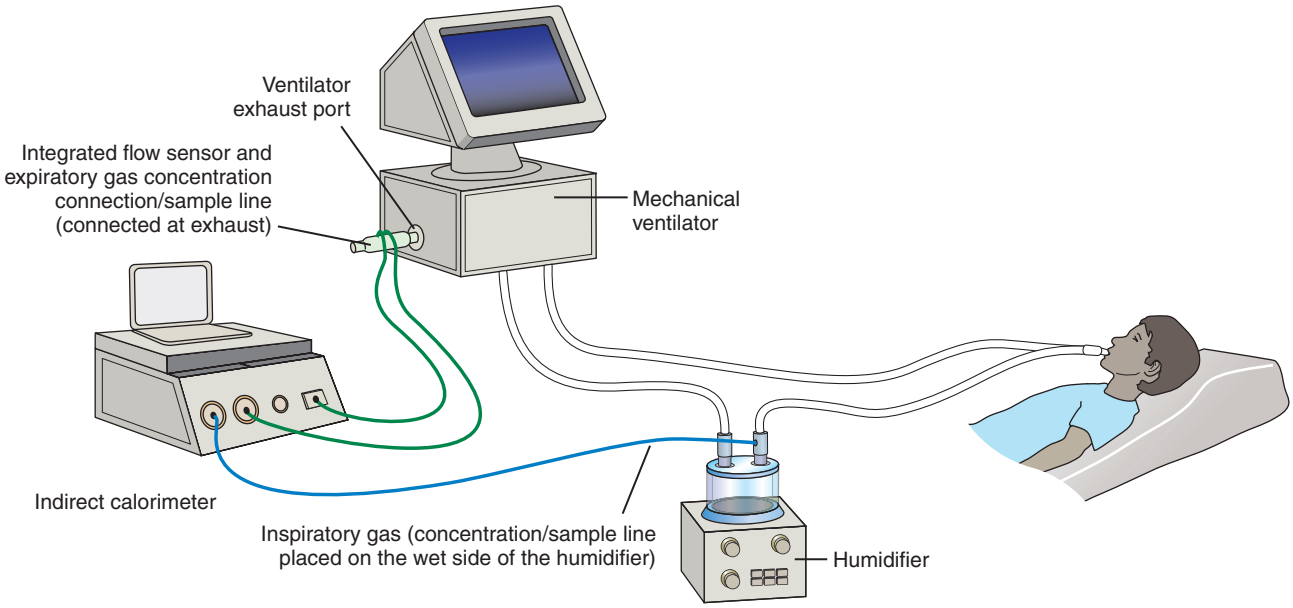


FIGURE 9-13 Typical setup of an indirect calorimeter used during mechanical ventilation.

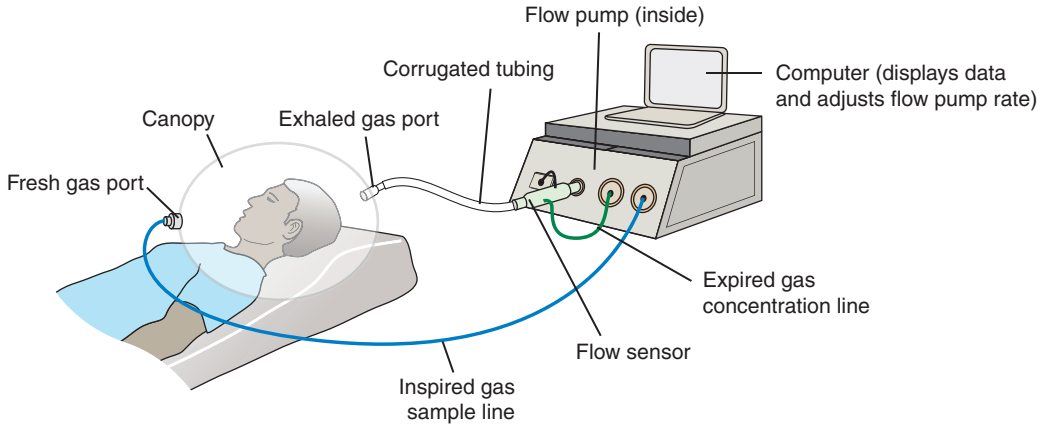


FIGURE 9-14 Typical setup of an indirect calorimeter for measurement of energy expenditure of a spontaneously breathing child or infant.

calorimeter, which draws exhaled gases into a sample line for volume and gas concentration analysis (Figure 9-14). The difference between inspired and expired gas fractions are multiplied by the volume measurement to yield Vo_2 and Vco_2. The modified Weir equation uses the Vo_2 and Vco_2 data to yield energy expenditure:

$$\text{energy expenditure} = [3.941(Vo_2) + 1.106(Vco_2)] \times 1440$$

where Vo_2 and Vco_2 are measured in L/minute.[21] Fluctuations in energy expenditure can occur over time and can be greatly affected by temperature, pain or agitation, activity level, changes in disease state, and ventilator parameters. It is important to gather data with minimal fluctuations in gas exchange. Therefore, for indirect calorimetry results to be valid and used to adjust nutrient intake, measurements must reflect a steady-state period. Often, a metabolic test lasts 30 minutes. The on-board algorithm (of the indirect calorimeter) looks for periods when minimal fluctuations in Vo_2, Vco_2, respiratory quotient (RQ), and other parameters are observed. The steady-state results are shown on the display.

Recently, new methods have been established to estimate energy expenditure in pediatric subjects using Vco_2 measurements from devices integrated into modern ventilators.[22,23] The Vco_2 is measured using the ventilator monitor, the respiratory quotient (Vco_2/Vo_2) is assumed to be 0.89, and the Weir equation is rearranged to offer the following:

$$EE = 5.534(Vco_2) \times 1440$$

Where Vco_2 is in L/minute and 1440 corresponds to the number of minutes in a day. Energy expenditure (EE) is expressed in kcal/day. The Vco_2 EE equation offers the following perceived benefits over traditional indirent calorimetry (IC): Vco_2 measurements are more readily available (since many ventilators offer integrated Vco_2 sensors), accuracy is far superior to other estimating equations based on demographics, the method can be applied continuously very readily, and it may be far less expensive. The method has important limitations though. Because the method assumes an RQ, the greater the difference between the subject's actual RQ and the assumed RQ, the greater the error in the estimated EE. Data shows, however, that the method provides EE estimates that are within 10% of IC if the subject has an RQ from 0.79 to 1.02.[22] In pediatrics, a typical RQ is 0.88 to 0.90, and therefore most subjects would have a reasonable estimate of EE.

LIMITATIONS

Direct calorimetry is cost prohibitive, equilibration and measurement are time consuming, and few exist in the United States. Indirect calorimetry is not without its limitations: Devices can be costly, dedicated and well-trained personnel are required, and measurement errors can be introduced during certain conditions. Conditions that preclude the use of indirect calorimetry include uncuffed endotracheal tubes, cuff or ventilator circuit leaks greater than 10% to 15%, Fio_2 greater than 50%, need for high-frequency ventilation or extracorporeal membrane oxygenation, and active chest tube leakage. As previously mentioned, certain patient conditions, such as unstable hemodynamics and agitation, may also limit the utility of indirect calorimetry because these conditions may not reflect the patient's typical energy expenditure.[24] However, with proper understanding of the appropriate calibration, application, and interpretation of indirect calorimetry data, it can be a valuable tool to aid clinicians in determining proper nutritional support of critically ill neonatal or pediatric patients.[25]

NEAR-INFRARED SPECTROSCOPY

PRINCIPLES OF OPERATION

Near-infrared spectroscopy (NIRS) is a noninvasive method of assessing oxygen supply and consumption balance in a tissue (such as the brain) and can be used to estimate blood flow.[26] NIRS devices use the relative

permeability of tissues to near-infrared light. A number of light-emitting diodes and receivers affixed at varying distances and wavelength combinations (typically from 650 to 950 nm) are used to estimate the relative concentrations of deoxygenated and oxygenated hemoglobin. An important concept in NIRS is that of the chromophore. A chromophore is the portion of a molecule that gives it color. In the specific context of NIRS, it is the portion of the hemoglobin molecule that absorbs NIR light, a property that changes when oxygen is added or removed. This property is used by NIRS to estimate oxygenation of tissues. NIRS assesses the ratio of oxyhemoglobin (HbO_2) to total hemoglobin (Hb_{tot}). The ratio (percentage) calculation is depicted here:

$$RSO_2 = \frac{HbO_2}{(HbO_2 + Hb_{tot})}$$

where RSO_2 is the regional oxygen saturation.

APPLICATION

Estimating **regional oxygen saturation in the brain ($bRSO_2$)** is the most common indication of NIRS because in infants brain injury is often related to cerebral oxygenation and cerebral blood flow disturbances.[27] In this case a NIRS probe is affixed to the patient's forehead. Cerebral $bRSO_2$ is a venous representation of cerebral oxygenation and is a gross indication of O_2 reserve and potentially ischemic risk. As $bRSO_2$ decreases, the likelihood of ischemic injury increases. An average cerebral $bRSO_2$ of less than 65% may be a global hypoperfusion indicator caused by low cardiac output.[28] Importantly, $bRSO_2$ measurement may aid in reducing the incidence of cerebral hypooxygenation and hyperoxygenation by guiding oxygen therapy in newborn babies.[29] Furthermore, SO_2 measurements may play a role in assessing severity of apnea and bradycardia events,[30] identifying derangements in cerebral blood flow in neonates,[31] and aiding in the early diagnosis of severe patent ductus arteriosis.[32] NIRS devices are available from several manufacturers, and most provide patient-specific sensors (neonatal and adult) that are affixed to the organ or tissue of interest and connected to a stand-alone monitor.

LIMITATIONS

The accuracy of NIRS is largely dependent on probe placement. Attaching the probe to bony or fatty areas or bruised areas or applying excessive pressure can introduce error and should be avoided. Probably the biggest limitation of NIRS is the lack of large trials identifying typical SO_2 values for tissue in various patient cohorts (preterm, infants, or children), which makes clinical interpretation somewhat difficult. Many studies of NIRS include relatively small populations, and broader application to a more heterogeneous population has not been adequately described in the literature. Further investigation is required for NIRS. Normative data for select patient populations needs to be described and derivation and validation of values that can be used prognostically or for assessing response to therapy are needed.

Key Points

- Fundamental monitoring methods to measure and assess heart rate, respiratory rate, and blood pressure include electrocardiography, impedance monitoring, and periodic cuff assessment, respectively.
- Pulse oximetry uses a sensor that includes light-emitting diodes and a photodiode sensor that measures the relative concentration of oxyhemoglobin to total hemoglobin in pulsatile arterial blood and displays the result as a percentage.
- Pulse oximeter sensors should be placed in a vascular area such as the finger or earlobe, with the diodes and the photodiode directly opposite each other and in good contact with the skin.
- *End-tidal CO_2 monitoring* refers to the measurement of CO_2 plotted against time and displays the partial pressure of CO_2 at end exhalation. *Volumetric capnography* refers to a plot of CO_2 and volume and typically provides a measure of carbon dioxide elimination, alveolar minute ventilation, and airway dead space.
- The gradient between end-tidal and arterial CO_2 measurements reflects dead-space ventilation and is normally between 0 and 5 mm Hg.
- Abnormalities that can be detected with capnograms include (but are not limited to) rebreathing exhaled gases, airway obstruction, and possible pneumothorax.
- Transcutaneous sensor placement is important to enhance accuracy and reduce risk of burns. Sensors should be placed in a highly vascular area such as the earlobe, upper chest, abdomen, or thighs or the lower back if the patient is supine; bony areas and those with limited perfusion, such as over the spine, should be avoided.
- Potential problems that can adversely affect the accuracy of transcutaneous monitoring include improper site selection, not following manufacturer's guidelines, and changes in peripheral perfusion.
- Indirect calorimetry seeks to measure the amount of energy that is used by a patient and help guide clinicians in determining optimal nutrition intake.
- Indirect calorimetry may not be reliable in children who require oxygen concentrations greater than 60%, during

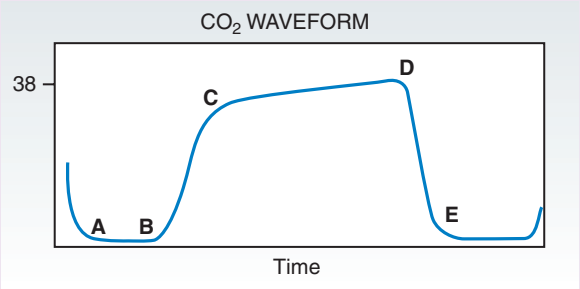
mechanical ventilation, in the presence of an endotracheal tube leak greater than 10%, in those requiring noninvasive or high-frequency ventilation, and for those in whom steady state is not achieved.

- Carbon-dioxide elimination (V_{CO_2})–based estimating equations are superior to demographic-based estimating equations and can be easily applied if V_{CO_2} is monitored on the ventilator.
- Near-infrared spectroscopy (NIRS) offers a noninvasive assessment of tissue oxygenation in infants and children based on the ratio of deoxyhemoglobin and oxyhemoglobin.
- Measuring regional oxygen saturation in the brain ($bRSO_2$) is the most common use of NIRS in infants and children.

Assessment Questions

See Evolve Resources for answers.

1. Which of the following demonstrates incorrect application of the pulse oximeter sensor?
   - **A.** Tight placement over a bony area
   - **B.** Placement over a vascular area
   - **C.** Diodes and photodiode directly opposite each other and in good contact with the skin
   - **D.** Firm placement to help prevent motion artifact
2. The following choices are all disadvantages of a pulse oximeter *except:*
   - **A.** Ease of use
   - **B.** Artifact
   - **C.** Poor tissue perfusion
   - **D.** Hypothermia
3. Which of the following measurements are obtained via transcutaneous monitoring in the neonatal and pediatric population?
   - **A.** Hemoglobin
   - **B.** pH, bicarbonate ion
   - **C.** P_{O_2}, P_{CO_2}
   - **D.** Oxygen saturation
4. Which of the following is *not* a disadvantage of transcutaneous monitoring?
   - **A.** Use is labor intensive because of required frequent site and membrane changes and calibration requirements.
   - **B.** Good correlation requires good peripheral blood perfusion.
   - **C.** Use requires the patient to be paralyzed and sedated.
5. Trending ET_{CO_2} via capnometry enables the clinician to have a good sense of the adequacy of _____ for the patient.
   - **A.** Oxygenation
   - **B.** Ventilation
   - **C.** Perfusion
   - **D.** Saturation
6. The normal capnogram can be divided into four phases. Phase B-C, as illustrated here, is indicative of which phase?



(Modified from *Advanced concepts in capnography.* Image used with permission from Nellcor Puritan Bennett, LCC, Boulder, CO, part of Covidien.)

   - **A.** The completion of expiration as the alveoli empty (alveolar plateau)
   - **B.** The initial expiratory phase, during which carbon dioxide rapidly increases as the alveoli begin to empty
   - **C.** The inspiratory phase, during which the sensor detects no carbon dioxide
   - **D.** The beginning of inspiration as the waveform returns to zero
7. A cleft in phase C-D of the capnogram in the figure accompanying question 7 may indicate:
   - **A.** An obstruction in the airway, possibly caused by a foreign body in the upper airway, increased secretions in the airways, bronchospasms, or partial obstruction of the ventilator circuit
   - **B.** That medication used to paralyze the infant is wearing off
   - **C.** Pneumothorax
   - **D.** Rebreathing of the previously exhaled carbon dioxide
8. What accounts for the difference between P_{aCO_2} and end-tidal CO_2?
   - **A.** Inadequate respiratory rate
   - **B.** Dead-space ventilation
   - **C.** Spontaneous ventilation
   - **D.** Postductal oxygen concentration
9. What is the normal gradient between P_{aCO_2} and end-tidal CO_2 (P_{aCO_2} minus end-tidal CO_2)?
   - **A.** −2 to −5 mm Hg
   - **B.** 8 to 10 mm Hg
   - **C.** 10 to 15 mm Hg
   - **D.** 0 to 5 mm Hg
10. Indirect calorimetry requires which of the following to calculate energy expenditure?
    - **A.** Oxygen saturation and end-tidal carbon dioxide
    - **B.** Oxygen consumption and respiratory rate
    - **C.** Oxygen consumption and carbon dioxide elimination
    - **D.** Transcutaneous oxygen and carbon dioxide concentration

REFERENCES

1. Folke M, Cernerud L, Ekström M, Hök B. Critical review of non-invasive respiratory monitoring in medical care. *Med Biol Eng Comput*. 2003;41:377.
2. Tipple M. Interpretation of electrocardiograms in infants and children. *Images Paediatr Cardiol*. 1999;1:3.
3. Jubran A. Pulse oximetry. *Crit Care*. 1999;3:R11.
4. Pulse Oximetry FORUM. The FORUM offers recommendations on best practices in pediatric pulse oximetry. *Am Assoc Respir Care Times*. 2000;2:36-44.
5. Barker SJ, Shah NK. The effects of motion on the performance of pulse oximeters in volunteers. *Anesthesiology*. 1997;86:101.
6. Gibson LY. Pulse oximeter in the neonatal ICU: a correlational analysis. *Pediatr Nurs*. 1996;22:511.
7. Tallon RW. Oximetry: state of the art. *Nurs Manage*. 1996; 27:43.
8. Trivedi NS, Ghouri AF, Lae E, Shah NK, Barker SJ. Pulse oximeter performance during desaturation and resaturation: a comparison of seven models. *J Clin Anesth*. 1997;9:184.
9. Dewhirst BE, Naguib A, Winch P, et al. Accuracy of noninvasive and continuous hemoglobin measurement by pulse co-oximetry during preoperative phlebotomy. *J Intensive Care Med*. 2014;29(4):238-242.
10. Walsh BK, Crotwell DN, Restrepo RD. Capnography/capnometry during mechanical ventilation: 2011. *Respir Care*. 2011;56:503.
11. Stock MC. Nonivasive carbon dioxide monitoring. *Crit Care Clin*. 1988;4:511.
12. Lindahl SG, Offord KP, Johannesson GP, Meyer DM, Hatch DJ. Carbon dioxide elimination in anaesthetized children. *Can J Anaesth*. 1989;36:113.
13. Dullenkopf A, Bernardo SD, Berger F, Fasnacht M, Gerber AC, Weiss M. Evaluation of a new combined $Spo_2/Ptcco_2$ sensor in anaesthetized paediatric patients. *Paediatr Anaesth*. 2003;13:777.
14. Bernet-Buettiker V, Ugarte MJ, Frey B, Hug MI, Baenziger O, Weiss M. Evaluation of a new combined transcutaneous measurement of Pco_2/pulse oximetry oxygen saturation ear sensor in newborn patients. *Pediatrics*. 2005;115:e64.
15. Tobias JD, Meyer DJ. Noninvasive monitoring of carbon dioxide during respiratory failure in toddlers and infants: end-tidal versus transcutaneous carbon dioxide. *Anesth Analg*. 1997;85:55.
16. Kocher S, Rohling R, Tschupp A. Performance of a digital Pco_2/Spo_2 ear sensor. *J Clin Monit Comput*. 2004;18:75.
17. Mehta NM, Bechard LJ, Cahill N, et al. Nutritional practices and their relationship to clinical outcomes in critically ill children—an international multicenter cohort study. *Crit Care Med*. 2012;40:2204.
18. Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. *Hum Nutr Clin Nutr*. 1985;39(suppl 1):S5.
19. Coss-Bu JA, Jefferson LS, Walding D, David Y, Smith EO, Klish WJ. Resting energy expenditure in children in a pediatric intensive care unit: comparison of Harris-Benedict and Talbot predictions with indirect calorimetry values. *Am J Clin Nutr*. 1998;67:74.
20. Mehta NM, Compher C. A.S.P.E.N. Clinical guidelines: nutrition support of the critically ill child. *JPEN J Parenter Enteral Nutr*. 2009;33:260.
21. Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. *Nutrition*. 1990;6:213.
22. Mehta NM, Smallwood CD, Joosten KF, Hulst JM, Tasker RC, Duggan CP. Accuracy of a simplified equation for energy expenditure based on bedside volumetric carbon dioxide elimination measurement–-a two-center study. *Clin Nutr*. 2015;34(1):151-155.
23. Kerklaan D, Augustus ME, Hulst JM, et al. Validation of ventilator-derived VCO2 measurements to determine energy expenditure in ventilated critically ill children. *Clin Nutr*. 2017 Apr;36(2):452-457.
24. Flancbaum L, Choban PS, Sambucco S, Verducci J, Burge JC. Comparison of indirect calorimetry, the Fick method, and prediction equations in estimating the energy requirements of critically ill patients. *Am J Clin Nutr*. 1999;69:461.
25. Mehta NM, Bechard LJ, Dolan M, Ariagno K, Jiang H, Duggan C. Energy imbalance and the risk of overfeeding in critically ill children. *Pediatr Crit Care Med*. 2011;12:398.
26. Van Bel F, Lemmers P, Naulaers G. Monitoring neonatal regional cerebral oxygen saturation in clinical practice: value and pitfalls. *Neonatology*. 2008;94(4):237-244.
27. Alderliesten T, Lemmers PM, Smarius JJ, van de Vosse RE, Baerts W, van Bel F. Cerebral oxygenation, extraction, and autoregulation in very preterm infants who develop peri-intraventricular hemorrhage. *J Pediatr*. 2013;162(4):698-704. e692.
28. Chakravarti SB, Mittnacht AJ, Katz JC, Nguyen K, Joashi U, Srivastava S. Multisite near-infrared spectroscopy predicts elevated blood lactate level in children after cardiac surgery. *J Cardiothorac Vasc Anesth*. 2009;23(5):663-667.
29. van Vonderen JJ, Roest AA, Siew ML, Walther FJ, Hooper SB, te Pas AB. Measuring physiological changes during the transition to life after birth. *Neonatology*. 2014;105(3): 230-242.
30. Pichler G, Urlesberger B, Müller W. Impact of bradycardia on cerebral oxygenation and cerebral blood volume during apnoea in preterm infants. *Physiol Meas*. 2003;24(3):671-680.
31. Lemmers PM, Toet M, van Schelven LJ, van Bel F. Cerebral oxygenation and cerebral oxygen extraction in the preterm infant: the impact of respiratory distress syndrome. *Exp Brain Res*. 2006;173(3):458-467.
32. Lemmers PM, Toet MC, van Bel F. Impact of patent ductus arteriosus and subsequent therapy with indomethacin on cerebral oxygenation in preterm infants. *Pediatrics*. 2008; 121(1):142-147.

Oxygen Administration

10

Brian K. Walsh

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. Discuss causes, clinical signs and symptoms, and evidence of hypoxemia.
2. Identify adverse physiologic effects and equipment-related complications associated with oxygen administration to neonates, infants, and children.
3. Differentiate between variable-performance and fixed-performance oxygen delivery systems and provide examples of each.
4. Discuss the indications and contraindications for use of oxygen delivery devices in neonatal and pediatric populations.
5. Describe the methods used to apply devices to deliver oxygen to neonates, infants, and children.

Key Terms

humidified high-flow nasal oxygen
hypoxemia
hypoxia
nasal cannula
oxygen hood
oxygen therapy
simple oxygen mask
Venturi mask

In 1774 Joseph Priestley was credited with discovering the colorless, odorless, tasteless gas that Antoine Lavoisier 1 year later named oxygen.[1] Nearly 150 years would pass before the Finnish pediatrician Arvo Ylppö recommended the intragastric administration of this gas to infants.[2] It was not until 1934 that Dr. Julius Hess, chief of pediatrics at the Michael Reese Hospital in Chicago, created the first inhaled oxygen delivery device for a premature infant. His "oxygen box," which consisted of a metal hood with a small window, was the first oxygen chamber used within an incubator.[3] Although the device was criticized both for making it difficult to view the infant and for its inability to maintain high oxygen concentrations, it led the way in the development of oxygen administration devices for premature infants and children.[4] Further development and use of these delivery devices has resulted in significant health care benefits, including a reduction in mortality. Today the administration of oxygen by inhalation continues to play an essential role in the survival of infants and children.

The goal of oxygen administration is to achieve adequate tissue oxygenation. The system used to provide supplemental oxygen must be appropriate to the patient's size, gestational and postnatal age, and clinical condition. Selection of the oxygen delivery device and flow rate is targeted to meet the specific physiologic needs and therapeutic goals of each patient.[5] Unfortunately, adverse reactions from the therapeutic use of oxygen are well documented in neonatal and pediatric patients. Therefore it is imperative that **oxygen therapy** be provided at accurate and safe levels with the lowest possible fractional concentration of inspired oxygen (Fio_2).

INDICATIONS

DOCUMENTED OR SUSPECTED HYPOXEMIA

A need to correct **hypoxemia** (low oxygen content in the blood) is the most common indication for oxygen therapy.[6] Left untreated, hypoxemia progresses to

Table 10-1 Estimated Inspiratory Flow Rates of a Wide Patient Population Range

WEIGHT (Kg)	AGE	RANGE L/kg/MINUTE
<2.9	Neonate (premature)	0.7-1.3
3.0-4.9	Neonate	0.6-1.2
5.0-9.9	<1 years	0.5-1.1
10-26.9	1-7 years	0.4-0.8
27-60.9	8-14 years	0.3-0.6
>61	>14 years	0.2-0.4

hypoxia (low tissue oxygen) and possibly anoxia (absent tissue oxygen), which, if severe enough, leads to anaerobic metabolism and development of lactic acidosis.

Hypoxemia occurs as a result of decreased alveolar ventilation, decreased inspired oxygen, poor ventilation–perfusion relationships, intrapulmonary or cardiac shunting, diffusion defects, or short red blood cell transit times. Table 10-1 identifies the most common causes of hypoxemia. In conditions such as anemia or carbon monoxide poisoning, the oxygen-carrying capacity of the blood is reduced despite the presence of normal arterial oxygen tension (Pao_2). Bradycardia, cardiac failure, hypotension, and hypothermia leave the circulatory system unable to provide adequate tissue oxygen. In rare cases, such as cyanide poisoning, the tissue is unable to accept and use oxygen, despite adequate oxygen delivery.[7] The documentation of hypoxemia through arterial blood gas sampling or pulse oximetry provides the most definitive evidence of actual or impending tissue hypoxia. Yet, PaO_2 or SpO_2 alone is inadequate to determine oxygen delivery. Oxygen delivery is determined by the concentration of hemoglobin in the blood, its oxygen saturation, the rate of blood circulation, and the efficiency with which oxygen is unloaded from the hemoglobin to the tissues. Oxygen delivery is often expressed in the following equation in Figure 10.1.

Administration of oxygen is also appropriate if hypoxia is strongly suspected on clinical grounds. However, substantiation of either the Pao_2 or the percentage of oxygen saturation (Spo_2) is required within an appropriate period after administration.[6,7] In emergency situations, such as severe respiratory distress, shock, or cardiopulmonary arrest, oxygen therapy is never withheld even if laboratory test results are unavailable.

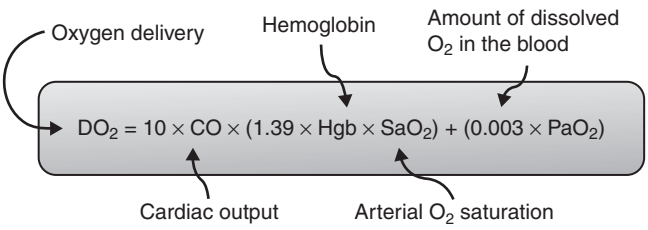


FIGURE 10-1 Oxygen delivery equation.

EVIDENCE OF HYPOXEMIA

Measurement of Oxygen Tension and Saturation

In children a Pao_2 less than 80 mm Hg and an Spo_2 less than 95% usually indicate hypoxemia. However, generally agreed-on practice is to only treat Spo_2 less than 90% or a Pao_2 less than 60 mm Hg. Because fetal hemoglobin has a much greater affinity for oxygen, the oxygen dissociation curve is shifted to the left, allowing a higher saturation for any given Pao_2. The normal immediate postnatal Pao_2 of 50 to 60 mm Hg corresponds closely with an Spo_2 of 85% to 90%. For this reason, it is generally agreed that a Pao_2 less than 50 mm Hg and an Spo_2 less than 88% in a neonate indicate hypoxemia and necessitate initiation of oxygen therapy. The Pao_2 and the Spo_2 are the principal clinical indicators used to begin, monitor, adjust, and terminate oxygen administration.

Clinical Signs and Symptoms

In neonates and children, the earliest clinical manifestations of hypoxia are typically tachycardia and tachypnea. Worsening hypoxia results in decreased ventilation, apnea, and bradycardia. This is especially true in both neonates and term infants. Other physical signs of hypoxia include grunting, nasal flaring, retractions, paradoxical breathing, cyanosis, irritability, and increased restlessness.[8] If prolonged, the neonate or child can experience a decreased level of consciousness and become lethargic and flaccid.

The presence of cyanosis has often been used to determine inadequate oxygenation before pulse oximetry. Although this clinical sign is somewhat useful in pediatric and adult patients, its presence in infants is often a late sign of severe hypoxia. Peripheral cyanosis (acrocyanosis) is the bluish discoloration of the skin or extremities. It occurs when a decrease in body temperature results in poor peripheral circulation or vasoconstriction. Central cyanosis involves the warm and well-perfused areas of the tongue and mucous membranes. It does not occur until reduced hemoglobin reaches 4 to 6 g/dL in arterial blood. In children and adults, the reduced hemoglobin concentration at which cyanosis occurs corresponds to a Pao_2 of approximately 50 to 60 mm Hg and an Spo_2 of 85% to 90%. In infants, the stronger affinity of fetal hemoglobin for oxygen results in the Pao_2 falling to a significantly lower level before reduced hemoglobin is present at 5 g/dL in arterial blood. In fact, by the time central cyanosis is present in an infant, oxygen delivery to the tissues is grossly insufficient. For this reason, central cyanosis is considered an unreliable indicator of the degree of tissue hypoxia. The clinical impression of cyanosis in an infant must be confirmed by arterial blood gas analysis or pulse oximetry.

COMPLICATIONS

Complications of therapeutic oxygen administration are separated into two categories: adverse physiologic effects and equipment-related complications. Adverse

reactions that result directly from using a specific oxygen delivery device are discussed in later sections describing that device. Although potential risks are present whenever oxygen is administered, the consequences of hypoxia are more severe.

In certain chronic lung disorders, including cystic fibrosis and bronchopulmonary dysplasia, the normal response to ventilation is blunted because of chronic carbon dioxide retention. Abrupt and excessive increases in supplemental oxygen decrease the respiratory drive and result in hypoventilation and respiratory acidosis that may lead to respiratory arrest.[9] The goal of oxygen therapy in patients with this degree of chronic lung disease is to correct the hypoxemia without decreasing the pH. Supplemental oxygen should be initiated at a low Fio_2 and increased on the basis of the results of Pao_2 or Spo_2 monitoring.

The role of excessive oxygen delivery in the development of retinopathy of prematurity (ROP) is clear. Hyperoxia and loss of maternal fetal interaction is believed to cause the suppression of growth factors and constriction of retinal and cerebral vessels in premature neonates, which can lead to ischemia, varying degrees of retinal scarring, and retinal detachment. ROP may resolve spontaneously or result in permanent visual impairment, including blindness. In the 1940s and 1950s when oxygen was administered to premature infants without blood gas monitoring, ROP reached epidemic proportions.[10,11] Many other factors, in addition to oxygen, appear to correlate with the development of ROP, including gestational age, swings in oxygenation, intraventricular hemorrhage, swings in blood pressure, sepsis, and low birth weight.[12]

Much has been described in the literature regarding the role of supplemental oxygen in the development of ROP.[13-16] The altered regulation of vascular endothelial growth factor (VEGF) has been suggested as one of the factors in the pathogenesis of ROP.[17,18] It thus is possible that repeated cycles of hyperoxia or hypoxia favor the progression of ROP.[19,20] Time outside the targeted oxygen saturation range may be evidence in preterm infants that combines these two factors, hyperoxia and hypoxia, and ROP. See Figure 10-2 for details.

Current practice supports oxygen therapy targeting Spo_2 levels at 88% to 95% and maintaining a Pao_2 value of 50 to 80 mm Hg in premature neonates. Studies that have examined the relationship between hospital policies concerning Spo_2 limits and the survival and ophthalmic and developmental outcome of premature infants who have received supplemental oxygen have concluded that vigilance concerning oxygen management, without adversely affecting death and disability, was in some part responsible for the current decline in severe ROP.[21-24] But despite the knowledge that hyperoxia (high levels of oxygen in the blood) can be detrimental to the premature infant, there remains a challenge in establishing limits for the rational use of supplemental oxygen in extremely premature infants. The optimal range of oxygenation that can balance the risks of mortality, ROP blindness, chronic lung disease, and brain damage continues to be studied.[25] A recent randomized trial of a lower target range of oxygenation (85%-89%) compared with a higher range (91%-95%) found that death before discharge occurred more often in the lower-oxygen-saturation group (19.9% vs. 16.2%), whereas severe retinopathy among survivors occurred less often in this group (8.6% vs. 17.9%). This has driven the practice to bridge the SpO_2 range by targeting the 88% to 95% range with practice algorithms such as that in Figure 10-3.

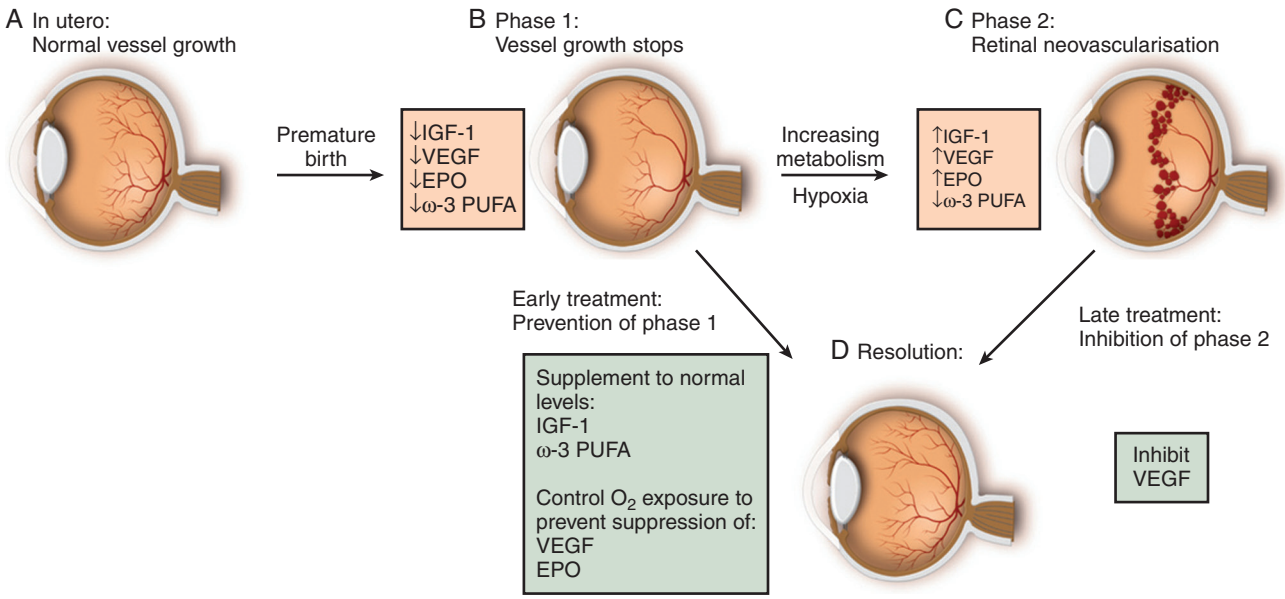


FIGURE 10-2 How premature birth contributes to ROP and how therapies can contribute to the resolution. (From Smith LE. Through the eyes of a child: understanding retinopathy through ROP: the Friedenwald lecture. *Invest Ophthalmol Vis Sci* 2008; 49: 5177–5182.)

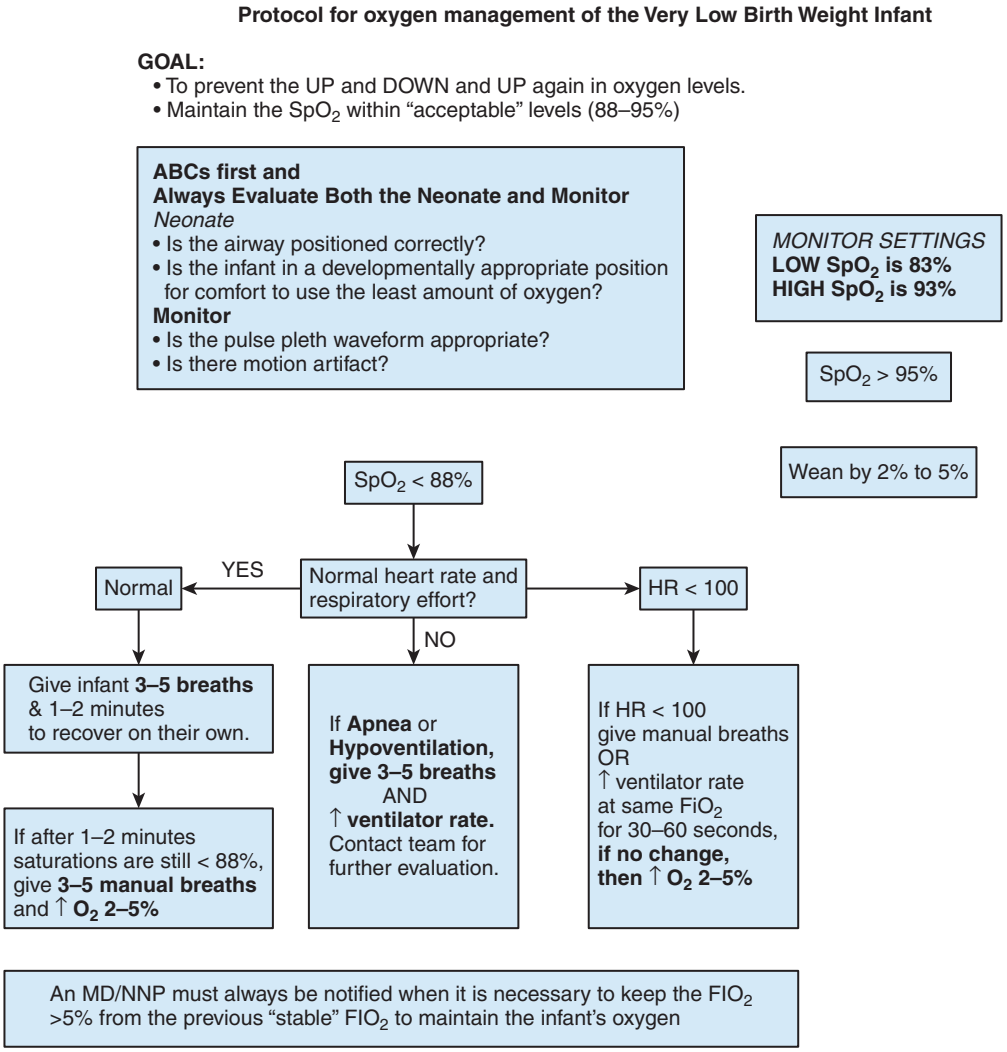


FIGURE 10-3 Protocol for oxygen management of a very-low-birth-weight infant.

Clinical Highlight

OXYGEN THERAPY FOR VERY-LOW-BIRTH-WEIGHT INFANTS (BIRTH WEIGHT <1500 G)

Keep saturations between 88% and 95%

1. Important to wean oxygen actively by 2%-5% at a time if >95%.
2. No increase in FiO_2 without assessing infant (and monitor). *Adjust ventilation first, then if additional oxygen is needed, increase by* only *2%-5%.*
3. Do not leave bedside if any changes in FiO_2 have been made.
4. No infant should be left as stable if the condition had required an increase in FiO_2 >3%-5%.
5. Do not keep increased FiO_2 without additional assessment. Changes in ventilator settings may be necessary.
6. No "preoxygenation" for suctioning, procedures, handling.

This can produce dangerous and risky "ups and downs" in infant's oxygenation levels.

Changes in ventilator settings may be necessary.

High concentrations of oxygen have been linked to atelectasis, pulmonary vasodilation, and pulmonary fibrosis. In the face of high oxygen levels, the alveolar oxygen tension (Spo_2) may increase and the alveolar nitrogen decrease, resulting in absorption atelectasis. As the nitrogen is replaced by oxygen, the blood rapidly absorbs the oxygen, gas volume decreases, and atelectasis develops. High Fio_2 levels may also result in pulmonary vasodilation. As the pulmonary vasculature dilates and alveolar volumes decrease, areas of ventilation–perfusion mismatch occur with increased intrapulmonary shunting and worsening of arterial oxygen delivery. In patients with a hypoplastic left ventricle or a single ventricle, the increased Pao_2 that occurs with oxygen therapy has been reported to compromise the balance between pulmonary and systemic blood flow.[26] There are also reports of pulmonary fibrosis occurring after oxygen administration to patients with Paraquat poisoning and to those receiving the chemotherapeutic agent bleomycin.[27,28]

OXYGEN ADMINISTRATION

Many of the devices used to deliver supplemental oxygen to neonatal and pediatric patients are simply smaller versions of the adult devices. They are similarly classified in the same manner as either variable-performance oxygen delivery systems (low-flow and reservoir systems) or fixed-performance oxygen delivery systems (high-flow systems).[5]

Variable-performance oxygen delivery systems include devices that are not capable of meeting the patient's inspiratory demand and therefore provide a fractional concentration of delivered oxygen (Fdo_2) that varies with the patient's rate and depth of ventilation and the flow rate of the gas. These devices include low-flow nasal cannulas, nasopharyngeal catheters, tracheostomy oxygen adapters, simple oxygen masks, partial-rebreathing masks, and nonrebreathing masks.

Fixed-performance oxygen delivery systems include devices that can meet or exceed the patient's inspiratory demand and thereby provide an accurate Fdo_2 that is not affected by changes in the ventilatory pattern. These devices include high-flow nasal cannulas, air-entrainment masks, air-entrainment nebulizer systems, and oxygen blender systems. The last category of oxygen delivery devices includes enclosure systems that provide some means of controlling oxygen concentration, temperature, and humidity. These devices include oxygen hoods, oxygen tents, and closed incubators.[5]

VARIABLE-PERFORMANCE OXYGEN DELIVERY SYSTEMS

Nasal Cannula

The **nasal cannula** consists of flexible small-bore tubing ending in two soft prongs that are about 0.25 to 1 cm in length (Figure 10-4). Oxygen flows from the cannula into the patient's nasopharynx, which acts as an anatomic reservoir. For many years, the cannula was used only in pediatric and adult patients. It was not until the 1980s that it was proposed for use in neonates as well.[29] Today its ease of administration makes it the preferred and most commonly used device for oxygen delivery to neonates, infants, and children. As with the nasopharyngeal catheter, the cannula is designed to provide low oxygen concentrations from approximately 24% to 45%, with the Fio_2 varying with the patient's inspiratory flow.[30,31]

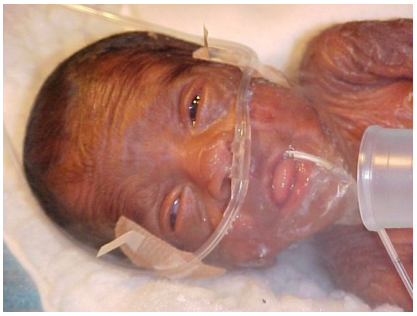


FIGURE 10-4 Infant with a neonatal nasal cannula.

Indications and contraindications. Caregivers are able to feed and provide for the patient without interrupting the delivery of oxygen. When compared with an oxygen hood, the nasal cannula allows the patient greater mobility, which may increase interactions with the patient's caregivers and environment.[32] Nasal cannulas are contraindicated in patients with nasal obstruction, such as facial trauma and choanal atresia.[5]

Application. The appropriately sized cannula is selected and the prongs inserted into the patient's nares, making sure that the nares are not completely occluded. The lightweight tubing is wrapped around the ears and held under the chin with an adjustable plastic notch. For a very small or active infant, the cannula is secured to the face to prevent dislodgment and the tubing is positioned past the ears, securing it behind the head, instead of under the chin, to prevent airway obstruction. Oxygen is delivered from a flow meter and bubble humidifier through the small-bore oxygen tubing.

When adhesive tape is used to secure the cannula to the fragile skin of the neonatal patient, epidermal stripping can result each time the tape is moved to readjust the tubing. Skin irritation can also occur from a local allergic reaction to polyvinyl chloride.[5] Popular alternatives to using adhesive tape or stoma adhesive are the NeoHold cannula/tubing holder (Neotech Products, Valencia, CA) and the Tender Grip skin fixation system (Salter Labs, Arvin, CA). These commercially available devices consist of a latex-free base with an adhesive backing of tinted microporous tape that is applied to the skin, usually on the patient's cheek. On top of this base is a clear tab with an adhesive backing. The tab folds over the cannula tubing and secures the cannula in place (the cannula lies between the base and the tab). To reposition the cannula the practitioner simply peels back the tab, adjusts the tubing, and reapplies the tab. The microporous tape allows the skin to breathe, and the tab makes it easy to adjust the cannula without irritating the skin. The devices usually adhere to the skin for 1 to 3 weeks, staying in place even during baths.

Blenders and low-flow flow meters. Two methods of providing oxygen at low flows through a nasal cannula are common in neonatal and pediatric units. The first method entails connecting the cannula to a flow meter attached to an air–oxygen blender. The second method consists of simply connecting the cannula to a low-flow flow meter attached to a 100% oxygen source.

Oxygen blenders set at specific oxygen concentrations can be used to regulate the Fio_2 to infants receiving

oxygen with nasal cannulas. Using this method, both the oxygen concentration and the flow rate of the gas can be adjusted to achieve the appropriate Fdo_2. With a cannula connected to the flow meter on the blender, the oxygen concentration is set at 100% and the flow rate at the lowest possible flow. Many protocols begin the flow rate at 1 L/minute. The flow rate is adjusted, decreasing it in small increments until reaching the flow necessary to maintain adequate Spo_2 levels. Weaning is continued by decreasing the flow rate until reaching the minimal flow setting of the flow meter and decreasing the oxygen concentration setting on the blender to maintain adequate Spo_2 levels, or until oxygen is no longer required. Although some centers lower the oxygen concentration first, a lower flow rate may maximize the stability of delivered oxygen over time, as well as minimize the degree of change in Fio_2 during the weaning process.[33,34] Tables have been constructed to estimate hypopharyngeal oxygen concentrations at various settings, but reproducibility is affected by the range of infant sizes and variable breathing patterns.[34-36]

Because hypopharyngeal oxygen concentrations tend to be more stable when using lower flows, the use of a low-flow flow meter helps optimize continuous oxygen administration in the infant population. Depending on the flow meter, the flow rates range from 0.1 to 3.0 L/minute, with some adjustable in increments of less than 0.125 L/minute.[5] Using this method, the cannula is connected to a low-flow flow meter receiving 100% oxygen. An appropriate flow rate, as determined by the Spo_2, is set and the oxygen is weaned by decreasing the flow rate in small increments of 0.1 to 0.2 L/minute. Weaning continues in small increments until the minimal desired Spo_2 is reached or until oxygen is no longer required.

Inspired oxygen determination. For infants and children, Fio_2 provided with a nasal cannula is controlled primarily by varying the flow rate of the gas or the oxygen concentration of the blender. At low flow rates, Fio_2 also varies with the patient's minute ventilation and the relative duration of inspiration and expiration.[34] Fio_2 may decrease as a result of room-air entrainment that occurs during the patient's inspiration. In a small or premature infant, inspiratory flow rates are quite small and result in less room-air entrainment during inspiration. On the other hand, sedated infants may have decreased minute ventilation, resulting in an increase in the actual Fio_2.[37] The Fio_2 is higher in infants receiving oxygen via nasal cannula than in adults and can exceed potentially toxic levels.[38] Several studies have documented high Fio_2 when supplemental oxygen is supplied to neonates via nasal cannula, ranging from 22% to 95% on various flows of 100% oxygen.[33,35,39]

Oxygen delivered by nasal cannula is measured in liters per minute rather than Fio_2. Translating a flow rate into an approximate Fio_2 is helpful in gauging the degree of respiratory compromise and comparing oxygen conditions in clinical studies. Tables and equations are available for this purpose and in fact were distributed in the multicenter Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) study on the safety of oxygen use and the progression of ROP.[21,34] Although potentially it provides a more rational basis for oxygen prescription through a nasal cannula, the calculation and subsequent documentation of the effective Fio_2 are rarely implemented in clinical practice. Perhaps this is because the calculations are too cumbersome to undertake during routine clinical care.[32]

Because the concentration of oxygen inhaled into the lungs varies according to respiratory rate, tidal volume, inspiratory flow, and other factors such as ratio of mouth-to-nose breathing, it is difficult to determine the Fio_2 with certainty.[34,40,41] When compared with an adult patient, an infant can experience a substantial difference in Fio_2 when there is just a fraction of a change in the flow rate. An approximation of Fio_2 at low flows can be determined using the regression equation (Box 10-1).[33] This equation incorporates minute ventilation, but it does not account for changes in respiratory pattern and is more accurate for infants weighing less than 1500 g. Such an equation should be used only as a comparative estimate; it should not be considered an accurate determination of breath-to-breath Fio_2. During most routine clinical situations, approximating the Fio_2 from cannula flow is unnecessary. However, when weaning a patient from a cannula, the clinician can determine the measure of improvement by monitoring the incremental decreases in oxygen flow rate.

Hazards and complications. Depending on the type of nasal cannula, the flow rate, and the infant's anatomy, an increase in exhaled resistance can result in substantial inadvertent positive expiratory airway pressure (PEP) being delivered to an infant's airway.[5,42] This occurs when using either the blender or the low-flow flow meter to deliver supplemental oxygen. Significant PEP tends to occur more often when the cannula has large-diameter prong tips and when flow rates are set above 2 L/minute in smaller infants and toddlers.[39,42-45] PEP that impedes venous return may precipitate intraventricular hemorrhage in neonates and can be detrimental to an infant with obstructive pulmonary

Box 10-1 Regression Equation for Estimating Nasal Cannula Fio_2 at Low Flow Rates

Approximate $Fio_2 = (O_2 \text{ flow} \times 0.79)[(0.21 \times V_E)/(V_E \times 100)]$

This equation is most predictive with an assumed tidal volume of 5.5 mL/kg for infants less than 1500 g.

Fio_2, Fractional concentration of inspired oxygen; *O_2 flow*, expressed as milliliters per minute; *V_E* (minute ventilation) = tidal volume × respiratory rate.

disease.[38] It also carries the potential risk of pneumothorax, pulmonary interstitial emphysema, and pneumopericardium. Although the amount and certainty of PEP may not be determined, keep in mind the possibility of such complications when improvement in response to nasal oxygen is less than expected.

Although the nasal cannula is relatively comfortable, lightweight, and easy to apply, the prongs are difficult to keep in the nares of active infants, often becoming displaced and resulting in loss of oxygen delivery.[46] Prongs that are too large can occlude the nares and increase the patient's work of breathing. An improperly sized cannula can cause irritation. Excessive flows may result in drying of the nasal mucosa as well as mucosal irritation. It is recommended that maximal flow be limited to 2 L/minute in infants and newborns.[5] There is a slight risk of airway obstruction caused by mucus, especially in low-birth-weight infants. Therefore it is important to inspect and clean the nostrils daily.[47] The nose can be kept clean and free of mucus by gently cleaning the nostril areas with a soft, moist cloth, being careful to avoid causing irritation and swelling of the nasal mucosa. The skin around the patient's ears and face should be monitored for irritation as well as proper fit and placement of the cannula and tubing.

Disadvantages to using a nasal cannula to deliver oxygen include the instability of oxygen administration in transitions between oral and nasal breathing and the lack of precise knowledge concerning the delivered oxygen concentration. Unknown Fio_2 values may contribute to inconsistent weaning practices that could potentially result in unnecessary days of supplemental oxygen, delays in hospital discharge, and high costs of care.[32]

Simple Oxygen Mask

The **simple oxygen mask** is a lightweight plastic reservoir designed to fit over the patient's nose and mouth and is secured by an elastic strap around the patient's head (Figure 10-5). Open ports on both sides of the mask allow exhalation and also allow the patient to draw in room air during inspiration. Fio_2 varies with the patient's inspiratory flow and the oxygen flow into the mask.[48] Room air is entrained through the exhalation ports in the mask if the patient's inspiratory flow rate exceeds the oxygen flow rate. Flow rates from 6 to 10 L/minute provide a variable Fio_2 of 0.35 to 0.5; however, there are no data concerning newborns and infants to predict the effective Fio_2.[49]

Indications and contraindications. Administration of oxygen with a simple mask is reserved for infants and children who need moderate concentrations of supplemental oxygen for short periods. Such situations include medical transport, emergency stabilization, postanesthesia recovery, and during medical procedures. The oxygen concentrations may be higher in patients with small tidal volumes, and therefore simple masks are not suitable for infants and small children who require low or precise concentrations of oxygen.[5,6]

Application. The mask is secured around the patient's head by a strap, and oxygen is delivered to the mask from a flow meter and bubble humidifier through small-bore tubing. The cone shape of the simple mask may act as a reservoir for accumulated exhaled carbon dioxide if a minimal flow of gas is not maintained. In older children and adults, 6 L/minute is the recommended minimal flow rate to flush accumulated carbon dioxide.

Hazards and complications. Because this mask is strapped to the face, infants and small children often refuse to keep the mask on. In addition, the confinement of the mask interferes with speech, eating, and breast- or bottle-feeding and may increase the risk for aspiration of vomitus. The elastic strap is often uncomfortable and can cause skin irritation with prolonged use.

Reservoir Masks

A reservoir mask consists of a soft, lightweight mask with a plastic reservoir bag attached to its front (Figure 10-6). Oxygen source gas flows directly into

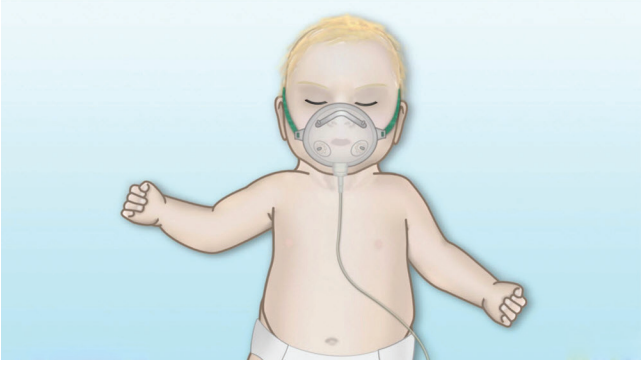


FIGURE 10-5 Infant with a simple oxygen mask. (From OPENPediatrics/Brittanie Marie Marques/used with permission.)

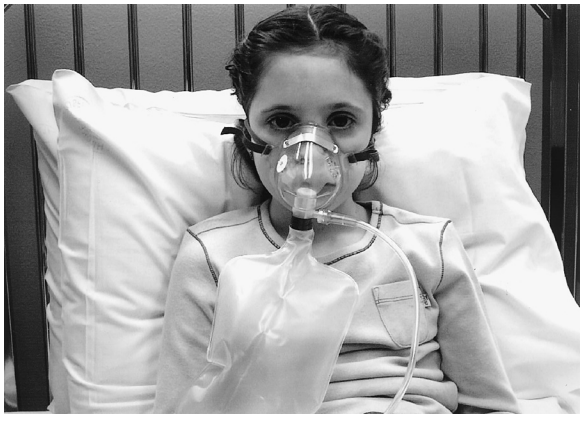


FIGURE 10-6 Pediatric patient with a partial-rebreathing mask, a type of reservoir mask.

the neck of the mask and is directed into the bag during exhalation. When the patient inhales, high concentrations of oxygen can be delivered from the bag through the mask. Currently, there are two types of reservoir masks: partial-rebreathing and nonrebreathing masks.

If functioning properly, reservoir masks have the advantage of providing high concentrations of oxygen. However, the tight fit necessary to achieve optimal performance makes the masks impractical for long-term therapy. As with the simple oxygen mask, the elastic straps may cause the reservoir masks to be uncomfortable, confining, and not well tolerated by infants and children. The use of reservoir masks is limited to short-term situations requiring high Fio_2 administration or specific gas mixture therapy. Reservoir masks are not recommended for use in the neonatal population.[5]

Partial-rebreathing mask. The partial-rebreathing mask is similar to a simple oxygen mask but contains a reservoir bag at the base of the mask. It is designed to conserve oxygen by receiving 100% oxygen along with a small portion of the patient's exhaled volume (approximately equal to the volume of the patient's anatomic dead space). The oxygen concentration of the exhaled gases combined with the supply of fresh oxygen permits the use of oxygen flows lower than those necessary for other devices, potentially conserving oxygen use. The remaining portion of the patient's exhaled volume is vented through open exhalation ports located on the sides of the mask.

The mask should be fit securely to the patient's face to minimize the amount of room air entrained during inspiration. The oxygen flow rate should be adjusted to a level sufficient to keep the bag partially inflated during inspiration; usually 6 to 15 L/minute is sufficient. If the reservoir bag becomes totally deflated when the patient inspires, the flow rate should be increased. When there is an adequate seal around the mask and an appropriate flow rate is maintained, an Fio_2 of up to 0.6 is delivered to the patient.[5,48] However, this Fio_2, as in other variable performance devices, is also influenced by the patient's ventilatory pattern.

Nonrebreathing mask. The nonrebreathing mask is similar in design to the partial-rebreathing mask but in addition has one-way valves that function to keep the patient from rebreathing any exhaled gas.[48] A one-way valve located between the face mask and the reservoir bag allows 100% source gas to enter the mask during inspiration, but unlike the partial-rebreathing mask, it prevents any of the patient's exhaled gas from entering the bag. Instead of entering the reservoir bag, the exhaled gas is directed through one-way leaflet valves located over the exhalation ports on the sides of the mask. The leaflet valves also ensure minimal dilution from the entrainment of room air.

The nonrebreathing mask is designed to provide a higher Fio_2 than the simple and partial-rebreathing masks and the nasal delivery devices.[30] If there is an adequate seal around the mask and the flow rate is sufficient to keep the bag partially inflated during inspiration, oxygen concentrations can conceivably reach greater than 90%. Because it is designed to provide almost 100% source gas, the nonrebreathing mask is the recommended device to deliver specific gas mixtures, as in helium–oxygen therapy, or specific concentrations from a blender.[6,49]

FIXED-PERFORMANCE OXYGEN DELIVERY SYSTEMS

Air-Entrainment Mask

Air-entrainment masks, or **Venturi masks**, are examples of high-flow systems that provide the patient's entire inspiratory requirements while delivering predetermined, precise oxygen concentrations (Figure 10-7). This is accomplished by providing a total flow of gas that exceeds the patient's ventilatory demands, thus eliminating dilution of the oxygen concentration with room air, as occurs in low-flow devices.

The performance of the mask is based on principles described by Bernoulli.[50] As 100% oxygen under pressure flows through a small jet orifice entering the mask, the velocity increases, creating viscous shearing forces. As a result, room air is entrained through open ports located at the base of a reservoir tube attached to the front of the mask. By varying either the diameter of the jet orifice or the size of the entrainment ports, the amount of room air entrained can be proportionally changed, resulting in higher total flows and specific concentrations delivered to the patient's proximal airway.

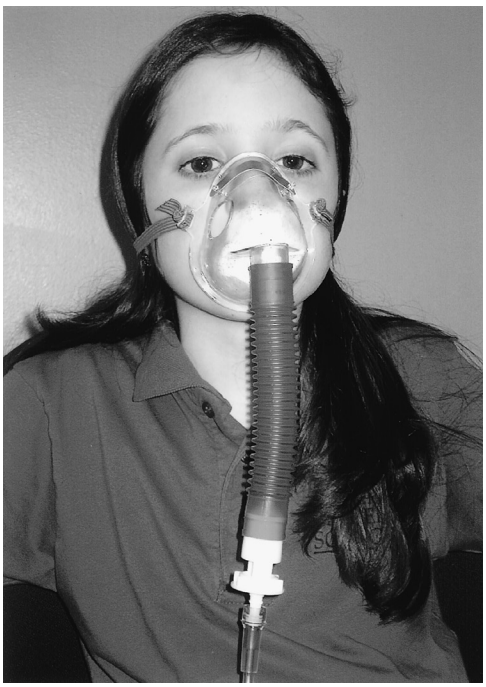


FIGURE 10-7 Pediatric patient with an air-entrainment mask.

Indications and contraindications. The air-entrainment mask is indicated for patients who require a controlled Fio_2 at either low or moderate levels. The commercially available masks are capable of providing oxygen concentrations ranging from 24% to 50%. In a hypoxic child with increased respiratory rates and tidal volumes, the air-entrainment mask is the preferred oxygen delivery system because it is capable of maintaining total flows in excess of the patient's inspiratory flow rate. For pediatric patients with chronic carbon dioxide retention who have the potential to hypoventilate with increased oxygen concentrations, the air-entrainment mask is ideal because it maintains a constant Fio_2 even at low concentrations.

Application. An air-entrainment mask is designed to fit over the patient's nose and mouth and contains a short corrugated hose with a jet orifice that is connected to oxygen supply tubing. Because the high total flows produced by this system can be quite drying, humidification is provided with a bubble-diffusion humidifier. At the lower concentrations of 24% and 28%, oxygen flow through the small, restricted orifice creates excessive backpressure in the humidifier. For these levels of oxygen concentration, an alternative method may be used in which a bland aerosol is applied through a 22-mm cuplike collar attached to the base of the corrugated hose at the air-entrainment ports. This collar is often placed on the hose even when no aerosol is applied, simply to act as a shield to prevent the accidental occlusion of the air-entrainment ports with bed linens.

Hazards and complications. Correct performance of the air-entrainment mask can be altered by resistance to the flow of gas that may occur distal to the restricted orifice. The resistance to flow at this particular point creates backpressure, resulting in less air entrainment. As a result, higher oxygen concentrations and lower total flows are delivered to the patient. If total flow decreases significantly, room air may be inhaled around and through the mask ports. This same phenomenon will occur if the entrainment ports are partially or completely obstructed. Also, at the 50% oxygen setting, total gas flow delivered by the device is less than that at the lower concentrations. Because of this, there is the potential for the patient with an increased inspiratory flow requirement to receive an oxygen concentration less than 50%.

Air-Entrainment Nebulizer

The gas-powered, large-volume, or all-purpose nebulizer is another fixed-performance system that provides particulate water and contains an adjustable air-entrainment port that controls oxygen concentrations.[51] The addition of heat gives this type of system the advantage of providing 100% body humidity when clinically indicated. The nebulizer provides oxygen at fixed concentrations by adjusting the size of the air-entrainment port located at the top of the nebulizer lid. The small size of the nebulizer jet restricts maximal flow to 15 L/minute from any 50-psi gas source.

Indications and contraindications. Air-entrainment nebulizers are used when high levels of humidity or aerosol are desired. Patient application devices used with the nebulizers include a tracheostomy collar, face tent, and aerosol mask.[5]

Application. Each patient application device is attached to the nebulizer unit with 4 to 6 feet of large-bore corrugated tubing that allows high gas flows and maximal aerosol delivery to the patient. Both the aerosol mask and the face tent apparatus are indicated primarily for short-term administration of oxygen with high humidity, as in postextubation or postanesthesia hypoxemia.[52]

When used to deliver oxygen to an older patient with an artificial airway, the aerosol is heated and the temperature of the gas–aerosol mixture is monitored. A tracheostomy collar is recommended for use with a tracheostomy; however, if a precise Fio_2 is required, a T-piece device may ensure delivery of a more exact Fio_2 because of its close fit on the tracheostomy tube. Provided that the gas flow from the nebulizer exceeds the patient's inspiratory flow rate, room-air entrainment is limited and the delivered Fio_2 is stable.

An air-entrainment nebulizer used with a collar or T-piece is not appropriate for oxygen delivery to infants and young children with a tracheostomy. Instead, a heated humidifier is recommended along with an oxygen blender used to regulate the Fio_2. Using small-bore oxygen supply tubing attached to the flow meter on the blender, the oxygen is directed through the humidifier where large-bore corrugated tubing is connected to the tracheostomy collar.

Hazards and complications. As with all masks used to deliver oxygen therapy to an infant or pediatric patient, the aerosol mask and face tent often provoke unnecessary agitation and anxiety, especially in the treatment of postanesthesia hypoxemia. Infants and young children often find it difficult to keep the masks in place. Nebulizers are susceptible to bacterial contamination and require replacement according to hospital policy. Condensate in the aerosol tubing is considered infectious waste and should never be drained back into the nebulizer.[5] The condensate can completely obstruct gas flow or cause increased resistance to flow, which may increase the Fio_2 above the desired setting.

The weight of the T-piece and tubing assembly often creates torque on the endotracheal or tracheostomy tube, causing tracheal irritation and possible displacement. The tracheostomy collar may cause skin irritation around the patient's neck, and condensate in the aerosol tubing may result in inadvertent tracheal lavage.[5]

A cool mist is not recommended for newborns because of the potential to induce cold stress.[53] If the gas flow from the oxygen source is cool and is directed toward the infant's face, stimulation of the trigeminal nerves may cause alterations in the respiratory pattern and lead to apnea.[54]

High-Flow Nasal Cannula

In the past the nasal cannula has always been classified as a low-flow, variable-performance oxygen delivery system, with recommendations that no more than 6 L/minute gas flows be used with adults and that the maximal flow to newborn infants not exceed 2 L/minute.[5,6,30] Flow limitations largely have been related to the airway cooling and drying that occur at higher flows. Using a bubble humidifier to humidify oxygen with a nasal cannula provides inadequate humidification to premature infants and has been associated with decreased airway patency, nasal mucosal injury, and coagulase-negative staphylococcal sepsis in extremely low-birth-weight infants.[55-57] Although face masks can safely deliver oxygen at higher flows, these devices are confining and often poorly tolerated by infants and children.

Using a nasal cannula at high flows is still a relatively new means to deliver oxygen to infants and children. It has been used only a few years more in the adult population. However, studies with neonates through adults have been favorable, with data showing the heated, **humidified high-flow nasal cannula** (HHFNC) providing moderate to high Fio_2 values and possibly providing a cost-efficient alternative for patients who require this level of oxygen concentration.[58-60] One study indicated that when the oxygen is delivered through a HHFNC, adult patients with advanced obstructive airway disease experience an increase in oxygenation. The warm humidification may have likely contributed to the improvement of airway function by maximizing mucociliary clearance and preventing inflammatory reactions. Also, nasal breathing of warm, humidified gas tends to inhibit the bronchoconstrictor reflex, which in turn prevents the increase in airway resistance that is often triggered by cold air.[61]

Washout of Nasopharyngeal Dead Space

Dead space has a significant and critical impact on the composition of inspiratory gas that reaches the lower, respiratory regions of the pulmonary system. When a breath begins, the first bolus of gas to be drawn into the lungs is the end-expiratory gas that was intended for exhalation. This phenomenon is the result of the anatomic dead space that must serve as a bidirectional conduit between nasal openings and the lung. Under normal conditions, this rebreathing of CO_2-rich and oxygen-depleted end-expiratory gas allows us to maintain an arterial CO_2 tension in the ideal range for our innate blood buffering system as well as protect the lower respiratory tract from the supraphysiologic partial pressure of oxygen found in atmospheric air. However, for a patient having trouble removing CO_2 or oxygenating the blood, elimination of anatomic dead space will improve breathing efficiency and therefore improve the composition of inspiratory gas within the lung.

Using HHFNC, gas flow rates that exceed inspiratory flow rates purge the nasopharyngeal cavity during the late expiratory phase and end-expiratory pause of respiration. This purging of anatomic dead space removes expiratory gas that is high in carbon dioxide concentrations and relatively depleted of oxygen. This creates an anatomic reservoir of the intended inspiratory gas mixture. Under these conditions, the subsequent breath is composed of less rebreathed expiratory gas and more delivered cannula gas. The new alveolar gas equilibrium supports alveolar ventilation (VA) with less minute ventilation (VE) and in this regard improves the efficiency of breathing.

Data from clinical studies on HHFNC confirm the reduction of dead space because of the immediate impact on ventilation rates.[62-65]

In the neonatal community, a number of clinical trials support the conclusion that dead-space washout provides a ventilation effect. Holleman-Duray and colleagues showed infants were able to be extubated to HHFNC from significantly greater ventilator rates (33 ± 8 vs. 28 ± 8 breaths per minute; $p < 0.05$) compared with other noninvasive support modes.[66] Additionally, a case report of a pediatric burn patient showed respiratory rate decreased immediately after initiation of HHFNC (63-38 breaths per minute), with a secondary sustained decrease in heart rate (175-144 beats per minute) after a short period of HHFNC.

Indications and contraindication. Oxygen delivery with a high-flow nasal cannula is most often indicated for use in patients with hypoxemia who have not responded to oxygen administered with a low-flow nasal cannula. It may also be indicated for use in infants and children with lung disorders who require improved oxygenation or a reduction in work of breathing. The high-flow nasal cannula has also been recommended for infants in the management of apnea of prematurity.[43] As a less intrusive method to deliver high flows of oxygen, its use may reduce the potential risk of the iatrogenic injuries associated with nasal continuous positive airway pressure (CPAP) and mechanical ventilation.[67] Contraindications for use of the high-flow nasal cannula may include suspected or confirmed pneumothorax, severe upper airway obstruction, and absence of spontaneous ventilation.

Application. To provide optimal humidification, the high-flow nasal cannula must be used with a hydration system. The Vapotherm 2000i (Vapotherm, Stevensville, MD) system is credited with starting the high-flow

therapy via nasal cannula. In 2004 the first HHFNC system was approved by the U.S. Food and Drug Administration to humidify and deliver high-flow air or oxygen by nasal cannula and other patient interfaces. It is not approved, nor is it recommended for use, as a CPAP delivery system.[42-45] The Vapotherm Precision Flow, Teleflex Comfort Flo, and Fisher & Paykel's Optiflow can provide oxygen flow at a relative humidity of 99.9% with a temperature setting of 37°C. Oxygen is supplied from either a built-in or external air–oxygen blender. The flow rate of the gas is controlled by the flow meter on the blender. The oxygen travels through the humidifier. After it is warmed and humidified, the oxygen flows through a heated delivery tube that is connected to the nasal cannula. This tubing maintains the temperature of the gas and minimizes condensation in the cannula.

Most systems offer several cannula sizes:

- Premature
- Neonatal
- Infant
- Intermediate infant
- Pediatric
- Adult

The cannula that is most appropriate for the size of the patient should be selected, making sure that the prongs do not occlude the patient's nares. The high-flow nasal cannula is attached to the patient in the same manner as one would a low-flow nasal cannula. The oxygen concentration is adjusted with the blender and the flow rate on the flow meter set at typically the lowest flow rate range for age. See Table 10-1 for initial flow rates. The flow is increased or decreased in small increments and the patient's breathing pattern, breath sounds, and vital signs reassessed. The Spo_2 and chest radiographs are monitored to determine appropriate flow rates. Table 10-1 represents estimated inspiratory flow rates of a wide patient population range. The assumptions in Table 10-1 are based on the notion that patients who are receiving HHFNC are in respiratory distress. Calculations are based on the highest known normal respiratory rate for each category, inspiratory time of 33%, and tidal volumes between 4 and 8 mL/kg.

Hazards and complications. To a greater extent than with the low-flow nasal cannula, there is considerable concern as to the lack of knowledge of the exact amount of positive pressure generated. Although most studies present low levels of positive pressure in flow range commonly used, the development of gastric distention or lung overexpansion is a possibility if not carefully monitored.[64] A second concern is the level of Fdo_2 that can be administered. An Fdo_2 of more than 0.6 can be easily administered at higher flows. When needed, this ability is a blessing; however, it may disguise a progressive disease when mistakenly considered a low-flow, low-Fdo_2 delivery device.

Clinical Highlight

It is theorized that to improve ventilation efficiency with humidified high-flow nasal cannula (HHFNC), the flow must be set to minimally exceed the expiratory flow rate of the patient. To provide additional low-level positive pressure with HHFNC, the flow must be set to exceed the inspiratory flow rate of the patient.

Exceeding expiratory flow rate (typically less than inspiratory flow rate) reduces dead space, increases oxygen delivery, and provides humidity. Exceeding inspiratory flow rates accomplishes dead space washout and possibly provides some positive pressure expiratory pressure.

More data supporting the clinical efficacy of HHFNC are produced each year. Research continues to focus on when HHFNC transitions from simple heated and humidified oxygen therapy to respiratory support by dead-space reduction and the application of low-level positive pressure.

Oxygen Hood

The **oxygen hood** is a transparent enclosure constructed of clear plastic material in a cylinder or boxlike design; they are rarely used currently. Oxygen is administered through large-bore corrugated tubing attached to hood. The hood surrounds the infant's head, leaving the body accessible for nursing care. This design also allows the infant to be placed in a neutral thermal environment, such as an incubator, and still receive controlled oxygen concentrations. Variations in hood design allow access to the infant's head by removing the top lid or by opening large ports on the sides or top of the hood.

Indications and contraindications. Hoods are indicated most often for neonates, infants, and small children who require supplemental oxygen with heated humidity. Hoods are used to provide a controlled Fio_2 and increased heated humidity to patients who are unable to tolerate other oxygen or humidification devices. An oxygen hood can also be used to perform an oxygen challenge (hyperoxia) test in a spontaneously breathing neonate. Oxygen concentration in a hood can be varied from 21% to 100% and is more stable than that provided by a tent.[5]

Application. Oxygen is delivered to the hood with heated humidification by means of an oxygen blender, dual air and oxygen flow meters, or a heated air-entrainment nebulizer. When using the heated air-entrainment nebulizer, the nebulizer is powered with compressed air, setting the oxygen concentration dial at 100% and bleeding oxygen into the nebulizer. In this way, oxygen concentrations are more easily regulated and noise levels are reduced.[68]

Table 10-2

SYSTEM	% FDO_2	DESIGN	INDICATIONS	COMMENTS
Blow by	< 30%	Low flow, variable	Low dose and does not tolerate mask	Inconsistent delivery and must monitor SpO_2
Nasal cannula (<2 L/minute)	25-40%	Low flow, variable	Low dose	Affected by changes in inspiratory flow rate
HFNC (1-70 L/minute)	21-100%	Can be high or low flow and variable or fixed	Low to high doses	Affected by changes in inspiratory and expiratory flow rates; requires heat and humidification
Simple mask	35-50%	Low flow, variable		
Partial rebreather mask	50-60%	Low flow, reservoir, variable	Moderate dose used to conserve oxygen	Must tolerate a mask
Nonrebreather mask	65-95%	Low-flow, reservoir, fixed	High dose	Tight fit required to get higher concentrations and must tolerate a mask
Oxymask	24-90%	High and low flow, variable and fixed	Low to high dose	Requires proper positioning of the diffuser and must be able to tolerate a mask
Hood/tent	25-90% (hood) 25-50% (tent)	High-flow enclosure, fixed (oxyhood), variable (tent)	Low to high doses	Imprecise dosing of oxygen, hot, and humidity
Manual resuscitators	21-100%	Reservoir, fixed	Low to high doses when mechanical support is required	May require a blender or a reservoir to deliver required dosing
Mechanical ventilators	21-100%	High flow, fixed	Low to high doses when mechanical support is required	Some subacute care and noninvasive devices cannot provide high-dose oxygen

The oxygen blender system premixes oxygen concentrations and passes the blended gas through a heated humidifier before entering the hood. This allows more precise control over both oxygen concentration and temperature and virtually eliminates noise inside the hood. With dual air and oxygen flow meters, both air and oxygen are titrated through the heated humidifier and tubing into the hood and analyzed until accurate prescribed oxygen concentrations are obtained. Regardless of which system is used, oxygen is analyzed on a continuous basis to ensure accurate concentrations.

It is important that adequate heat and humidity be maintained inside the hood. Administration of cool, dry gas induces cold stress in infants, resulting in increased oxygen consumption. Likewise, delivery of overheated gases induces apnea.[54] Temperature is maintained at or near body temperature with a thermometer placed inside the hood for continuous monitoring.

Hazards and complications. Limited mobility may be an issue with the oxygen hood if the infant requires oxygen for a prolonged period. Opening the hood decreases the oxygen concentration and can result in hypoxia. If the hood is opened for an extended period, such as during feeding and nursing procedures, it is appropriate to provide nasal oxygen with a cannula while the patient is eating or until the procedure is completed. Just as a loss of gas flow to the hood can result in hypoxia, hypercapnia, and even death, excessive oxygen concentrations can lead to irreversible complications. For these reasons, an oxygen analyzer should be used to continuously monitor the oxygen concentration in the hood, maintaining high and low alarms on the analyzer at all times. Although the oxygen hood is usually well tolerated, irritation to the infant's skin, especially around the neck, may occur because of pressure from an improperly sized hood or active movement of the patient. Cutaneous fungal infections have been associated with prolonged exposure to humidified oxygen in hoods.[69] High gas flow into the hood may produce noise levels that induce hearing impairment.[68]

Case Study

You are presented with providing oxygen therapy for a mildly hypoxic 12-year-old child with an Spo_2 of 86% to 88%. The child has been recently diagnosed with moderate persistent asthma. She is admitted for a moderate exacerbation. The patient is in moderate distress, tachypneic, with good air entry and prolonged expiratory wheezes. The last blood gas obtained from a referral hospital is only remarkable for a mild respiratory alkalosis. The physician asks you to initiate oxygen therapy with the device of your choice and to maintain the Pao_2 above 60 torr. Which of the following answers best describes the device you would choose and what noninvasive oxygen saturation range you would target?

A. A nasal cannula and an Spo_2 of 92% to 95%
B. A nasal cannula and an Spo_2 of 89% to 92%
C. A ventimask set at 28% to achieve an Spo_2 of 92% to 95%
D. Do nothing because the patient's Pao_2 is already above 60

See Evolve Resources for answers.

Key Points

- Oxygen is a drug and should be treated as one. Withholding oxygen can have detrimental effects; however, continuing to provide oxygen therapy when it is no longer indicated can prolong hospitalization and increase the cost of care.
- Oxygen therapy is only one aspect of the oxygen delivery equation. One must ensure that oxygen content and cardiac output are considered when assessing the effectiveness of oxygen therapy.
- Oxygen therapy device selection is vitally important. Care must be taken in the application process of such a wide patient population. Smaller pediatric patients are not small adults; therefore assumed Fio_2 calculation cannot be assumed.
- Oxygen therapy has several physiologic effects that are similar to adults. However, there are several differences that, if not carefully monitored, can lead to blindness, poor perfusion (CHD patients), or brain injury.
- Abnormal breathing patterns such as apnea of prematurity, abnormal neurogenic breathing, or obstructive sleep apnea can make oxygen therapy more difficult to manage. Inappropriately providing oxygen therapy in the face of one of these abnormal breathing patterns will lead to larger swings in oxygen delivery. In some cases it may mask apnea.

Assessment Questions

See Evolve Resources for answers.

1. Bedside evaluation of the degree of hypoxemia may best be accomplished by which of the following?
   A. Auscultation
   B. Pulse oximetry
   C. Capillary blood gas analysis
   D. Capillary refill time
2. A 5-year-old patient with a history of asthma is admitted to the emergency department after complaining of chest tightness and wheezing. The pulse oximeter reading drops from 95% to 88%. Which of the following devices should be selected to deliver oxygen to this patient?
   A. Nasal cannula
   B. Oxygen hood
   C. Oxygen mist tent
   D. Nonrebreathing mask
3. What is the minimal flow rate that should be used to deliver oxygen through a hood to an infant?
   A. 5 L/minute
   B. 6 L/minute
   C. 10 L/minute
   D. 15 L/minute
4. The physician orders 32% oxygen for a 12-year-old patient with cystic fibrosis. Which of the following oxygen delivery devices would best ensure this oxygen concentration?
   A. Low-flow nasal cannula
   B. Simple mask
   C. Nonrebreathing mask
   D. Air-entrainment mask
5. A 9-year-old patient is admitted to the hospital after smoke inhalation. While receiving oxygen with a nonrebreathing mask, it is noted that the reservoir bag becomes totally deflated when the patient inspires. Which of the following actions should be taken?
   A. Increase the oxygen flow rate
   B. Decrease the oxygen flow rate
   C. Change to a nasal cannula
   D. Change to a partial rebreathing mask
6. A premature infant is receiving oxygen by nasal cannula at 1.5 L/minute. The following capillary blood gas and pulse oximetry values are obtained:

pH	7.37
$Ptcco_2$	41 mm Hg
Pco_2	43 mm Hg
Hco_3	23 mEq/L
BE	−1 mEq/L
Spo_2	98%

BE, Base excess in blood; *Hco_3−*, bicarbonate; *$Ptcco_2$*, partial pressure of carbon dioxide, determined transcutaneously; *Pco_2*, partial pressure of oxygen, determined transcutaneously; *Spo_2*, percentage of oxygen saturation.

Which of the following should be recommended?
A. Replace the nasal cannula with an oxygen hood
B. Decrease the nasal cannula flow to 1 L/minute
C. Increase the nasal cannula flow to 2 L/minute
D. Discontinue the nasal cannula

7. What plausible ways does HHFNC improve oxygenation?
   - **A.** Nasal pharyngeal CO_2 washout at flows that exceed expiratory gas flow
   - **B.** Filling the nasal cavity with oxygen-enriched gas
   - **C.** Positive pressure
   - **D.** All of the above

8. What is a concern when using a HHFNC?
   - **A.** A lack of understanding of the actual fraction of oxygen delivered
   - **B.** An increased risk of developing chronic lung disease
   - **C.** A lack of knowledge concerning the actual amount of positive pressure applied to the patient's airways
   - **D.** A and C

REFERENCES

1. In: Partington JR, ed. *A Short History of Chemistry*. 3rd ed. New York: Dover; 1989:110-152.
2. Saugstad OD. Oxygen toxicity in the neonatal period. *Acta Pediatr Scand*. 1990;79:881.
3. Hess JH. Oxygen unit for premature and very young infants. *Am J Dis Child*. 1934;47:916.
4. In: Baker JP, ed. *The Machine in the Nursery: Premature Technology and the Origins of Newborn Intensive Care*. Baltimore: Johns Hopkins University Press; 1996:152.
5. American Association for Respiratory Care. Clinical practice guideline: selection of an oxygen delivery device for neonatal and pediatric patients. *Respir Care*. 2002;47:707.
6. American Association for Respiratory Care. Clinical practice guideline: oxygen therapy for adults in the acute care facility. *Respir Care*. 2002;47:717.
7. Fulmer JD, Snider GL. American college of chest physicians/National heart, lung, and blood institute: National conference on oxygen therapy. *Chest*. 1984;86:234.
8. Bonadio W. The history and physical assessments of the febrile infant. *Pediatr Clin North Am*. 1998;45:65.
9. Fisher AB. Oxygen therapy: side effects and toxicity. *Am Rev Respir Dis*. 1980;122:61.
10. Lanman JT, Guy LP, Dancis J. Retrolental fibroplasia and oxygen therapy. *JAMA*. 1954;155:223.
11. Patz A. The role of oxygen in retrolental fibroplasia. *Pediatrics*. 1957;19:504.
12. Hellström A, Smith LE, Dammann O. Retinopathy of prematurity. *Lancet*. 2013;382(9902):1445-1457.
13. Gaynon MW, Stevenson DK, Sunshine P, Fleisher BE, Landers MB. Supplemental oxygen may decrease progression of prethreshold disease to threshold retinopathy of prematurity. *J Perinatol*. 1997;17:434.
14. Phelps DL. Reduced severity of oxygen-induced retinopathy in kittens recovered in 28% oxygen. *Pediatr Res*. 1988;24:106.
15. Stuart MJ, Phelps DL, Setty BN. Changes in oxygen tension and effects on cyclooxygenase metabolites: III. Decrease of retinal prostacyclin in kittens exposed to hyperoxia. *Pediatrics*. 1988;82:367.
16. Kinsey VE, Arnold HJ, Kalina RE, et al. Pao_2 levels and retrolental fibroplasia: a report of the cooperative study. *Pediatrics*. 1977;60:655.
17. Pierce EA, Foley ED, Smith LE. Regulation of vascular endothelial growth factor by oxygen in a model of retinopathy of prematurity. *Arch Ophthalmol*. 1996;114:1219.
18. Robbins SG, Rajaratnam VS, Penn JS. Evidence for upregulation and redistribution of vascular endothelial growth factor (VEGF) receptors flt-1 and flk-1 in the oxygen-injured rat retina. *Growth Factors*. 1998;16:1.
19. Penn JS, Henry MM, Wall PT, Tolman BL. The range of Pao2 variation determines the severity of oxygen-induced retinopathy in newborn rats. *Invest Ophthalmol Vis Sci*. 1995;36:2063.
20. Saito Y, Omoto T, Cho Y, Hatsukawa Y, Fujimura M, Takeuchi T. The progression of retinopathy of prematurity and fluctuation in blood gas tension. *Graefes Arch Clin Exp Ophthalmol*. 1993;231:151.
21. STOP-ROP Multicenter Study Group. Supplemental therapeutic oxygen for pre-threshold retinopathy of prematurity (STOP-ROP), a randomized, controlled, trial: primary outcomes. *Pediatrics*. 2000;105:295.
22. Tin W, Milligan DW, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. *Arch Dis Child Fetal Neonatal Ed*. 2001;84:F106.
23. Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen-saturation targets and outcomes in extremely preterm infants. *N Engl J Med*. 2003;349:959.
24. Chow LC, Wright KW, Sola A. Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? *Pediatrics*. 2003;111:339.
25. Silverman WA. A cautionary tale about supplemental oxygen: the albatross of neonatal medicine. *Pediatrics*. 2004;113:394.
26. El-Lessy HN. Pulmonary vascular control in hypoplastic left-heart syndrome: hypoxic- and hypercarbic-gas therapy. *Respir Care*. 1995;40:737.
27. Fairshter RD, Rosen SM, Smith WR, Glauser FL, McRae DM, Wilson AF. Paraquat poisoning: new aspects of therapy. *Q J Med*. 1976;45:551.
28. Ingrassia TS, Ryu JH, Trastek VF, Rosenow EC. Oxygen-exacerbated bleomycin pulmonary toxicity. *Mayo Clin Proc*. 1991;66:173.
29. Kloor Jr TH, Carbajal D. Infant oxygen administration by modified nasal cannula. *Clin Pediatr*. 1984;23:447.
30. Leigh JM. Variation in performance of oxygen therapy devices. *Anaesthesia*. 1970;25:210.
31. Ooi R, Joshi P, Soni N. An evaluation of oxygen delivery using nasal prongs. *Anaesthesia*. 1992;47:591.
32. Walsh M, Engle W, Laptook A, et al. Oxygen delivery through nasal cannulae to preterm infants: can practice be improved? *Pediatrics*. 2005;116:857.
33. Finer NN, Bates R, Tomat P. Low flow oxygen delivery via nasal cannula to neonates. *Pediatr Pulmonol*. 1996;21:48.
34. Benaron DA, Benitz WE. Maximizing the stability of oxygen delivered via nasal cannula. *Arch Pediatr Adolesc Med*. 1994;148:294.
35. Vain NE, Prudent LM, Stevens DP, Weeter MM, Maisels MJ. Regulation of oxygen concentration delivered to infants via nasal cannulas. *Am J Dis Child*. 1989;143:1458.
36. Stevens DP, et al. Hypopharyngeal O_2 concentration in infants breathing O_2 by nasal cannula [abstract]. *Respir Care*. 1986;31:988.
37. Hammer J, Reber A, Trachsel D, Frei FJ. Effect of jaw-thrust and continuous positive airway pressure on tidal breathing in deeply sedated infants. *J Pediatr*. 2001;138:826.

38. Kuluz JW, McLaughlin GE, Gelman B, et al. The fraction of inspired oxygen in infants receiving oxygen via nasal cannula often exceeds safe levels. *Respir Care*. 2001;46:897.
39. Fan LL, Voyles JB. Determination of inspired oxygen delivered by nasal cannula in infants with chronic lung disease. *J Pediatr*. 1983;103:923.
40. Miller MJ, Martin RJ, Carlo WA, Fouke JM, Strohl KP, Fanaroff AA. Oral breathing in newborn infants. *J Pediatr*. 1985;107:465.
41. Miller MJ, Carlo WA, Strohl KP, Fanaroff AA, Martin RJ. Effect of maturation on oral breathing in sleeping premature infants. *J Pediatr*. 1986;109:515.
42. Locke RG, Wolfson MR, Shaffer TH, Rubenstein SD, Greenspan JS. Inadvertent administration of positive end-distending pressure during nasal cannula flow. *Pediatrics*. 1993;91:135.
43. Sreenan C, Lemke RP, Hudson-Mason A, Osiovich H. High-flow nasal cannulae in the management of apnea of prematurity: a comparison with conventional nasal continuous positive airway pressure. *Pediatrics*. 2001;107:1080.
44. Frey B, McQuillan PJ, Shann F, Freezer N. Nasopharyngeal oxygen therapy produces positive end-expiratory pressure in infants. *Eur J Pediatr*. 2001;160:556.
45. Courtney SE, Pyon KH, Saslow JG, Arnold GK, Pandit PB, Habib RH. Lung recruitment and breathing pattern during variable versus continuous flow nasal continuous positive airway pressure in premature infants: an evaluation of three devices. *Pediatrics*. 2001;107:304.
46. Thilo EH, Comito J, McCulliss D. Home oxygen therapy in the newborn: costs and parental acceptance. *Am J Dis Child*. 1987;141:766.
47. Weber MW, Palmer A, Oparaugo A, Mulholland EK. Comparison of nasal prongs and nasopharyngeal catheter for the delivery of oxygen in children with hypoxemia because of a lower respiratory tract infection. *J Pediatr*. 1995;127:378.
48. Cairo JM, Pilbeam SP, ed. Administering medical gases: regulators, flowmeters, and controlling devices. In: *Mosby's Respiratory Care Equipment*. 7th ed. St. Louis: Mosby; 2004:71-72.
49. Redding JS, McAfee DD, Gross CW. Oxygen concentrations received from commonly used delivery systems. *South Med J*. 1978;71:169.
50. Scacci R. Air entrainment masks: jet mixing is how they work: the Bernoulli and Venturi principles are how they don't. *Respir Care*. 1979;24:928.
51. Cairo JM, Pilbeam SP, ed. Humidity and aerosol therapy. In: *Mosby's Respiratory Care Equipment*. 7th ed. St. Louis: Mosby; 2004:73-74.
52. Amar D, Brodman LE, Winikoff SA, Hollinger I. An alternative oxygen delivery system for infants and children in the post-anesthesia care unit. *Can J Anaesth*. 1991;38:49.
53. Scopes JW, Ahmed I. Ranges of critical temperatures in sick and premature newborn babies. *Arch Dis Child*. 1966; 41:417.
54. Daily WJR, Klaus M, Meyer HB. Apnea in premature infants: monitoring, incidence, heart rate changes, and an effect of environmental temperature. *Pediatrics*. 1969;43:510.
55. Walsh B. Comparison of Vapotherm 2000i with a bubble humidifier for humidifying flow through an infant nasal cannula. *Respir Care*. 2003;48:1086.
56. Kopelman AE, Holbert D. Use of oxygen cannulas in extremely low birthweight infants is associated with mucosal trauma and bleeding and possibly with coagulase-negative staphylococcal sepsis. *J Perinatol*. 2003;23:94.
57. Kopelman AE. Airway obstruction in two extremely low birthweight infants treated with oxygen cannulas. *J Perinatol*. 2003;23:164.
58. Wettstein RB, Shelledy DC, Peters JI. Delivered oxygen concentration using low-flow and high-flow nasal cannulas. *Respir Care*. 2005;50:604.
59. Wilkinson D, Andersen C, O'Donnell CP, De Paoli AG. High flow nasal cannula for respiratory support in preterm infants. *Cochrane Database Syst Rev*. 2005;(5):CD006405. doi:10.1002/14651858.CD006405.pub2.
60. Frizzola M, Miller TL, Rodriguez ME, et al. High-flow nasal cannula: impact on oxygenation and ventilation in an acute lung injury model. *Pediatr Pulmonol*. 2011;46:67. doi:10.1002/ppul.21326.
61. Chatila W, Nugent T, Vance G, Gaughan J, Criner GJ. The effects of high-flow versus low-flow oxygen on exercise in advanced obstructive airways disease. *Chest*. 2004;126:1108.
62. Byerly FL, Haithcock JA, Buchanan IB, Short KA, Cairns BA. Use of high flow nasal cannula on a pediatric burn patient with inhalation injury and post-extubation stridor. *Burns*. 2006;32:121. doi:S0305-4179(05)00150-6 [pii] 10.1016/j.burns.2005.05.003.
63. Calvano TP, Sill JM, Kemp KR, Chung KK. Use of a high-flow oxygen delivery system in a critically ill patient with dementia. *Respir Care*. 2008;53:1739.
64. Price AM, Plowright C, Makowski A, Misztal B. Using a high-flow respiratory system (Vapotherm) within a high dependency setting *Nurs Crit Care*. 2008;13:298. doi:NCR299 [pii] 10.1111/j.1478-5153.2008.00299.x.
65. Roca O, Riera J, Torres F, Masclans JR. High-flow oxygen therapy in acute respiratory failure. *Respir Care*. 2010;55:408.
66. Holleman-Duray D, Kaupie D, Weiss MG. Heated humidified high-flow nasal cannula: use and a neonatal early extubation protocol. *J Perinatol*. 2007;27:776. doi:10.1038/sj.jp.7211825.
67. Juretschke R, Spoula R. High flow nasal cannula in the neonatal population. *Neonatal Intensive Care*. 2004;17:20.
68. Beckham RW, Mishoe SC. Sound levels inside incubators and oxygen hoods used with nebulizers and humidifiers. *Respir Care*. 1982;27:33.
69. Lanska MJ, Silverman R, Lanska DJ. Cutaneous fungal infections associated with prolonged treatment in humidified oxygen hoods [letter]. *Pediatr Dermatol*. 1987;4:346.

11 Aerosols and Administration of Inhaled Medications

Arzu Ari, James B. Fink

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. Describe the impact of differences in patient size and age on aerosol delivery.
2. Understand the basic mechanisms of operation of nebulizers, pressurized metered-dose inhalers, and dry powder inhalers.
3. Select the best device for a pediatric patient for specific clinical applications.
4. Select the best interface for infants and pediatrics.
5. Initiate and modify aerosol therapy.
6. Discuss the range of medications available for administration via aerosol.

Key Terms

aerosol therapy
aerosols
dry powder inhaler
nebulizer
pressurized metered-dose inhaler
spacers
valved holding chamber

Decades of research have established the scientific principles underlying the use of therapeutic **aerosols**. In general, the advantages of **aerosol therapy** include a smaller but targeted dose, lower cost, fewer side effects, efficacy comparable to or better than that observed with systemic administration of the drug, and usually a more rapid onset of action.[1] When inhaled drugs are delivered directly to the conducting airways, their systemic absorption is limited and systemic side effects are minimized, providing a high therapeutic

index.[2] On the other hand, peptides and other macromolecules can be targeted to the terminal airways and alveoli for systemic administration across the pulmonary vascular bed. This is an exciting and evolving use for therapeutic aerosols.

The uses for aerosol devices vary widely, ranging from bronchodilation to insulin administration, and the range of uses for aerosol devices continues to increase. **Nebulizers, pressurized metered-dose inhalers** (pMDIs), and **dry powder inhalers** (DPIs) are often used as aerosol generators because they produce respirable particles with a mass median aerodynamic diameter (MMAD) of 0.5 to 5.0 μm.[3] Other types of nonpressurized metered-dose inhalers, such as nasal sprays, produce particles in the 10- to 100-μm range, too large for pulmonary delivery. Although pMDIs and DPIs are used chiefly to deliver bronchodilators and steroids, nebulizers can be used to administer antibiotics, mucoactive agents, and other drugs.[4] Given the appropriate formulation, even complex molecules can potentially be delivered by aerosol. The operating characteristics and limitations of aerosol-generating devices, how they are matched to the needs of specific patients, and how they are used largely determine the efficacy of aerosol therapy. This chapter reviews the key principles of how aerosols are generated, deposited, and administered in neonatal and pediatric patients.

NEONATAL AND PEDIATRIC MEDICATION DELIVERY

Compared with adults, infants and children have smaller airway diameters, have higher and more irregular breathing rates, engage in nose breathing (which filters out large particles), and often have difficulty with mouthpiece administration. Cooperation and ability to perform aerosol inhalation techniques effectively vary with the child's age and developmental ability.

The size of the airways changes dramatically in the first years of life. Breathing patterns, flows, and volumes all change with growth and development. The resting respiratory rate decreases with age as tidal volume and minute ventilation increase. Tidal volume is approximately 7 mL/kg in newborns, with a 300% increase in tidal volume in the first year. Inspiratory flow also increases with vital capacity. The low tidal volume, vital capacity, functional residual capacity, and short respiratory cycles of infants result in a low residence time for small particles, resulting in a further decrease in pulmonary deposition (Box 11-1).[5]

Direct information regarding inhaled particle mass, lung deposition, and regional distribution of aerosols is limited concerning neonates, infants, and young children. Nevertheless, the data suggest that aerosol delivery is substantially less efficient for this population. Pulmonary deposition of aerosol to neonates may be less than 1% of the nominal dose being nebulized, compared with 8% to 22% in an adult.[5]

Box 11-1 Factors That Reduce Rate and Depth of Aerosol Particle Deposition in Neonatal and Pediatric Patients

- Large tongue in proportion to oral airway
- Nose breathing
- Narrow airway diameter
- Fewer and larger alveoli
- Fewer generations of airway
- More rapid respiratory rate
- Small tidal volume
- Inability to hold breath and coordinate inspiration
- High inspiratory flow rate during respiratory distress and crying

This reduced efficiency may result in infants receiving weight-appropriate dosing compared with adults. For example, the deposition efficiency of 0.5% of a standard dose of albuterol sulfate (2500 μg) would result in a lung dose of 12.5 μg, or 6.25 μg/kg for a 2-kg infant, whereas a 70-kg adult with 10% deposition has a lung dose of 250 μg, equivalent to 3.6 μg/kg. In this example, the infant actually receives a similar but slightly greater dose per unit weight. To some extent, the reduced deposition of aerosolized bronchodilators results in safety and efficacy profiles for infants and children similar to those reported for adults. Extrapolation of data from Wildhaber and colleagues[6] (Figure 11-1) demonstrates that whereas deposition from a pMDI with a nonelectrostatic **valved holding chamber** varies with child age, the amount of drug per kilogram of body weight is consistent across ages. This suggests that the same dose that is effective for an adult will probably be safe in infants. In contrast, rationales to reduce drug doses for infants and small children have not been well substantiated in the literature.

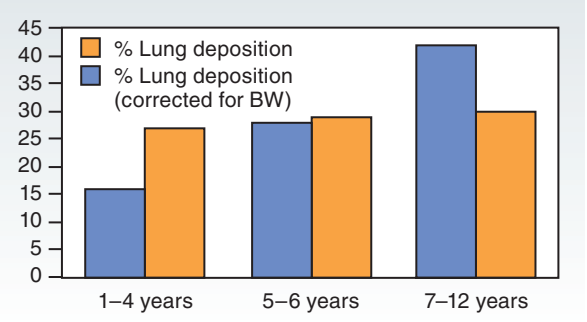


FIGURE 11-1 Although the percentage of drug deposited in the lung varies with age *(blue columns)*, the percentage of lung deposition corrected for body weight *(BW; orange columns)* is consistent across age groups. (Adapted from Wildhaber JH, Janssens HM, Pierart F, et al: High-percentage lung delivery in children from detergent-treated spacers. *Pediatr Pulmonol* 29:389–393, 2000.)

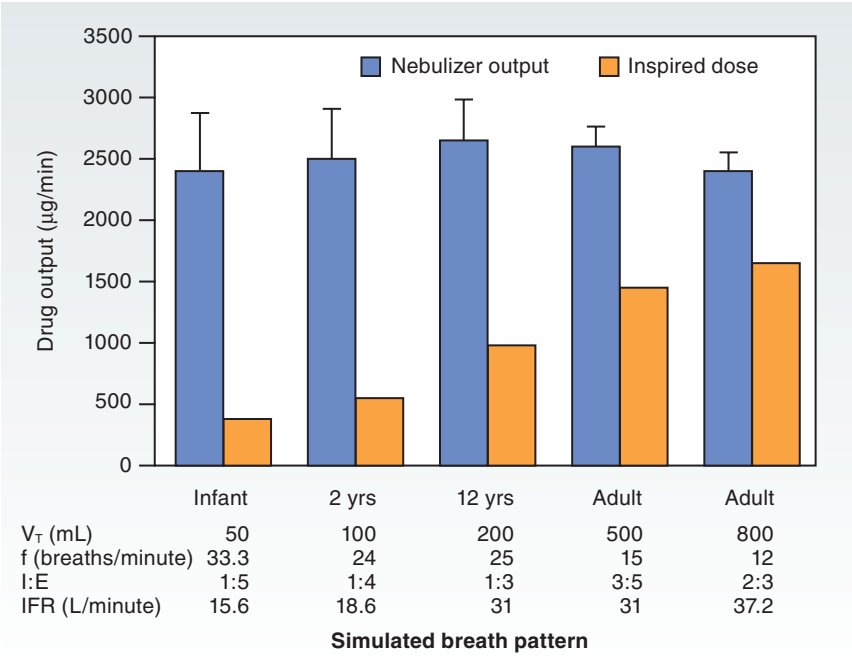


FIGURE 11-2 Assessing nebulizer performance. *f*, Frequency; *I:E*, ratio of inspiratory to expiratory time; *IFR*, inspiratory flow rate; *Vt*, tidal volume. (Redrawn from Dolovich MB: Assessing nebulizer performance. *Respir Care* 47(11): 1290–1301, 2002.)

Figure 11-2 illustrates the impact of changes in breathing patterns in the transition from infant to child to adult, with a lung simulator inhaling aerosolized drug from a continuous breath-enhanced nebulizer (PARI LC Star; PARI, Starnberg, Germany) producing a relatively consistent output.[7] The drug inhaled at the "mouth" of this *in vitro* model varies with the different simulated breath patterns, so infants and small children are apt to inhale less of the aerosol emitted from the nebulizer than larger adults. Tidal volume, inspiratory-to-expiratory (I:E) ratio, and inspiratory flow rates are key to the ability to efficiently inhale output from a nebulizer. In infants younger than 6 months of age, reduced inspiratory flow rates and broad I:E ratios result in less aerosol inhaled than by a larger child or adult.

These factors may decrease the rate and depth of aerosol deposition to the respiratory tract to as little as 0.1% to 1% of the medication dose placed in a nebulizer, or the dose emitted from a pMDI, regardless of whether the infant is breathing spontaneously or is intubated.[8]

AEROSOL CHARACTERISTICS

DEPOSITION OF PARTICLES

An aerosol is a group of particles that remain suspended in air for a relatively long time because of low terminal settling velocity. The terminal settling velocity of a particle is the velocity at which the particle will fall, because of gravity, through the air; it is related to the size and density of the particle.[9] Aerosols are also described by their geometric standard deviation (GSD), a measure of the particle size distribution. A monodisperse aerosol has a GSD less than 1.22, and a heterodisperse aerosol has a GSD greater than 1.22. Monodisperse aerosols are used for diagnostic and research purposes. Most therapeutic aerosols are heterodisperse, which means they contain a wider range of particle sizes. The greater the MMAD, the larger the median particle size, the greater the GSD, and the more heterodisperse is the aerosol. The particle size and size distribution of an aerosol are the major factors determining deposition efficiency and distribution in the lung.[10]

Gravitational sedimentation occurs when the aerosol particles lose inertia and settle onto the airway as a result of gravitational forces. The greater the mass of the particle, the faster it settles, affecting particles with diameters of 0.5 µm or less. Breath holding for 4 to 10 seconds increases the residence time for particles in the lung, extending the time allowed for deposition through gravitational sedimentation, especially in the last six generations of the airway.[11] A breath hold can increase deposition of an aerosol by up to 10% and is associated with a shift of deposition from the central to peripheral airways. This marginal increase in deposition may explain why breath holding has not been demonstrated to significantly improve the clinical response to aerosolized medications. Breath holding after inhalation does not appear to influence the response to administration of a bronchodilator given by DPI to children with asthma.[12]

Inertial impaction is the primary mechanism for deposition of particles with diameters of 5 µm or greater and an important mechanism for particles as

small as 2 μm in diameter. A particle traveling in a stream of gas that is diverted by a turn in the airway tends to continue on its initial path, impacting with and depositing on the surface of the airway. This tendency increases with the velocity and mass of the particle. The higher the inspiratory flow of gas, such as during crying, the greater the velocity and inertia of the particles, which increases the tendency for even smaller particles to impact and deposit in large airways. Common factors that increase the rate of inertial impaction of particles larger than 2 μm include turbulent flow, bifurcations, complex passageways, narrow or obstructed airways, and inspiratory flows greater than 30 L/minute.

Diffusion, also known as brownian movement, is the primary mechanism for deposition of particles less than 3 μm in diameter in the airway. As gas reaches the more distal regions of the lung, gas flow ceases. Aerosol particles bounce against air molecules and each other and deposit on contact with the airway surfaces. Particle deposition in the particle size range of 0.5 to 3.0 μm is reported to be divided between the central and peripheral airways.[10]

Aerosol droplets in the respirable range (MMAD, 1.0-5.0 μm) have a better chance to deposit in the lower respiratory tract than larger or smaller particles.[10,11] For particles greater than 1.0 μm, the depth of penetration into the lung is inversely proportional to the size of the particles, whereas particles less than 1.0 μm are so small, light, and stable that a significant proportion entering the lung do not deposit and are exhaled. However, nanoparticles less than 0.1 μm have greater lung deposition than common medical aerosols; very large particles may be filtered out by impacting surfaces en route and "rain out" before reaching the airway.

TRANSLOCATION OF AEROSOLS

To be effective as a therapeutic agent, an aerosol medication first must efficiently deposit in the airway and then must translocate across the mucous barrier, retaining bioactivity in this process. The optimal site of action depends on the agent administered. Bronchodilators and steroids need to reach the epithelium to be effective. Aerosolized antibiotics and mucolytics are most effective when dispersed in infected airway secretions at sites of maximal airway obstruction. Gene transfer therapy must not only access the epithelium through the mucous barrier but must then gain access to the submucous glands or basal progenitor cells of the epithelium.

Particle size, charge, and solubility and the biophysical properties of secretions all affect the ability of an aerosol to penetrate the mucous barrier. A consistent inverse relationship exists between molecular mass and particle diffusion through mucus, especially at molecular masses greater than 30 kD.[13] Turbulent flow and airway obstruction can affect the airway deposition pattern. Other factors limiting efficacy, especially of macromolecules, include binding to constituents of mucus, including mucin and DNA, and the breakdown of bioactive molecules by proteases and other enzymes. Translocation of macromolecules can be further compromised by the hypersecretion that accompanies inflammation and chronic pulmonary disease. These secretions can be a barrier to the penetration of any aerosol.[14,15]

The antibiotic diffusion barrier represented by mucin may be significant *in vitro,* particularly for nebulized antibiotics.[16] Some antibiotics bind to whole cystic fibrosis (CF) sputum, with the degree of binding dependent on the DNA concentration and the presence of acidic mucins.[17] Mucolytic agents might be able to increase diffusion and increase antibiotic levels in the sputum.[18] Similarly, treatment of the sputum-covered cells with recombinant human deoxyribonuclease at 50 μg/mL significantly improved gene transfer in patients with CF.[19]

Factors promoting translocation include an effective surfactant layer and increased particle retention time. Discontinuity of mucus in the airway may assist deposition and translocation. The translocation of particles through the mucus layer is likely to depend partly on the presence of bronchial surfactant. *In vitro* experiments have shown that pulmonary surfactant promotes the displacement of some particles from air to the aqueous phase and that the extent of particle immersion depends on the surface tension of the surface-active film.[20,21]

DRUG DOSE DISTRIBUTION

Dosing of aerosolized medication is an imprecise science. It is unclear how much, if any, drug is delivered to targeted areas of the lung with progressive disease states or during acute exacerbations. All the factors previously discussed decrease the rate and depth of aerosol deposition to the respiratory tract to as little as 0.5% of the medication dose placed in a nebulizer, regardless of whether the patient is breathing spontaneously or intubated. High flow increases aerosol impaction in larger airways, whereas lower inspiratory flow with high-resistance DPIs can reduce the amount of medication inhaled.

Humidity also influences medication delivery, especially for DPIs and in ventilator circuits. Droplets of solution may evaporate or grow, depending on the water content and temperature of the gas, and powder can clump or aggregate in high humidity. High ambient humidity can also result from a child exhaling into a DPI or from a DPI being brought into a warm indoor environment from the cold outdoors (or from inside a car on a very cold day), with condensation forming inside the device.[22]

Drug formulations dictate in part which aerosol options are available for medication delivery. Most solutions can be nebulized if the medication is soluble

(corticosteroids are a notable exception), but the physical characteristics of the solution (or suspension) can affect particle size and nebulizer output. Furthermore, some macromolecules may not enter suspension well and can shatter into nonbioactive forms with the force of air required to generate an aerosol. Because of development costs, many aerosol medications are initially developed as nebulizer solutions and later reformulated for DPI or pMDI delivery.

Theoretically, if a particle can be milled to a respirable size while retaining bioactivity, it can be delivered by DPI or pMDI. However, development costs are greater for these devices than for nebulizer solutions. At present, DPI formulations are limited to only a few preparations. With more effective DPI devices being developed and the need to eliminate chlorofluorocarbon (CFC)–based propellants in accordance with the Montreal Protocol on Substances that Deplete the Ozone Layer (see http://www.unep.org/OZONE/pdfs/Montreal-Protocol2000.pdf), it is anticipated that a greater variety of DPI medications and devices will soon be commercially available. A greater variety of formulations are available for pMDIs, and more are being developed for the newer hydrofluoroalkane (HFA)–based pMDIs.

AEROSOL DELIVERY

The most common methods of generating therapeutic aerosols are with nebulizers (jet pneumatic, ultrasonic [USN], and vibrating mesh [VMN]) and inhalers (pMDIs and DPIs). Older methods based on the spray "atomizer" or the addition of medications to room humidifiers are ineffective, and their use should be discouraged.

PNEUMATIC JET NEBULIZERS

Pneumatic jet nebulizers use the Bernoulli principle to drive a high-pressure gas through a restricted orifice and draw the fluid into the gas stream from a capillary tube immersed in the solution. Shearing of the fluid stream in the jet forms the aerosol stream that impacts against a baffle, removing larger particles that may return to the reservoir.

An effective pneumatic nebulizer should deliver more than 50% of its total dose as aerosol in the respirable range in 10 minutes or less of nebulization time. Performance varies with diluent volume, operating flow, pressures, gas density, and manufacturer.[23] The amount of drug that is nebulized increases as the volume of diluent is increased. The residual volume of medicine that remains in commercial small-volume nebulizers (SVNs) varies from 0.5 to 2.0 mL depending on the specific device; thus increasing the fill volume allows a greater proportion of the active medication to be nebulized. For example, with a residual volume of 1 mL, a fill of 2 mL would leave only 50% of the nebulizer charge available for nebulization, whereas a fill of 4 mL would make 3 mL, or 75%, of the medication available for nebulization. No significant difference in clinical response has been shown with varying diluent volumes and flow rates.[24]

Droplet size and nebulization times are both inversely proportional to gas flow through the jet. Proper operating gas flow varies with each model of nebulizer, from 2 L/minute (MiniHEART, Westmed Inc., Tucson, AZ) to 10 L/minute (Misty Max, Cardinal Health, Dublin, OH). For any given nebulizer, the higher the flow to the nebulizer, the smaller the particle size generated and the shorter the time required to nebulize the full dose.[25,26] Nebulizers that produce smaller particle sizes by use of baffles such as one-way valves may have a lower total drug output per minute than the same nebulizer without baffling, requiring more time to deliver a standard dose of medication.

Gas density affects both aerosol generation and delivery of aerosol to the lungs, especially with low-density helium–oxygen mixtures. The lower the density of a carrier gas, the less turbulent the flow, which theoretically decreases aerosol impaction, allowing more aerosol to pass beyond an obstructed airway.[27] This is true with virtually any aerosol, with high-concentration heliox increasing aerosol delivery by as much as 50%. Heliox concentrations as low as 40% can improve aerosol delivery. When using heliox to drive a jet nebulizer, the aerosol output is much less than with air or oxygen, requiring double the flow to produce a comparable output of respirable aerosol per minute. Thus, although helium can increase the amount of aerosol reaching the lungs, it impairs the production of aerosol from jet nebulizers.[28]

Humidity and temperature affect the particle size and the concentration of drug remaining in the nebulizer. Evaporation of water and adiabatic expansion of gas can reduce the temperature of the aerosol to as much as 5°C below ambient temperature. Aerosol particles entrained into a warm and fully saturated gas stream increase in size. These particles can also stick together, further increasing the MMAD, and with a DPI this can severely compromise the output of respirable particles.

With three different fill volumes, albuterol delivery from a nebulizer was found to cease after the onset of inconsistent nebulization (sputtering).[29] Aerosol output declined by one-half within 20 seconds of the onset of sputtering. The concentration of albuterol in the nebulizer cup increased significantly once the aerosol output declined, and further weight loss in the nebulizer was caused primarily by evaporation. The conclusion was that aerosolization past the point of initial jet nebulizer sputter is ineffective.

Nebulizer selection affects aerosol delivery. Only nebulizers that have been shown to work reliably under specific conditions, with specific medications, and with specific compressors should be used.[30] When used to treat small children or during mechanical

ventilation, nebulizers producing aerosols with an MMAD of 0.5 to 3.0 μm are more likely to achieve greater deposition in the lower respiratory tract.[5]

Continuous aerosol generation wastes medication, because the aerosol is produced throughout the respiratory cycle and is largely lost to the atmosphere (Figure 11-3, A). Patients with an I:E ratio of 1:3 lose a minimum of 75% of the aerosol generated to the atmosphere. Because only 50% of the dose is available from the nebulizer as aerosol in the respiratory range and only 25% of that is inhaled by the patient, less than 10% deposition is typically measured with nebulizer therapy.

A reservoir on the expiratory limb of the nebulizer conserves drug aerosol.[30] A simple approach is to place 6 inches of aerosol tubing on the expiratory side of the nebulizer T-tube device.

On the other hand, breath-enhanced nebulizers use a one-way inspiratory valve on the inlet of the nebulizer, and another on the mouthpiece or mask directing exhaled aerosol away from the nebulizer.[31,32] Theoretically, breath-enhanced nebulizers provide more aerosol when ambient air vents through the nebulizer during inhalation, and less aerosol is cleared from the device when exhaled gas is routed out the expiratory one-way valve in the mouthpiece. Thus, breath-enhanced nebulizers may increase the inhaled dose by as much as 50% compared with continuous simple jet nebulizers (see Figure 11-3, B).

Several systems integrating a bag reservoir and one-way valves, such as the Piper (Piper Medical Products, Carmichael, CA) or Circulaire (Westmed, Tucson, AZ) systems collect aerosol in simple bag reservoirs during exhalation, allowing the small particles to remain in suspension for inhalation with the next breath while larger particles rain out in the bag or on the valves. The valves direct the aerosol from the reservoir to the patient and from the patient to the air, without exhaling back into the reservoir. These systems are also more efficient than simple jet nebulizers.

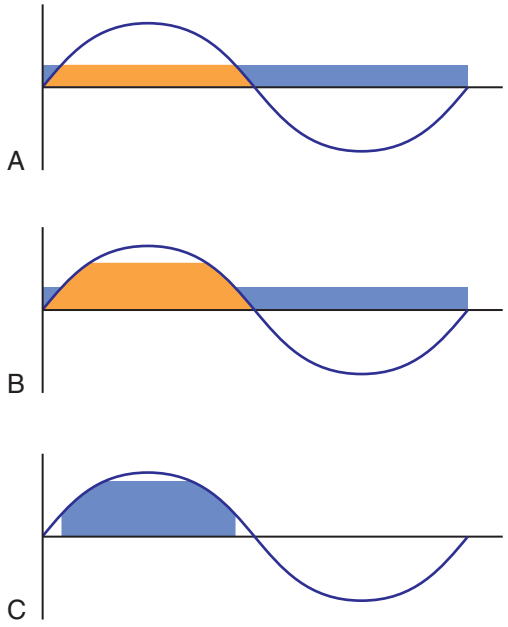


FIGURE 11-3 Aerosol generated and inhaled during nebulization therapy. **A,** Continuous nebulization; **B,** breath-enhanced nebulization; **C,** breath-actuated nebulization.

As another alternative to continuous nebulization, a three-way thumb control port, placed between the oxygen tubing and the gas inlet of the nebulizer, allows the patient to direct gas to the nebulizer only on inspiration. This improves efficiency by as much as threefold, but only if there is good hand–breath coordination. This increase of inhaled dose comes at the cost of longer administration time. An alternative to having the patient manually control when nebulization occurs, a mechanical or electronic design can automate breath actuation.[33]

Breath-actuated nebulization occurs by generating aerosol in synchrony with inspiration. Nebulizing only during inspiration is more efficient than continuous or vented systems (Figure 11-3 , C). Previous studies showed that breath-actuated nebulizers (BANs) produce smaller particles and more lung dose than continuous pneumatic nebulizers.[31,34-36] However, to nebulize the same total dose placed in the nebulizer, the breath-actuated system may take two to four times longer than the continuous nebulizer.[31] The AeroEclipse (Monaghan Medical, Plattsburgh, NY) is a purely mechanical pneumatic device that generates aerosol when the patient produces sufficient inspiratory flow (approximately 20 L/minute) during inspiration. On the other technical extreme, the I-Neb with adaptive aerosol delivery (AAD) systems (Philips Respironics, Murrysville, PA) and Akita (Activaero, Wohra, DE) use a microprocessor and pressure transducer to sense inspiratory efforts and regulate nebulization during the first half of or all of inspiration.

A number of *in vitro* studies have shown greater deposition in adults and large children with BANs. Lin et al[37] studied the influence of nebulizer type with different pediatric aerosol masks on drug deposition in a model of a spontaneously breathing small child. After modeling toddler breathing patterns, they demonstrated substantial reductions in inhaled dose with a mechanical BAN, rather than simple continuous nebulizers, despite the BAN appearing to be actuating with every inspiratory maneuver.[37] This suggests that the appearance of breath actuation *in vivo* with young children may not ensure superior aerosol delivery.

There is no randomized trial in the literature showing greater bronchodilator efficacy with BANs than with pneumatic nebulizers. In a recent clinical study by Sabato et al.,[35] it was reported that the admission rate with the breath-actuated nebulizer and pneumatic jet nebulizer were both 40%. Lin and Huang[36] compared a breath-actuated nebulizer with a constant-flow pneumatic nebulizer in the treatment of children with acute asthma and showed a change in pulse rate

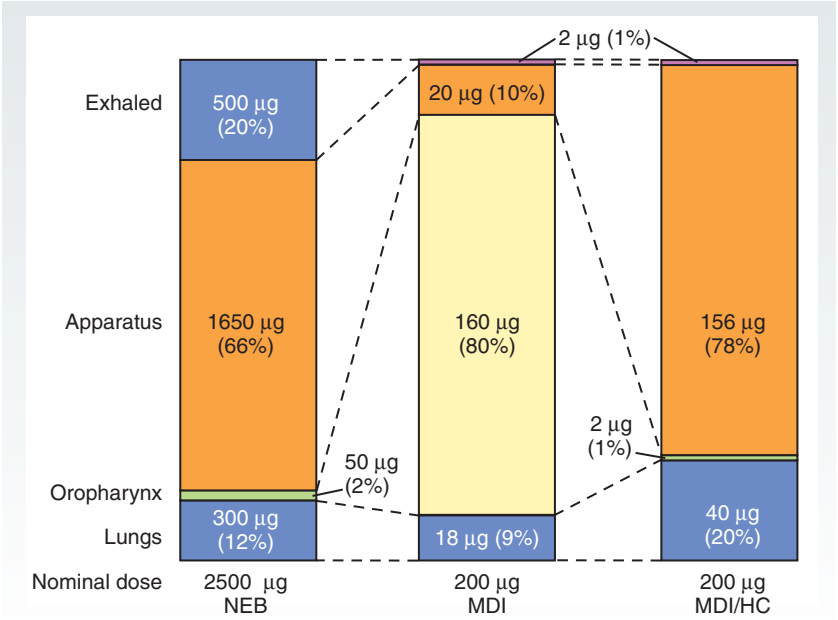


FIGURE 11-4 Distribution of albuterol delivered via nebulizer *(NEB)*, pressurized metered-dose inhaler *(MDI)*, and pressurized metered-dose inhaler with holding chamber *(MDI/HC)*.

5 minutes after the treatment. Although these studies provide us with valuable information about BANs, future research is warranted to understand the efficacy, safety, and satisfaction measures of BANs in the treatment of children.[38,39]

A typical dose of albuterol sulfate solution is 2.5 mg (2500 µg). If only 34% (850 µg) leaves the nebulizer and is inhaled by the patient, and some of that drug deposits in the upper airways (50 µg) and is exhaled (500 µg), it should not be surprising that 12% deposition of the nominal dose, typical of ambulatory adult patients, would be 300 µg (Figure 11-4). In small children and infants, deposition can be less than 1%, representing less than 25 µg delivered to the lung.

Gas pressure and flow affect particle size distribution and output. A nebulizer that produces an MMAD of 2.5 µm when driven by a gas source at 50 psi with a flow rate of 6 to 10 L/minute may produce an MMAD greater than 8 µm when used with a home compressor (or ventilator) providing only 10 psi. Insufficient flow can result in negligible respirable nebulizer output. As a consequence, nebulizers used for home care should be matched to the compressor on the basis of data supplied by the manufacturer so that the specific combination of equipment will efficiently nebulize the desired medications prescribed. European standards require equipment manufacturers to demonstrate that their nebulizer and compressor combination can nebulize the appropriate fill volume of drug within 10 minutes, deliver more than 50% of the drug in the nebulizer as respirable particles, and identify all medications with which the nebulizer and compressor might reliably meet these two criteria.[40] Until such time that standards are required in the United States, clinicians should ascertain that patients are prescribed only systems that have been demonstrated to meet these criteria.

Repeated use of a nebulizer will not alter the MMAD, or output, as long as it is properly cleaned (rinsed and dried between treatments). Failure to clean the nebulizer properly results in degradation of performance, from clogging the jet (Venturi) nebulizer to increasing bacterial contamination, and buildup of electrostatic charge in the device.[41] The Centers for Disease Control and Prevention (CDC) recommend cleaning and disinfecting nebulizers or rinsing with sterile water between uses, and then air drying.[42] Storage of multidose solutions at room temperature and reuse of syringes to measure the solution represent the main sources of nebulizer microbial contamination.[43] Refrigerating the solution and disposing of syringes every 24 hours help eliminate bacterial contamination.

LARGE-VOLUME NEBULIZER

The large-volume pneumatic nebulizer (LVN) has a reservoir volume greater than 100 mL and can be used to administer an aerosol solution over a prolonged period. Indications for using an LVN to administer a bland solution (i.e., sterile water or saline) include the need to humidify medical gases when the upper airway is bypassed, control stridor with a cold aerosol, and induce sputum. Because nebulizers provide a route of transmission for pathogens, pass-over humidifiers and heater wire humidifiers are preferable.

LVNs work on the same principles as SVNs, except that the residual volume is greater and the effects of evaporation, changing the concentration of medication over time, are more profound.

Caution should be exercised when using LVNs with incubators or hoods because of the noise produced. The American Academy of Pediatrics recommends a sound level less than 58 dB to prevent hearing loss in patients in incubators and hoods. Many LVNs are designed to deliver controlled concentrations of oxygen and use a Venturi system to entrain air into the stream of gas administered to the patient. Standard entrainment nebulizers may deliver a fractional concentration of delivered oxygen approaching 1.00 but cannot provide a fractional concentration of inspired oxygen (FiO_2) greater than 0.40. High-flow nebulizers are designed to deliver high flow rates of oxygen, bringing the FiO_2 up to 0.60 to 0.80. Closed dilution and gas injection nebulizers provide high-flow access to the nebulizer from two gas sources, allowing gas to mix without compromising FiO_2.

Some LVNs are used for continuous medication delivery over a prolonged period. These nebulizers are also powered by a compressed gas source, and evidence indicates that continuous nebulization is safe, effective, and less time consuming compared with intermittent nebulization in the treatment of patients with asthma.[44-46] However, use of these nebulizers for a prolonged period results in changes in drug concentration over time. Therefore emptying and refilling the LVN every 5 hours is recommended.[47]

SMALL-PARTICLE AEROSOL GENERATOR

The small-particle aerosol generator (SPAG; Valeant Pharmaceuticals International, Aliso Viejo, CA) is a jet aerosol generator used to nebulize the antiviral agent ribavirin (Figure 11-5). The SPAG incorporates a secondary drying chamber that reduces the MMAD to 1.2 μm, with a GSD of 1.4 and relatively high output. The SPAG reduces the 50 psi of line pressure medical gas to 26 psi, which supplies gas to separate flow meters controlling flow to the nebulizer and the drying chamber. As the aerosol leaves the medication reservoir, it enters the long cylindrical drying chamber, where additional flow of dry gas reduces the size of the aerosol particles through evaporation. The nebulizer flow is adjusted to maximum, approximately 7 L/minute, with a total flow from both flow meters equal to at least 15 L/minute.

Ribavirin is an expensive antiviral agent that has been used to treat high-risk infants and children with severe respiratory syncytial viral infections. The effectiveness of ribavirin is poor, with few data to support its use for such a broad population. In addition, concerns about the secondhand exposure of health care workers to ribavirin have resulted in recommendations to avoid open-air administration, use specific room filtration techniques, and use personal protective equipment for staff and visitors.[48] Ribavirin tends to precipitate into a thick powder that forms on the surfaces of tubing and tents. Recommendations for ribavirin use are now limited to treatment of patients who have severe respiratory syncytial virus infection and require mechanical ventilation.[49] Risks of using ribavirin during mechanical ventilation include delivering excessive volume and pressure, so care should be taken to place and frequently change filters in the expiratory limb of the circuit.[50] While a VMN produced larger MMAD particles (3.63 μm) than the SPAG (1.84 μm) the proportion of respirable drug mass (0.7– 4.7 μm) was similar, resulting in similar drug delivery with spontaneously breathing and mechanical ventilation models.

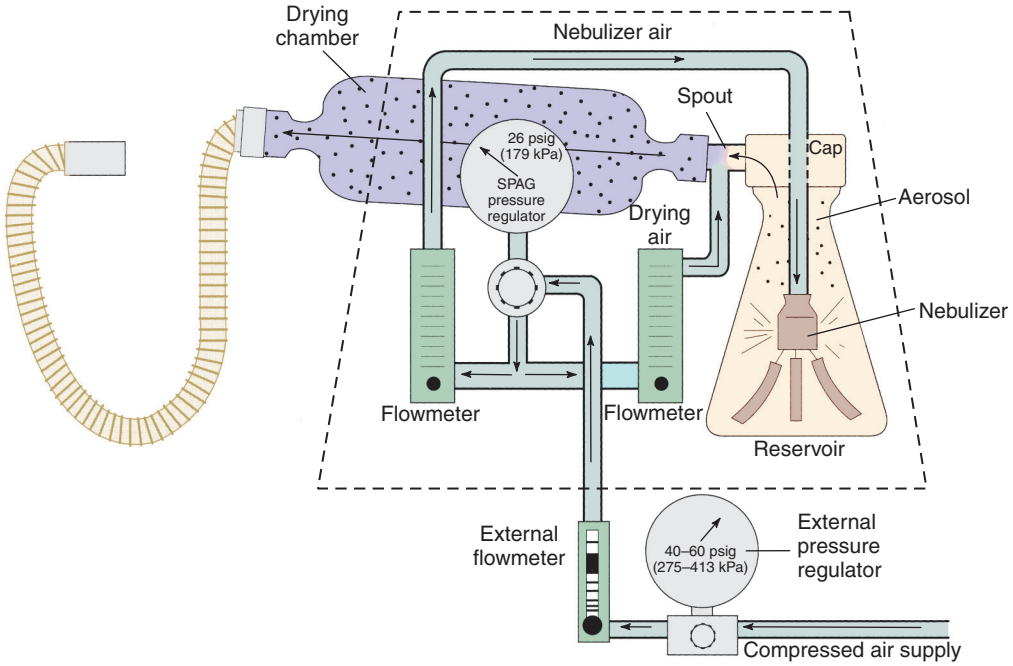


FIGURE 11-5 A small-particle aerosol generator *(SPAG)*, which may be used with a hood, tent, mask, or ventilator. *psig*, Pounds-force per square inch gauge. (Courtesy ICN Pharmaceuticals, Costa Mesa, CA.)

ULTRASONIC NEBULIZERS

The USN uses a piezoelectric crystal vibrating at a high frequency (1.3 to 1.4 mHz) to create an aerosol. The crystal transducer converts electricity to sound waves, which creates motion and standing waves in the liquid immediately above the transducer, forming a geyser of droplets (Figure 11-6). USNs are capable of a broader range of aerosol output (0.5 to 7.0 mL/minute) and higher aerosol densities than most conventional jet nebulizers. Particle size is affected by frequency, whereas output is affected by the amplitude of the signal. Particle size is inversely proportional to the frequency of vibrations. Frequency is device specific and is not user adjustable. For example, the DeVilbiss Porta-Sonic (DeVilbiss Healthcare, Somerset, PA) operates at a frequency of 2.25 MHz and produces a MMAD of 2.5 μm, and the DeVilbiss Pulmo-Sonic operates at 1.25 MHz and produces particles in the 4- to 6-μm range. Large-volume USNs, used mainly for bland aerosol therapy or sputum induction, incorporate air blowers to carry the mist to the patient. Low flow rates of gas through the nebulizer are associated with higher mist density. Unlike jet nebulizers, which cool through evaporation, USNs increase the temperature of the drug during use, which is associated with increased concentration; however, some medications may be denatured by the increased operating temperature.[51,52]

A number of small-volume USNs are available for aerosol drug delivery.[53] Unlike the larger reservoir USNs, these systems do not always use a water-filled coupling compartment; instead, medication is placed directly into the manifold on top of the transducer. The patient's inspiratory flow draws the aerosol from the nebulizer into the lungs. As the USN operates, the aerosol remains in the medication cup/ or chamber until a flow of gas draws the aerosol from the nebulizer. Thus, during exhalation, aerosol generated by the USN remains in the chamber, awaiting the next breath.

Small-volume USNs may have less residual drug volume than SVNs, reducing the need for a large quantity of diluent to ensure delivery of drugs. The contained portable power source provides convenience and mobility. These advantages of USNs may be outweighed by their high cost, however, which can be several orders of magnitude greater than that of pMDI therapy. USNs have been promoted for administration of a wide variety of formulations, ranging from bronchodilators to antiinflammatory agents and antibiotics.[54] In general, however, USNs have been shown to be less effective than other aerosol delivery devices.[55] This is particularly true with suspensions.

Several hazards, in addition to bacterial contamination, are associated with using a USN. The high-density aerosol from USNs has been associated with bronchospasm, increased airway resistance, and irritability in a substantial portion of the population. Overhydration may occur when using a USN for prolonged treatment of a neonate or small child or patients with renal insufficiency. The structure of the medication may be disrupted by acoustic power output rated greater than 50 W/cm^2.[52,56,57] Several ventilator manufacturers have provided USNs for administration of aerosols during mechanical ventilation. The advantage of the USN during ventilation is that no driving gas flow is added to the circuit; therefore there is no need to change ventilator parameters and alarm settings during aerosol drug delivery in ventilator-dependent children.[58] Disadvantages may be the weight of the USN in the ventilator circuit, a

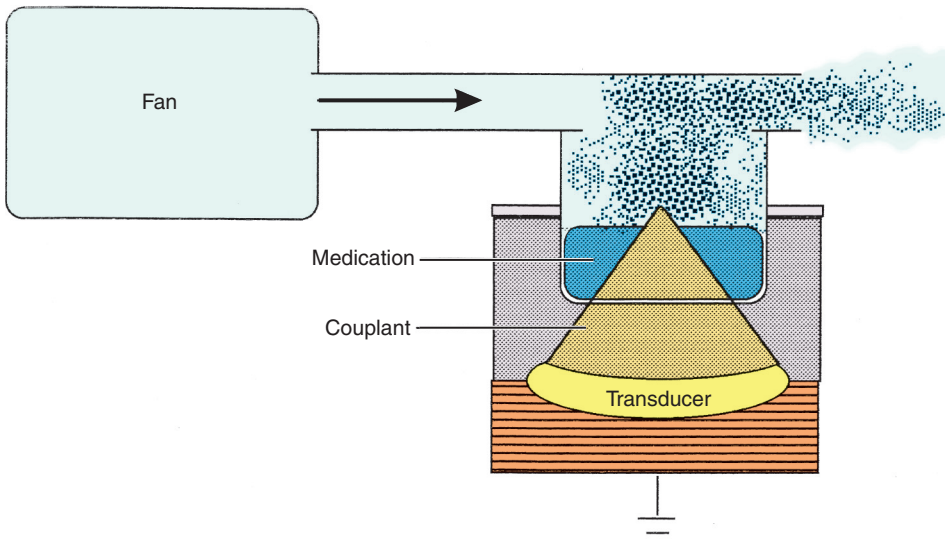


FIGURE 11-6 Aerosol is produced in an ultrasonic nebulizer by focusing sound waves, which disrupt the surface of the fluid, creating a standing wave that produces droplets. Flow from a fan pushes the aerosol out of the chamber. (From Fink J, Cohen N: Humidity and aerosols. In Eubanks DH, Bone RC, editors: *Principles and applications of cardiorespiratory care equipment*, St. Louis, 1994, Mosby.)

tendency to heat up over time, and the potential for reduced therapeutic efficacy of medications.

VIBRATING MESH NEBULIZERS

VMNs use electricity to stimulate a piezo element to vibrate a ceramic or metal disk, which in turn presses or pumps medication through multiple orifices. VMNs are of two types: Passive (static) mesh nebulizers use an ultrasonic horn to generate vibrations that produce aerosol to be inhaled by pushing medication through the static mesh, whereas active mesh nebulizers use a piezo ceramic element positioned surrounding a dome-shaped aperture plate containing 1000 to 4000 tapered apertures to vibrate the mesh at a frequency greater than 120 kHz, creating a micropumping action that makes liquid pass through the apertures and break up into fine droplets.[32] Particle size is dependent on the diameter of the orifices through which the medication passes, and VMNs can be manufactured to produce specific MMADs between 2 and 6 μm. VMNs typically operate at one-tenth the frequency and consume less than one-tenth the power of a USN, so medications are not heated or reconcentrated. This class of nebulizer can efficiently nebulize suspensions, with mean particle sizes that are smaller than the diameter of the apertures. These nebulizers are quite efficient, having residual drug volumes of medication ranging from 1 to 100 μL. Because the VMN does not add gas to the patient airway or ventilator circuit, greater aerosol concentrations can be reached than with jet nebulizers. VMNs produce the same size aerosol particles with air, oxygen, or helium. Handheld VMN nebulizers tend to be much more efficient than continuous jet nebulizers or USNs, with inhaled mass ranging from 25% to 55%. When used with mechanical ventilators, VMNs do not change volumes or flows.

Technique

The effectiveness of aerosol therapy with nebulizers can be optimized using the right technique. Box 11-2 describes the optimal technique with each type of nebulizer used in the treatment of children with pulmonary diseases.

Care and Cleaning

To limit the transmission of airborne pathogens, cleaning and disinfection of nebulizers are essential. When pneumatic nebulizers are used at the hospital, they should be changed every 24 hours or at a frequency determined by the infection control team of the hospital.[32,42,59-63] Also, pneumatic nebulizers should be cleaned, rinsed with sterile water, and air dried after each treatment.[32,59,61,62] Box 11-3 describes cleaning and disinfection procedures of nebulizers for home use. Cleaning and disinfection procedures of vibrating mesh and ultrasonic nebulizers should be done based on the manufacturer's recommendations.[32,59]

Box 11-2 Technique for Using Nebulizers

1. Assemble the tubing or cable, the nebulizer, and the mouthpiece or mask.
2. Place the prescribed amount of medication in the nebulizer's reservoir.
3. For a pneumatic nebulizer:
   - Connect the tubing to the flow meter or compressor.
   - Set the flow according to the manufacturer's recommendation (often 6-10 L/minute).
4. For a vibrating mesh or small ultrasonic nebulizer:
   - Connect a clean nebulizer or medication reservoir to the mask or mouthpiece.
   - Attach the nebulizer or reservoir to the electronic controller.
   - Attach the nebulizer to a power source or make sure the device's battery has a sufficient charge.
5. Instruct the patient to sit in an upright position, as tolerated.
6. Apply the mouthpiece or mask and encourage the patient to breathe through the mouth. If an artificial airway is used, make sure the nebulizer is positioned appropriately and does not put undue pressure on the airway.
7. Encourage relaxed tidal breathing with low inspiratory flow rates and occasional deep breaths.
8. Operate the nebulizer in an upright position, 45 degrees from vertical.
9. Run the nebulizer until the onset of sputter or until aerosol is no longer produced.
10. At the conclusion of therapy, rinse, wash, disinfect, and air dry the nebulizer or reservoir or dispose of it.
11. Do not submerge the electronic controller or compressor in water or disinfectant.
12. Store the nebulizer in a clean, dry place.

Box 11-3 Cleaning and Disinfection of Nebulizers for Home Use[235]

After each use:
- Disassemble the nebulizer and mouthpiece or mask.
- Wash them in warm, soapy water.
- Rinse with tap water.
- Shake off the excess water.
- Place the parts on a clean, absorbent towel and allow them to air dry.
- Reassemble the nebulizer and store it in a clean, dry place.

Once a day:
- After washing the nebulizer and mouthpiece or mask, place them in a disinfectant solution to soak for 1 hour.
- Rinse with sterile or distilled water.
- Shake off the excess water and allow the parts to air dry.
- Reassemble the nebulizer and store it in a clean, dry place.

Some types of homemade disinfecting solutions:
- 1 oz quaternary ammonium compound (QAC) to 1 oz distilled water; discard weekly.
- 1 part vinegar (5% acetic acid) to 3 parts hot water; discard after each use.
- 1 teaspoon household chlorine bleach to 1 gallon of water; discard after use.

PRESSURIZED METERED-DOSE INHALERS

The pMDI is the most commonly prescribed device for aerosol delivery. pMDIs are used to administer bronchodilators, anticholinergics, and antiinflammatory agents. More drug formulations are available for administration by pMDIs than by any other nebulization system. Properly used, pMDIs are at least as effective as other nebulizers for drug delivery.[64] Therefore pMDIs are often the preferred method for delivering bronchodilators to spontaneously breathing, as well as intubated, ventilated patients.

A pMDI is a pressurized canister containing a drug in the form of a micronized powder or solution that is suspended with a mixture of propellants along with a surfactant or a dispersal agent (Figure 11-7).[5] Dispersing agents are present in concentrations equal to or greater than that of the medication. In some patients these agents may be associated with coughing and wheezing.[65] The bulk of the spray, up to 80% by weight, is composed of a propellant, typically a CFC such as Freon. Adverse reactions to CFCs are extremely rare.[66-68] More recently pMDIs have been developed to use more environmentally safe propellants such as HFA-134a. As HFA pMDIs are introduced, they represent newer technologies with potentially improved performance.

The output volume of the pMDI varies from 30 to 100 μL and contains 20 μg to 5 mg of drug. Lung deposition is estimated to be between 10% and 25% in adults, with high intersubject variability largely dependent on user technique. When proper technique is used, the pMDI delivers as much or more of the dose of medication to the lung than an SVN.

The pMDI canister contains a pressurized mixture containing propellants, surfactants, preservatives, and sometimes flavoring agents, with approximately 1% of the total contents being active drug. This mixture is released from the canister through a metering valve and stem that fits into an actuator boot, designed and tested by the manufacturer to work with the specific formulation. Small changes in actuator design can change the characteristics and output of the aerosol from a pMDI.

Up to 80% of the emitted dose from a pMDI impacts in the oropharynx. Actuation of a pMDI into a valved holding chamber decreases impaction losses by reducing the velocity of the aerosol jet,[5] allowing time for evaporation of the propellants and for the particles to "age" before impacting a surface. The nominal dose of medication with a pMDI is much smaller than with a nebulizer. The quantity of albuterol exiting the actuator nozzle of a pMDI is 100 μg with each actuation, or 90 μg from the opening of the actuator boot; this is how pMDI aerosol actuations are characterized in the United States. Thus a dose of 2 to 4 actuations (200- to 400-μg nominal dose) is typically used. In ambulatory patients, 10% deposition may deliver a dose of 20 to 40 μg for an effective bronchodilator response.

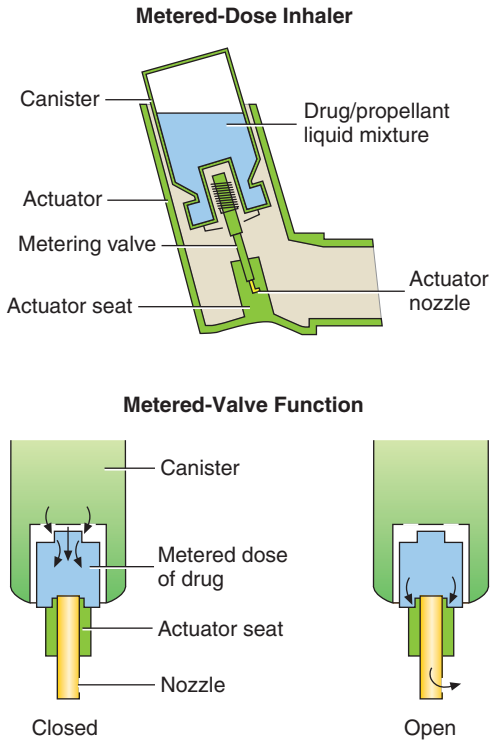


FIGURE 11-7 Cross-sectional diagrams of a pressurized metered-dose inhaler. (Modified from Rau JL Jr: *Respiratory care pharmacology,* ed 5. St. Louis, 1998, Mosby.)

Technique

Effective use of a pMDI is technique dependent. Up to two-thirds of patients who use pMDIs and health professionals who prescribe pMDIs do not perform the procedure well enough to derive benefit from the medication.[69,70] Box 11-4 outlines the recommended

Box 11-4 Optimal Self-Administration Technique for Using a Pressurized Metered-Dose Inhaler

- Warm pMDI canister to hand or body temperature.
- Shake the canister vigorously.
- Assemble the apparatus and uncap the mouthpiece.
- Ensure that no loose objects are in the device that could be aspirated or could obstruct outflow.
- Open the mouth wide.
- Keep the tongue from obstructing the mouthpiece.
- Hold the pMDI vertically with the outlet aimed at the mouth.
- Place the canister outlet between the lips, or position the pMDI 4 cm (two fingers) away from the mouth.*
- Breathe out normally.
- Begin to breathe in slowly (<0.5 L/sec).
- Squeeze and actuate ("fire") the pMDI.
- Continue to inhale to total lung capacity.
- Hold breath for 4–10 seconds.
- Wait 30 seconds between inhalations (actuations).
- Disassemble the apparatus, and recap the mouthpiece.

pMDI, Pressurized metered-dose inhaler.
*Open-mouth technique is not recommended with ipratropium bromide.

steps for self-administering a bronchodilator with a pMDI.[71,72] Good patient instruction can take 10 to 30 minutes and should include demonstration, return demonstration, practice, and confirmation of patient performance (demonstration placebo units should be available for this purpose). Repeated instruction with every visit improves performance.[71]

All pMDIs require priming, firing one to four actuations, before first use, and after the device has not been used for a prolonged period (1 to 4 days). The HFA pMDIs require less frequent priming than CFC devices (check the label for each specific device).

Problems with home use of pMDI devices include not only poor technique but also poor storage. The pMDI should always be stored with the cap on, both to prevent foreign objects from entering the boot and to reduce humidity and microbial contamination.[71]

Each type of pMDI contains a specific number of actuations (between 60 and 400 actuations). After those doses have been administered the pMDI will continue to actuate, with or without medication emitted (tailing-off effect), placing the patient at risk of not receiving prescribed medication. Pressurized MDIs should always be discarded when empty to avoid administering propellant without medication. The suggestion that pMDIs can be tested for drug remaining by floating the canister in water has proven not to be accurate and to compromise performance of the pMDI.

It is more accurate for the patient or parent to note when the medication was started, the number of doses to be taken each day, and the number of doses in the canister, and from this information to calculate a discard date. For example, if 200 actuations are in a canister (information always indicated on the canister label) and four "puffs" are taken per day, the canister should be discarded 50 days, or 7 weeks, after the start date. This discard date should be written on the canister label on the day the new canister is started. A more user-friendly alternative is to attach a dose counter to the pMDI. In the near future, the U.S. Food and Drug Administration will require new pMDIs to be manufactured with dose counters. Because pMDIs deposit up to 80% of their emitted dose in the oropharynx and hypopharynx, patients should "rinse and spit" to remove excess drug from the mouth and back of the throat.

Infants, young children up to age 3 years, and patients in acute distress may not be able to use a pMDI effectively. A "cold Freon effect" can occur when the aerosol plume reaches the back of the mouth and the patient stops inhaling. These problems can be corrected by using the proper pMDI accessory device (see the next section).

Accessory Devices

Various pMDI accessory devices have been developed to overcome the primary limitations of pMDI administration: hand–breath coordination problems, high oropharyngeal deposition, and difficulty in tracking doses. Accessory devices include flow-triggered pMDIs, **spacers,** valved holding chambers, and dose counters.

Flow-triggered device. The Maxair Autohaler (Graceway Pharmaceuticals, Bristol, TN) and Easyhaler (Orion Pharma, Espoo, Finland) are flow-triggered pMDIs designed to reduce the need for hand–breath coordination by firing in response to the patient's inspiratory effort.[73] To use the Autohaler, the patient cocks a lever on the top of the unit that spring-loads the canister against a vane mechanism. When the patient's inspiratory flow exceeds 30 L/minute, the vane moves, allowing the canister to be pressed into the actuator, firing the pMDI. This device is available only with the β-agonist pirbuterol in the United States, but other formulations are in development. The Easyhaler has been introduced in Europe with several medications and may soon be available in North America. The flow required to actuate these devices may be too great for some children to generate, especially during acute exacerbations of disease.

Spacers and holding chambers. When properly designed, spacers and valved holding chambers do the following:

- Reduce oropharyngeal deposition of drug
- Relieve the bad taste of some medications by reducing oral deposition
- Eliminate the cold Freon effect
- Decrease aerosol MMAD
- Increase respirable particle mass
- Improve lower respiratory tract deposition
- Significantly improve therapeutic effects[55,72,74]

Spacers should be differentiated from valved holding chambers (VHCs). A spacer device is a simple open-ended tube, chamber, or bag that has sufficiently large volume to provide space for the pMDI plume to expand by allowing the propellant to evaporate. To perform this function, a spacer device must have an internal volume greater than 100 mL and must provide a distance of 10 to 13 cm between the pMDI nozzle and the first wall or baffle. Smaller, inefficient spacers can reduce respiratory dose by 60% and offer no protection against poor coordination between actuation and breathing pattern. Spacers with internal volumes greater than 100 mL generally provide some protection against early firing of the pMDI, although exhaling immediately after the actuation clears most of the aerosol from the device, wasting the dose.

The valved holding chamber, usually 140 to 750 mL in volume, allows the plume from the pMDI to expand. It incorporates a one-way valve that permits the aerosol to be drawn from the chamber during inhalation only, diverting the exhaled gas to the atmosphere and not disturbing the remaining aerosol suspended in the chamber (Figure 11-8). Patients with small tidal

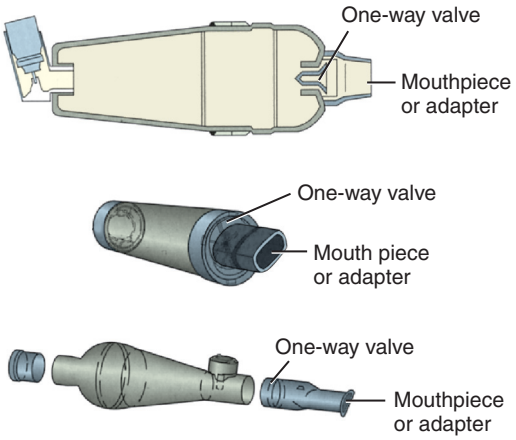


FIGURE 11-8 Metered-dose inhaler holding chambers are spacers with one-way valves that allow the chamber to be emptied only when the patient inhales, by preventing the exhaled gas from reentering the chamber. (From Fink J, Cohen N: Humidity and aerosols. In Eubanks DH, Bone RC, editors: *Principles and applications of cardiorespiratory care equipment.* St. Louis, 1994, Mosby.)

volumes may empty the aerosol from the chamber with five to six breaths, except when there is a large dead space. A valved holding chamber can also incorporate a mask for use by an infant or child. These devices allow effective pMDI administration in a patient who is unable to use a mouthpiece because of size, age, coordination, or mental status.[75] With infants these masks should have minimal dead space, should be comfortable on the child's face, and should have a valved chamber that will open and close with the low inspiratory flow and volume generated by the patient. Box 11-5 describes the correct technique for using a pMDI with a holding chamber.

Valved holding chambers, which reduce the need to coordinate breathing with actuation, should be used with infants, small children, and any child taking steroids. In addition, the chambers reduce the pharyngeal dose of aerosol from the pMDI 10- to 15-fold over administration without a holding chamber. This decreases the total body dose from swallowed medications, which is an important consideration with steroid administration.[74,76,77] The high percentage of oropharyngeal drug deposition with steroid pMDIs can increase the risk of oral yeast infections (thrush). Rinsing the mouth after steroid use can reduce this problem, but most pMDI steroid aerosol impaction occurs deeper in the pharynx, which is not easily rinsed. For this reason, steroid MDIs should always be used in combination with a valved holding chamber.

Box 11-5 Optimal Technique for Using a Pressurized Metered-Dose Inhaler With a Valved Holding Chamber

- Warm the pMDI to hand or body temperature.
- Shake the canister vigorously, holding it vertically.
- Assemble the apparatus.
- Ensure that no loose objects are in the device that could be aspirated or could obstruct outflow.
- Place the holding chamber in the mouth (or place the mask completely over the nose and mouth), encouraging the patient to breathe through the mouth.
- Have the patient breathe normally, and actuate at the beginning of inspiration.
- For small children and infants, have them continue to breathe through the device for five or six breaths.
- For patients who can cooperate and clear the chamber with one breath, encourage larger breaths with breath holding.
- Allow 30 seconds between actuations.

pMDI, Pressurized metered-dose inhaler.

Wheezing Infants

Valved holding chambers make pMDIs as reliable as SVNs for aerosol administration. In one study, 34 infants between 1 and 24 months of age and with acute asthma received two doses of terbutaline, 20 minutes apart, as either 2 mg/dose in 2.8 mL of 0.9% saline by nebulizer or as 0.5 mg/dose (5 puffs) by pMDI with a valved holding chamber.[78] No difference was found in the rate of improvement or clinical score, and both devices were reported equally effective. Similarly, 60 children 6 years of age or younger who had an acute asthma exacerbation were randomized to receive albuterol through a nebulizer or pMDI with valved holding chamber for three treatments over 1 hour.[79] All patients showed improvement over baseline, with no difference between treatment groups.

In another study, 84 children were enrolled in the emergency department to receive inhaled medication with or without a valved holding chamber to determine whether a single brief demonstration of the proper use of a valved holding chamber would result in improved outcomes.[80] The valved holding chamber group reported significantly faster resolution of wheezing, fewer days of cough, and fewer missed days of school.

Evidence-based research does not support the belief that an SVN is better than a pMDI if the patient is not able to inhale with optimal technique. In fact, if unable to perform an optimal maneuver with a pMDI, the patient cannot perform an optimal maneuver with an SVN. Although optimal technique is always preferred, it is often difficult to attain with an infant, small child, or severely dyspneic patient. For such patients, an alternative may be to increase the pMDI or nebulizer dose (see later discussion).

Care and Cleaning

Particles containing drug settle and deposit within these devices, causing a whitish buildup on the inner chamber walls. This residual drug poses no risk to the patient but should be rinsed out periodically. After washing a plastic chamber or spacer with tap water, it is less effective for the next 10 to 15 puffs, until the static charge in the chamber (which attracts small

particles) is once again reduced. Use of regular dish soap to wash the chamber reduces or eliminates this static charge. Metal and nonelectrostatic plastic spacers should be cleaned as recommended by their manufacturers.

Accessory devices either use the manufacturer-designed boot that comes with the pMDI or incorporate a "universal canister adapter" to fire the pMDI canister. Different formulations of pMDI drugs operate at different pressures, and devices have different orifice sizes in the boot specifically designed for use exclusively with the specific pMDI. Output characteristics of pMDIs will change when using an adapter with a different-size orifice; therefore spacers or holding chambers with universal canister adapters should be avoided. Devices that include the manufacturer's boot with the pMDI should be used when available.

DRY POWDER INHALERS

DPIs create aerosols by drawing air through a dose of dry powder medication. The powder contains micronized drug particles (MMAD less than 5 μm) with larger lactose or glucose particles (greater than 30 to 100 μm in diameter), or it contains micronized drug particles bound into loose aggregates.[81] Micronized particles adhere strongly to each other and to most surfaces. Addition of the larger particles of the carrier decreases cohesive forces in the micronized drug powder so that separation into individual respirable particles (disaggregation) occurs more readily. Thus the carrier particles aid the flow of the drug powder from the device. These carriers also act as "fillers" by adding bulk to the powder when the unit dose of a drug is small. Usually the drug particles are loosely bound to the carrier,[82] and they are stripped from the carrier by the energy provided by the patient's inhalation (Figure 11-9). The release of respirable particles of the drug requires inspiration at relatively high flow (30 to 120 L/minute).[83,84] A high inspiratory flow results in pharyngeal impaction of the larger carrier particles that comprise the bulk of the aerosol and, as with pMDIs, results in up to 80% of the drug dose being deposited in the oropharynx and hypopharynx. Impaction of lactose carrier particles gives the patient the sensation of having inhaled a dose. Like with pMDIs, patients should rinse and spit after inhalation of steroid preparations from a DPI.

The internal geometry of the DPI device influences the resistance offered to inspiration and the inspiratory flow required for disaggregating and aerosolizing the medication. Devices with higher resistance require a higher inspiratory flow to produce a dose. Inhalation through high-resistance DPIs may improve drug delivery to the lower respiratory tract compared with pMDIs as long as the patient can reliably generate the required flow rate.[66,85] High-resistance devices have not been shown to improve either deposition or bronchodilation compared with low-resistance DPIs. DPIs with multiple components require correct assembly of the apparatus and priming of the device to ensure aerosolization of the dry powder. Periodic brushing is needed to remove any residual powder accumulated within some DPIs.

DPIs produce aerosols in which most of the drug particles are in the respirable range, with distribution of particle sizes (GSD) differing significantly among various DPIs.[67] High ambient humidity produces clumping of the dry powder, creating larger particles that are not as effectively aerosolized.[68] Air with a high moisture content is less efficient at disaggregating particles of dry powder than dry air, such that high ambient humidity increases the size of drug particles in the aerosol and may reduce drug delivery to the lung. Newer DPI devices contain individual doses more protected from humidity. Humidity can accumulate once the device is opened, or if the DPI is stored with the cap off, or by condensation when the device is brought from a very cold environment into a warmer area.

Because the energy from the patient's inspiratory flow disperses the drug powder, the magnitude and duration of the patient's inspiratory effort influence aerosol generation from a DPI. Failure to perform inhalation at a sufficiently fast inspiratory flow reduces the dose of the drug emitted from DPIs and increases the distribution of particle sizes within the aerosol with a variety of devices.[86] For example,

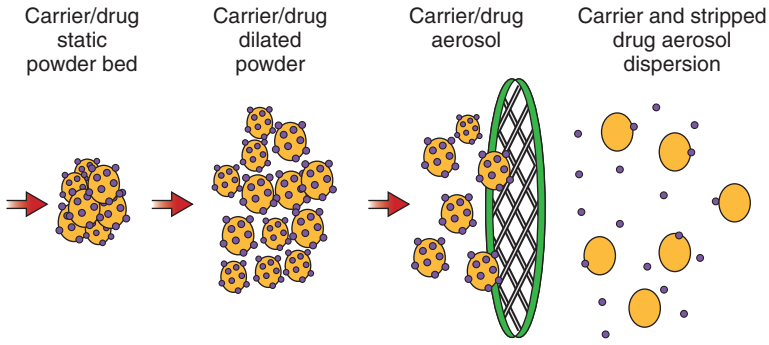


FIGURE 11-9 As patient inhales through a dry powder inhaler, inspiratory flow disaggregates particles from the powder bed or capsule and is drawn through a screen that strips the small drug particles from the larger carrier particles, creating an aerosol dispersion. (Modified from Dhand R, Fink J: Dry powder inhalers. *Respir Care* 44:940–951, 1999.)

the Advair Diskus (GlaxoSmithKline, London, UK) delivers approximately 90% of the labeled dose at an inspiratory flow ranging from 30 to 90 L/minute, whereas the dose delivered by the high-resistance Pulmicort Turbuhaler (AstraZeneca, Lund, Sweden) is significantly lower at an inspiratory flow of 30 L/minute compared with the dose delivered at 90 L/minute. The variability between doses at different inspiratory flows is higher with the Turbuhaler.[87,88] Figure 11-10 shows the effect of two inspiratory flows (30 and 55 L/minute) when using a pMDI, a breath-actuated MDI (Autohaler), a Rotahaler (previously GlaxoSmithKline) (DPI 1), a Turbuhaler (DPI 2), and a Diskhaler (GlaxoSmithKline) (DPI 3).[89] The peak inspiratory flow rate of children is limited and associated with age, making it unlikely that a child younger than 6 years could reliably empty a DPI requiring greater than 50 L/minute (Figure 11-11).[89]

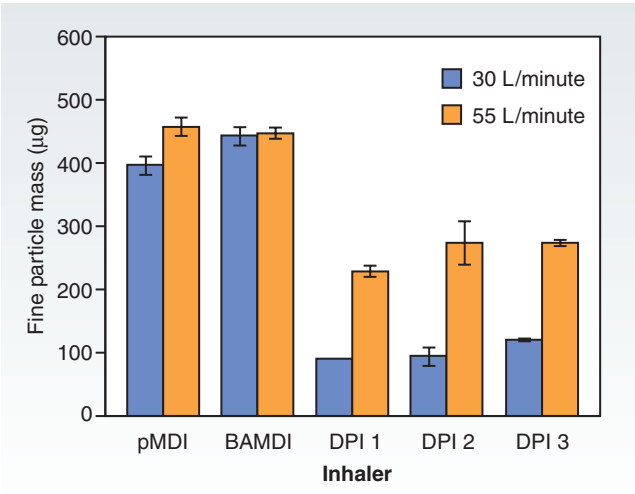


FIGURE 11-10 Fine particle mass delivered from a 100-μg target dose (± the standard deviation) as a function of flow rate. *BAMDI*, Breath-actuated MDI (Autohaler); *DPI 1*, Rotahaler; *DPI 2*, Turbuhaler; *DPI 3*, Diskhaler; *pMDI*, Pressurized metered-dose inhaler.. (From Smith KJ, Chan H-K, Brown KF: Influence of flow rate on particle size distributions from pressurized and breath actuated inhalers. *J Aerosol Med* 11:231–245, 1998.)

Technique

All commercially available DPIs are passive, requiring energy from the patient to disaggregate the powder from its carrier and container to form aerosol, and therefore are breath actuated, reducing the problem of coordinating inspiration with actuation. The technique of using DPIs differs in important respects from the technique used to inhale drugs from a pMDI (Table 11-1). Although DPIs are easier to use than pMDIs, up to 25% of patients may use DPIs improperly.[89] DPIs are critically dependent on inspiratory airflow to generate the aerosol. The lower the inspiratory flow, the less drug is emitted by the device. Children younger than 6 years may not be able to generate sufficient inspiratory flow for effective dosing with units requiring more than 60 L/minute. Exhalation into a DPI may blow the powder from the container and into the device, away from the patient, reducing drug delivery. Moreover, the humidity in the exhaled air reduces subsequent aerosol generation from the DPI. Therefore patients must be instructed not to exhale into a DPI. Thus DPIs should be used with caution, if at all, in a very young or ill child, weak patients, elderly persons, and those with altered mental status. Patients may need repeated instruction before they can master the technique of using DPIs, and periodic assessment is necessary to ensure that patients continue

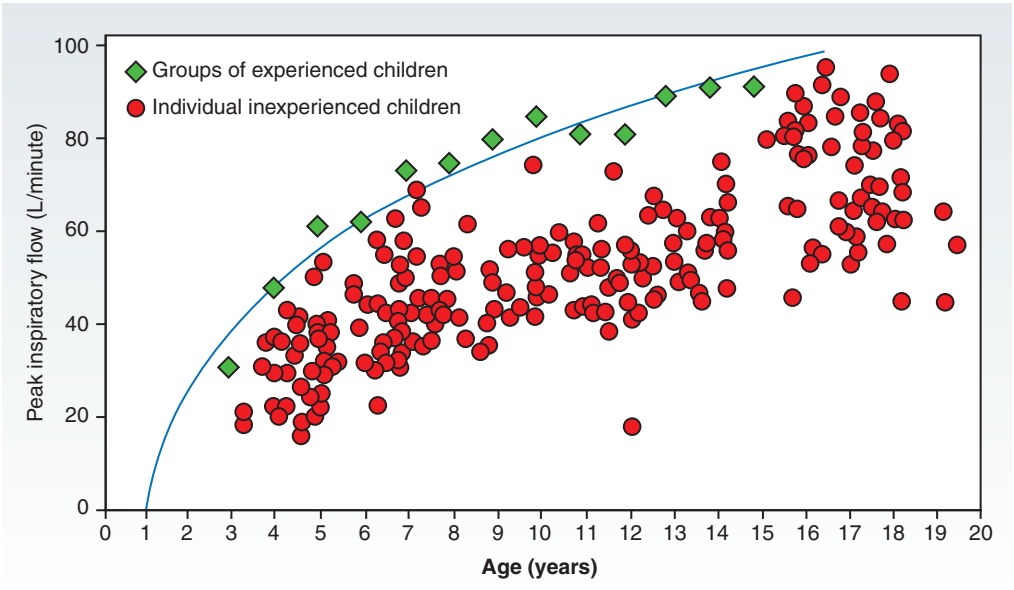


FIGURE 11-11 Peak inspiratory flows in individual inexperienced children and in groups of experienced children. (From Pederson S: Delivery options for the inhaled therapy in children over the age of 6 years. *J Aerosol Med* 10:41–44, 1997.)

Table 11-1 Differences in Inhalation Technique Between Pressurized Metered-Dose Inhaler With Holding Chamber and Dry Powder Inhaler

STEP	pMDI/HC	DPI
Shaking the inhaler	Yes	No
Actuation with inspiration	Optional	Essential
Inspiration	Slow, deep; improves deposition	Fast, prolonged; required for deposition
Interval between doses	30-60 sec	20-30 sec
Exhalation into device	Small decrease in dose	Large decrease in dose

DPI, Dry powder inhaler; *pMDI/HC*, pressurized metered-dose inhaler with holding chamber.

Box 11-6 Technique for Using a Dry Powder Inhaler

Priming instructions: Before using a new dry powder inhaler (DPI) for the first time, check the manufacturer's instructions and prime the DPI.

Steps for using DPIs:

- Assemble the apparatus.
- Load the dose based on the manufacturer's instruction.
- Exhale slowly to functional residual capacity.
- Exhale away from the mouthpiece.
- Seal lips around the mouthpiece.
- Inhale deeply and forcefully (>60 L/minute). A breath-hold should be encouraged but is not essential.
- If more than one dose is required, repeat the previous steps.
- Monitor adverse effects.
- Replace the cover on the inhaler.
- Keep the inhaler clean and dry at all times (following the manufacturer's instructions).
- Keep the device in a dry place at a controlled room temperature (i.e., 20 to 25°C [68 to 77°F]). Do not submerge in water.

to use an optimal technique.[89-91] Clinicians must also learn the correct technique of using DPIs to train their patients in the proper use of these devices. Box 11-6 outlines the basic steps in the use and care of DPIs.

Care and Cleaning

DPIs should be cleaned in accordance with the product label. Patients should be trained not to submerge DPIs in water, which will dramatically reduce available dose.[32]

DEVICE SELECTION AND COMPLIANCE

Whenever possible, patients should use only one type of aerosol-generating device for inhalation therapy. Each type requires a different technique, and repeated instruction is necessary to ensure that the patient uses a device appropriately. The use of different devices for inhalation can be confusing for patients and may decrease their compliance with therapy. This has been referred to as "device dementia."[71]

At present, DPIs may be considered alternatives to pMDIs for patients who can generate inspiratory flow rates greater than 30 to 60 L/minute but who are unable to use pMDIs effectively. DPIs are recommended for therapy for patients with stable asthma and chronic obstructive pulmonary disease but not for patients with acute bronchoconstriction or children younger than 6 years. Therefore one drawback of DPIs is that they do not substitute for pMDIs in all clinical situations. Moreover, dose adjustment may be needed when the same drug is administered by a DPI instead of a pMDI. Table 11-2 compares DPIs, pMDIs, and nebulizers. Determining the appropriate dose of inhaled corticosteroids may be particularly vexing, because it is difficult to assess bioequivalence with these agents. Further research is needed to determine equivalent doses when both the drug and the device used for inhalation therapy are altered.[92,93]

Table 11-2 Comparison of Pressurized Metered-Dose Inhaler With Holding Chamber, Dry Powder Inhaler, and Nebulizer as Aerosol Delivery Device

FACTOR	pMDI/HC	DPI	NEBULIZER
Performance			
Most aerosol particles <5 μm in size	+	+	±
High pulmonary deposition	+	±	±
Low mouth deposition	+	±	–
Reliability of dose	+	±	±
Influenced by humidity	–	+	–
Physical and chemical stability	+	+	+
Breath actuated	–	+	–
Risk of contamination	–	–	+
Convenience			
Lightweight, compact	+	+	–
Multiple doses	+	+	–
Dose indicator	–	+	–
Inexpensive	+	+	–
Easy and quick operation	±	±	–
Suitable for all ages	+	–	+
Suitable for multiple clinical situations	+	±	+

DPI, Dry powder inhaler; *pMDI/HC*, pressurized metered-dose inhaler with holding chamber.

SELECTING AN AEROSOL DEVICE FOR INFANTS AND TODDLERS (BIRTH TO 4 YEARS)

Children younger than 4 years of age may not be able to master specific breathing techniques and be unable to reliably use BANs, breath-actuated pMDIs, or DPIs, and such devices may not be appropriate for this patient population; therefore administering aerosolized medications to infants should be done via a nebulizer or pMDI with VHC.[32,94,95]

SELECTING AN AEROSOL DEVICE FOR PRESCHOOL CHILDREN (4-5 YEARS)

Nebulizers and pMDIs with VHC are suggested for use with preschool children.[32,94,96,97] Although the efficiency of both devices are similar, the shorter treatment time and portability of the pMDI with VHC makes it more desirable than the nebulizer. Once children reach age 5 years, their physical and cognitive abilities should be assessed to determine whether they can generate the sustained inspiratory flow rates required for specific devices. Children who can successfully master the more complex breathing techniques may be given breath-actuated pMDIs or DPIs.

SELECTING AN AEROSOL DEVICE FOR YOUNG CHILDREN (6-12 YEARS)

Young children can control their breathing. Their hand–breath coordination is usually good, and they can master complex inhalation techniques. Therefore several aerosol devices, such as pMDI with or without VHC, DPI, and breath-actuated pMDI, can be used for this patient population.[94] The selection of an aerosol device should be based on patients' physical and cognitive abilities as well as their preference and acceptance.

INTERFACE SELECTION FOR AEROSOL DRUG DELIVERY TO INFANTS AND CHILDREN

Many interfaces are available for aerosol drug delivery to infants and children. Although it is important to choose the right interface for children, the emphasis is usually on the right drug–device combination. Therefore selecting the right interface for infants and children is commonly disregarded by clinicians.

Blow-by: Infants and small children younger than 4 years may not be able to use a mouthpiece, requiring a mask for administration.[98] Because some children may cry when a mask is applied, some clinicians have recommended the use of blow-by, that is, directing a stream of aerosol from a nebulizer toward the mouth and nose of an infant, often from up to 6 inches away. According to a recent *in vitro* study conducted by Mansour and Smaldone, aerosol delivery via blow-by can be a good alternative for uncooperative children if a breath-enhanced nebulizer is used for aerosol therapy as opposed to a standard jet nebulizer.[99] However, several studies indicated that aerosol delivery to children reduces as the distance between mask and face increases.[99-101]

Hood: If a face mask is not tolerated by the infant, use of a hood provides an option for administering inhaled medications via a nebulizer because it is better tolerated by some infants and preferred by parents. Some studies showed that the hood and face mask have comparable efficacy in infants and that the hood leads to a better therapeutic index with minimal deposition at the infant's eyes.[102-105] Another alternative to a face mask is the high-flow nasal cannula (HFNC), with which aerosol delivery at a lower flow appears to be as good as or better than use of a tight-fitting mask. Although its efficiency has been reported by a few *in vitro* studies,[106,107] clinical studies are still needed in this area of research.

Mouthpiece: Previous research reported that aerosol delivery via a mouthpiece may deliver twice as much drug compared with face mask in spontaneously breathing older children.[108,109] However, it is well known that children younger than 3 years cannot keep the mouthpiece in their mouth constantly with an adequate seal during aerosol drug delivery.[96-98,110,111] Although the mouthpiece is an option for children, use of a face mask, hood, or HFNC should be considered for aerosol therapy if the child cannot comfortably use a mouthpiece.[94]

Face mask: Selecting a face mask with optimal features is important. A lightweight, flexible face mask with anatomic contours and small dead space is considered optimal for aerosol drug delivery to children.[112,113] Face mask designs are divided into two categories: (1) front-loaded face masks and (2) bottom-loaded face masks. Although front-loaded face masks direct aerosolized medication toward the oronasal area of the patient and have small entrainment ports on the side of the mask, bottom-loaded masks direct aerosol toward the upper part of the mask. Delivery efficiency of front-loaded face masks such as the Bubble Fish II Mask (Pari, Midlothian, Virginia) is greater than a bottom-loaded face mask.[100,114-116] In addition, front-loaded masks have lower deposition in the eye and face than bottom-loaded face masks.[114,116,117] The main problem with the use of face masks is crying and intolerance of the face mask by children during aerosol therapy.

Crying greatly reduces lung delivery of aerosol.[118-120] Studies demonstrate that inhaled drugs should be given to infants when they are settled and breathing quietly; the administration of inhaled drugs to patients during sleep, when infants have quiet breathing, results in greater inhaled dose.[121] However, it may be difficult to deliver aerosolized drugs to infants without waking

them. An *in vivo* study showed that 69% of children woke up during aerosol therapy, and 75% of them were distressed.[122] Multiple *in vitro* studies reported the importance of face mask seal during aerosol therapy[100,101] with both nebulizers and pMDIs with VHC. Several studies reported the importance of face mask seal[116,120,123-128] and showed differences in the efficiency to achieve a good face mask seal for the different face mask designs.[116,124,126-128] Therefore it is important to teach infants to not play with their mask and learn to tolerate it being placed on the face. This takes some time, but with a little patience from the care provider, it can greatly enhance the efficacy of the aerosol therapy and the trauma to both patient and parent. Comforting babies and providing other effective forms of distraction will also help ptimize aerosol therapy in infants.

Pacifier mask: The pacifier mask is a newer innovative interface that is designed to increase lung dose in children and to eliminate discomfort and cry with a pacifier that is integrated into the face mask (Figure 11-12). The infant sucks the pacifier during aerosol therapy, which keeps the SootherMask (InspiRx, Somerset, NJ) sealed to the face during aerosol drug delivery, while inhaling aerosols through the nose. Sucking helps the infant calm down and improves tolerance and compliance to aerosol therapy.[110,129-131] Also, a scintigraphic study of aerosol deposition in infants showed that lung dose with the SootherMask was similar to that with the standard bottom-loaded face mask without pacifier.[131]

HFNC: Because infants and young children are nose breathers, nasal delivery of aerosols to the lung is more effective than oral delivery in this patient population.[132,133] Previous *in vitro* studies showed that aerosolized medications could be efficiently delivered to infants and pediatrics through HFNC with a mesh nebulizer.[94,107,134] However, it is also important to note that the amount of lung deposition differs based on the cannula size, flow rates and models used with HFNC.[135] A nonhuman primate model of radiotagged aerosol via HFNC confirmed levels of deposition previously reported *in vitro* by Sunbul.[136] Skin irritation and condensate accumulating in the cannula may be an issue in terms of the comfort, safety, and efficacy of aerosol drug delivery with HFNC in infants and children.

Nasal mask: The nasal mask is another interface that is used for aerosol therapy in infants and children. Delivery efficiency of the nasal mask is not well studied. There is only one *in vitro* study in the literature that reported lower aerosol deposition than the face mask in simulated spontaneously breathing infants and young children using a jet nebulizer.[115]

AEROSOL ADMINISTRATION IN NONINTUBATED INFANTS AND CHILDREN

Limited studies are available that directly quantify deposition of aerosols in nonintubated infants and children.

Wildhaber and colleagues[9] studied children, 2 to 9 years of age, with stable asthma inhaling radiolabeled albuterol (salbutamol) from a nebulizer and a pMDI through a nonstatic holding chamber. Mean (absolute dose) total lung deposition expressed as a percentage of the nebulized dose was 5.4% (108 μg) in younger children (younger than 4 years) and 11.1% (222 μg) in older children (older than 4 years). Mean (absolute dose) total lung deposition expressed as a percentage of the metered dose was 5.4% (21.6 μg) in

FIGURE 11-12 The pacifier mask (SootherMask, InspiRx, Somerset, NJ). (Reproduced with permission from InspiRx.)

younger children and 9.6% (38.4 μg) in older children. The authors reported equivalent percentages of total lung deposition of radiolabeled salbutamol aerosolized by either a nebulizer or a pMDI with holding chamber within each age group. However, the delivery rate per minute and the total dose of salbutamol deposited were significantly higher for the nebulizer.

Erzinger[120] studied eight asymptomatic children between 18 months and 3 years of age with a history of recurrent wheeze for the administration of radiolabeled salbutamol with either a vent-assisted nebulizer or a pMDI attached to a holding chamber. After the measurement of aerosol deposition with a gamma camera, they reported that lung deposition with a face mask leak was 0.2% and 0.3% with pMDI and nebulizer, respectively. Screaming children without a face mask leak had 0.6% lung deposition with pMDI and 1.4% with a nebulizer. Lung deposition in children who were quietly breathing and without a face mask leak ranged from 4.8% to 8.2%.

EMERGENCY BRONCHODILATOR RESUSCITATION

When a patient comes to the emergency department with an acute exacerbation of asthma, the onset of the exacerbation is often 12 to 36 hours earlier. These children have often taken rescue medications without obtaining sufficient relief. They, and their parents, are anxious, uncomfortable, and exhausted. The goal is to provide relief as soon as possible and to decrease the work of breathing until antiinflammatory medications take effect. Administration of selective β2-agonists and anticholinergics such as ipratropium (Atrovent) by aerosol is usually the first therapy given. Albuterol (salbutamol outside the United States) reaches 85% of bronchodilator effect in the first 5 minutes after administration. The national asthma guidelines recommend albuterol administration with either 2.5 or 5.0 mg by jet nebulizer or 4 to 8 puffs of albuterol by pMDI with a valved holding chamber at 20-minute intervals for the first hour.[137,138]

Inhaled short-acting bronchodilators are a mainstay of asthma treatment in the emergency department. A current debate is regarding which aerosol device should be used for the delivery of inhaled bronchodilators to children in the emergency department. A few studies showed that the efficacy of pMDI and VHC is similar to the nebulizer for the treatment of acute asthma exacerbation in the emergency department.[139-148] A recent study also showed that use of a pMDI and VHC in the emergency room does not increase hospital admission and decreases not only length of inpatient stay but also cost per patient for children admitted to the hospital.[149] Despite the evidence, nebulizers are still commonly used for the treatment of acute exacerbation in the emergency department. The reasons for resistance to using pMDI and VHC in the emergency department include increased equipment costs, myths about the superiority of nebulization, concerns about its safety, increased workload, perceived resistance from patients and parents, interprofessional conflict, and lack of consensus about the benefits of pMDI with spacers among staff.[150-152] Overcoming all these barriers can be accomplished through the education programs tailored to physicians and health care professionals who will implement the change from nebulizers to pMDIs with spacers in the emergency department.[153]

INTERMITTENT VERSUS CONTINUOUS THERAPY

If the patient does not experience relief of symptoms with standard dosing, frequency of administration is often increased to hourly, or even every 15 to 20 minutes, in the emergency department. Treatments can be continued at this frequency until symptoms are relieved. The standard SVN treatment takes 10 to 15 minutes and requires that a clinician be at the bedside constantly. An alternative to intermittent treatments is continuous nebulization delivered at a controlled rate of medication over an extended period, with the patient monitored for rapid identification of increases in heart rate. Doses of albuterol between 2.5 and 15 mg/hour have been shown to be effective in treating acute exacerbation of asthma in adults and children.[154-156]

One strategy for continuous nebulization is to use an intravenous infusion pump to drip a premixed bronchodilator solution through a port into the reservoir of a standard SVN (operating at 6 to 8 L/minute) or specialty nebulizer such as the Mini-HEART nebulizer (Westmed) (operating at 2 L/minute). More recently a VMN, the Aeroneb Solo (Aerogen, Dangan, Galway, Ireland), with a port for drip feed and continuous operation, has been introduced. Another solution is to use an LVN that produces an MMAD in the respirable range and that is known to deliver a consistent output of medication at a specific flow. Albuterol solution and normal saline are mixed in the reservoir, and the LVN is operated at a specific flow, identified by the manufacturer, to deliver the desired dose. Several LVNs are now commercially available for continuous administration of bronchodilators. The HEART high-output nebulizer (Westmed) has an output of approximately 30 mL/hour at a flow of 10 L/minute for up to 6 or 8 hours. The HOPE nebulizer (B&B Medical Technologies, Loomis, CA) is a closed dilution nebulizer that allows drug output and oxygen or heliox administration. The medication can be delivered through an aerosol mouthpiece or mask or in-line with a ventilator circuit. For patients with moderately severe asthma, continuous therapy and intermittent therapy have similar effects with either low-dose or high-dose β-agonists. For patients with a severe asthma exacerbation, or forced

expiratory volume in 1 second (FEV_1) less than 40% of predicted values, continuous therapy may work more rapidly.[156]

Although β2-agonists are the first-line agents for acute exacerbation of asthma, data from both adults and children suggest that ipratropium bromide is synergistic with β-agonists for the therapy of acute asthma.[157-162] Combination bronchodilator therapy using albuterol and ipratropium in patients with severe asthma significantly reduced the percentage of patients hospitalized.[161] It is important to remember that poor relief of acute asthma with bronchodilators may signify a nonasthmatic cause of wheezing, such as foreign body aspiration or tracheitis. Infants with bronchiolitis respond poorly to bronchodilator medications, which are therefore not recommended for this condition.

UNDILUTED BRONCHODILATOR

A faster method of administering albuterol is achieved by placing undiluted medication into the nebulizer. Diluent is typically added to medication in the nebulizer to reduce the fraction of the dose that is trapped as residual volume. With undiluted administration, enough medication must be added to the nebulizer to exceed the residual volume of the nebulizer and to allow 1.0 to 2.0 mL of albuterol solution (5 to 10 mg) to be nebulized. Patients should be monitored closely during administration, and the treatment should be terminated if the patient has significant reduction of symptoms and begins to develop tremor or other side effects. Undiluted albuterol administered with specialty nebulizers achieves similar improvements in clinical status in less time. The osmolarity of undiluted medication may be a problem for some patients, especially children younger than 2 years old.

AEROSOL DRUG DELIVERY TO CHILDREN RECEIVING NONINVASIVE VENTILATION

Research on aerosol therapy during pediatric noninvasive ventilation (NIV) is limited. Using an *in vitro* lung model, White *et al.* compared different nebulizer positions in a pediatric lung model receiving NIV and reported greater drug delivery with the mesh nebulizer placed proximally to the mask than before the humidifier.[163]

AEROSOL DRUG DELIVERY TO INTUBATED INFANTS AND CHILDREN

In the past the consensus was that the efficiency of aerosol delivery to the lower respiratory tract in mechanically ventilated patients was much lower than that in ambulatory patients. In 1- to 4-kg infants, Fok and colleagues[8] demonstrated less than 1% deposition with jet nebulizers and pMDIs with spacers during mechanical ventilation and spontaneous breathing.

Data suggest that this might be overly pessimistic, however, because a number of variables affect aerosol delivery during mechanical ventilation (Box 11-7).

FACTORS AFFECTING AEROSOL DELIVERY DURING MECHANICAL VENTILATION

Ventilator–Patient Interface

The ventilator circuit is typically a closed system that is pressurized during operation, requiring the nebulizer or pMDI to be attached with connectors that maintain the integrity of the circuit during operation. The pMDI cannot be used with the actuator designed by the manufacturer, and use of a third-party actuator is required (Figure 11-13). The size, shape, and design of these actuators greatly affect the amount of respirable

Box 11-7 Variables That Affect Aerosol Delivery and Deposition During Mechanical Ventilation

VENTILATOR RELATED
Mode
Tidal volume
Respiratory frequency
Duty cycle
Inspiratory flow waveform
Trigger mechanism

DEVICE RELATED
Metered-Dose Inhaler
Type of spacer or adapter
Position of spacer in circuit
Timing of actuation
Nebulizer
Type of nebulizer
Fill volume
Gas flow
Cycling: inspiration versus continuous
Duration of nebulization
Position in circuit

CIRCUIT RELATED
Endotracheal tube
Inhaled gas humidity
Inhaled gas density

DRUG RELATED
Dose
Formulation
Aerosol particle size
Targeted site for delivery
Duration of action

PATIENT RELATED
Severity of airway obstruction
Mechanism of airway obstruction
Presence of dynamic hyperinflation
Patient–ventilator synchrony

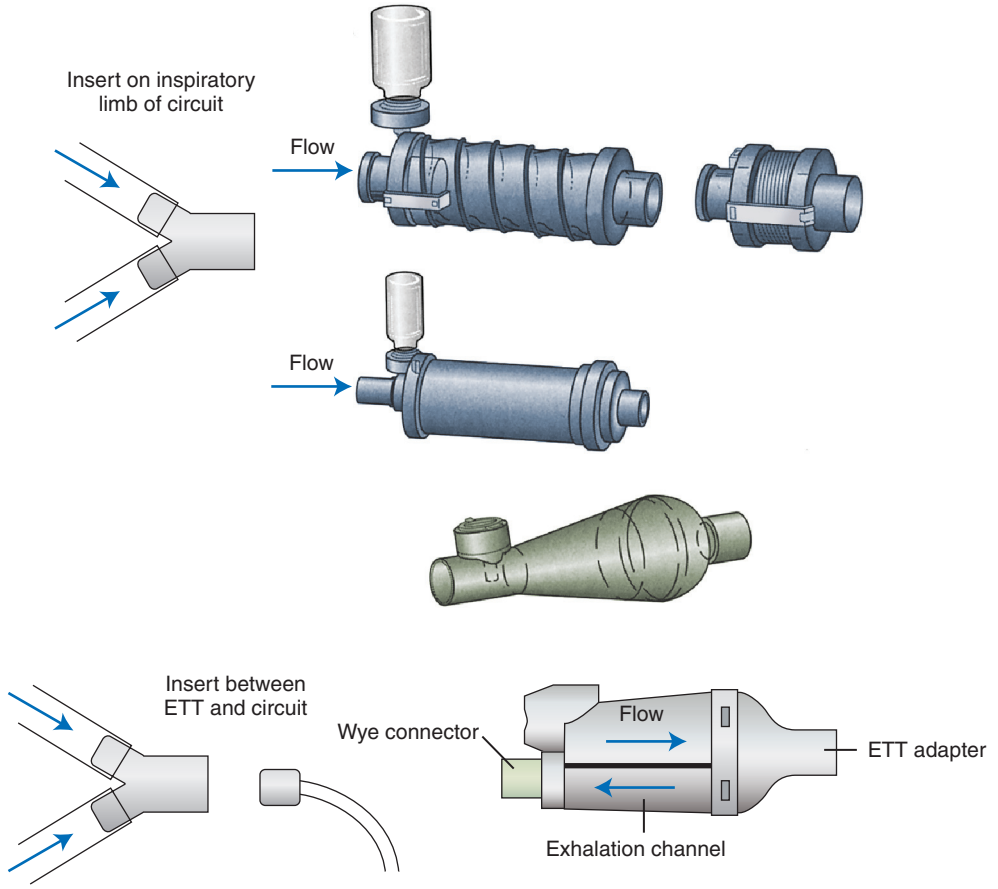


FIGURE 11-13 Metered-dose inhaler holding chambers to use in-line with mechanical ventilator circuits or in intubated patients or those with tracheostomies. *ETT,* Endotracheal tube. (Redrawn from Fink J, Cohen N: Humidity and aerosols. In Eubanks DH, Bone RC, editors: *Principles and applications of cardiorespiratory care equipment.* St. Louis, 1994, Mosby.)

drug available to the patient and may vary with different pMDI formulations.[164]

Breath Configuration

During controlled mechanical ventilation (CMV), the pattern and rate of inspiratory gas flow and breathing differ from spontaneous respiration. Ambulatory adult patients under normal stable conditions tend to have sinusoidal inspiratory flow patterns of about 30 L/minute, whereas ventilators may use square or decelerating waves with considerably higher flow. Also, the airways are pressurized on inhalation when using CMV, whereas spontaneous inspiration is generated by negative airway pressure drawing gas deep into the lungs. All these factors influence aerosol delivery to the lung.

Airway

In a mechanically ventilated patient, the conduit between the aerosol device and lower respiratory tract is narrower than the oropharynx and trachea. Although the endotracheal tube (ETT) is narrower than the trachea, its smooth interior surface may create a more laminar flow path than the structures of the glottis and larynx and may be less of a barrier to aerosol delivery than the ventilator circuit. *In vitro* studies demonstrate that three times more aerosol from the pMDI is delivered past the ETT during CMV under dry conditions than deposits in the lung through an intact upper airway, raising some doubt that the ETT is the primary barrier to aerosol.[165]

Environment

Ventilator circuits are typically designed to provide heat and humidity for inspired gas to compensate for bypassing the normal airway. Humidity can increase particle size and reduce deposition during CMV, but no data suggest that this reduction is unique to the ventilated patient. An ambulatory patient receiving aerosol, from either an inhaler or nebulizer, in a hot, high-humidity climate may experience a similar reduction in delivered dose.

Response Assessment

The most common method by which to assess patient response to bronchodilator administration is through changes in expiratory flow. During mechanical ventilation, forced expiratory maneuvers are impractical, poorly reproducible, and rarely performed, requiring other, less sensitive methods such as monitoring pressure changes (peak and plateau) during ventilator-generated breaths (e.g., passive inspiration). Fok and colleagues demonstrated differences in the response in a rabbit model of ventilated infants and found that a

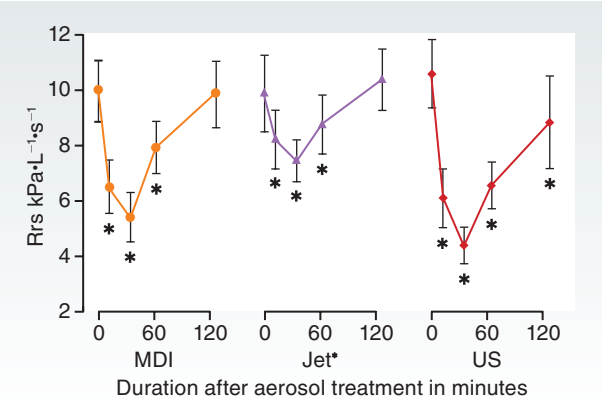


FIGURE 11-14 Measurements of respiratory system resistance *(Rrs)* before and 15, 30, 60, and 120 minutes after salbutamol treatment via a metered-dose inhaler *(MDI)*, a jet nebulizer (*Jet:* Sidestream), and an ultrasonic nebulizer *(US)*. *Posttreatment values were significantly lower than the pretreatment Rrs; $p < 0.0001$. (Reproduced with permission from the ©ERS 1998. *Eur Respir Journal* 1998;12(1): 159-164.)

pMDI was more effective than a jet nebulizer and that a USN was more effective than either (Figure 11-14).[166] Other changes in mechanics consistent with bronchodilator therapy include decreasing the pressure needed to deliver a set tidal volume during volume ventilation, decreasing the mean airway pressure (now continuously monitored electronically by most mechanical ventilators), and decreasing the requirement for supplemental oxygen. Flow–volume loops have been used to demonstrate bronchodilator response in infants, but unless the patient is sedated and paralyzed, respiratory efforts can provide misleading differences before and after bronchodilator administration. Chest auscultation to detect changes in wheezing is notoriously inaccurate and should never be used as the sole criterion for evaluating the effect of inhaled bronchodilators. For example, wheezing may become more prominent as severe bronchospasm is relaxed and the lungs begin to open up.

Nebulizer Placement

Placement of a continuous jet nebulizer 30 cm from the ETT is more efficient than placement between the patient Y-device and the ETT, because the inspiratory ventilator tubing acts as a spacer for the aerosol to accumulate between inspirations.[167] Addition of a spacer device between the nebulizer and ETT modestly increases aerosol delivery.[168] Placement of an ultrasonic or vibrating mesh nebulizer near the patient Y-device is more efficient than placement near the ventilator, unless bias flow exceeds 2 L/minute. Operating the nebulizer only during inspiration is marginally more efficient for aerosol delivery compared with continuous aerosol generation.[167]

Ari *et al.* compared aerosol delivery from four types of generators (jet, USNs, VMNs, and pMDI) in three positions (between the ETT and Y, in the inspiratory limb near the Y, and proximal to the ventilator) during continuous mechanical ventilation with no bias or trigger flow.[169] When operated in the inspiratory limb near the Y, the pMDI, USN, and VMN delivered 16% to 17% of the dose distal to the ETT, whereas the jet nebulizer delivered 3.5% in a heated, humidified circuit. Moving the aerosol generator back toward the ventilator increased the jet nebulizer to 6% but reduced efficiency of the other generators. In a similar experiment with 2 and 5 L/minute of bias flow, both the VMN and jet nebulizer were more efficient placed near the ventilator before the humidifier than in the inspiratory limb near the Y. This was demonstrated with both adult and pediatric circuits and parameters.[169,170] Figure 11-15 illustrates the experimental setup used by Ari *et al.* with a jet nebulizer and VMN; Figure 11-16 shows the effect of nebulizer type, placement, and bias flow on aerosol delivery in adult and pediatric lung models.[169]

Inhaler Adapters

Several types of commercial adapters are available to connect the pMDI canister to the ventilator circuit. Pressurized MDIs can be used with adapters that attach directly to the ETT, with inline chamber or nonchamber

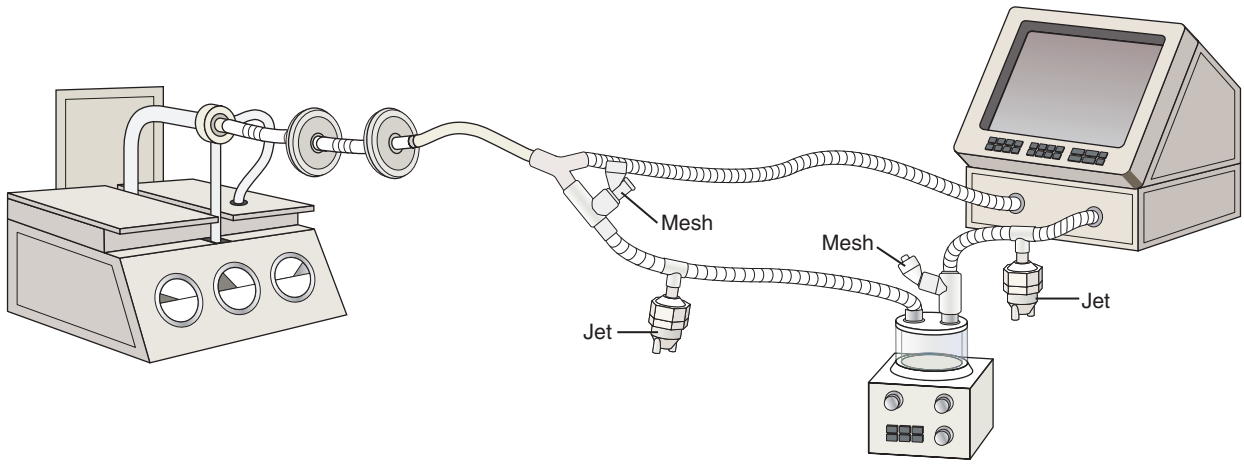


FIGURE 11-15 Experimental setup used with jet nebulizer and vibrating mesh nebulizer placed in two positions in an adult (22 mm ID) and pediatric (15 mm ID) ventilator circuits.

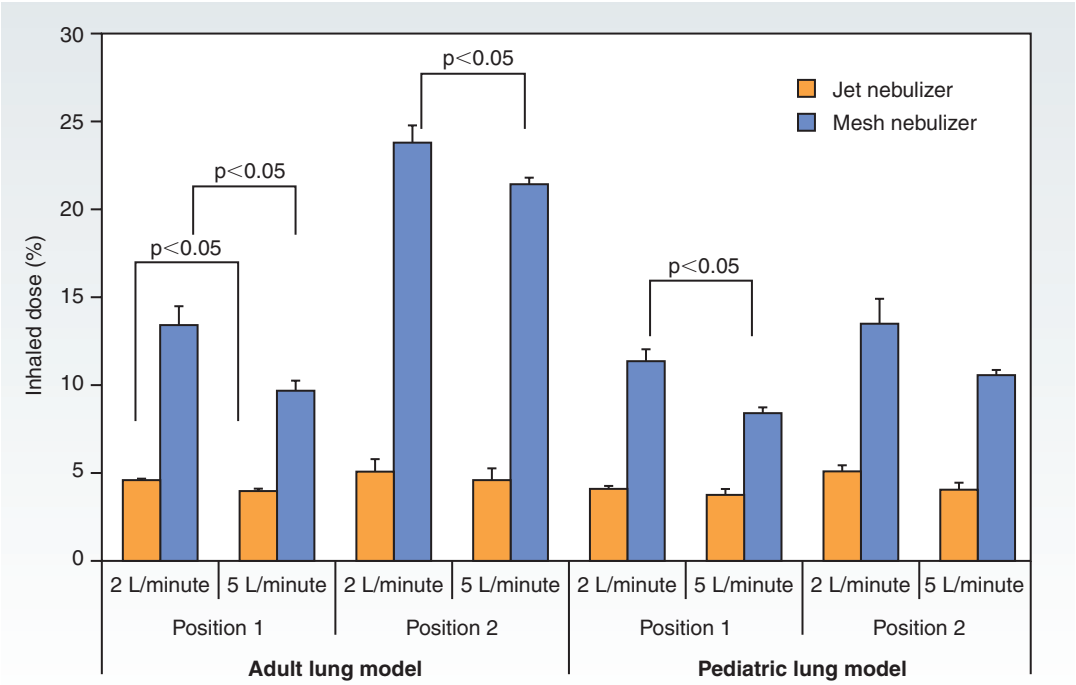


FIGURE 11-16 Effect of nebulizer type, placement, and bias flow on aerosol delivery from jet and mesh nebulizers in adult and pediatric lung models.

adapters placed in the inspiratory limb of the ventilator circuit. *In vitro* and *in vivo* studies have shown that the combination of a pMDI and an accessory device with a chamber results in a fourfold to sixfold greater delivery of aerosol than pMDI actuation into a connector attached directly to the ETT or into an inline device that lacks a chamber.[167,168,171-173] When using the elbow adapter connected to the ETT, actuation of the pMDI out of synchrony with inspiratory airflow delivers little aerosol to the lower respiratory tract. This observation may explain the lack of therapeutic effect with this type of adapter after administration of high doses (100 puffs, 1 mg of albuterol) of aerosol from a pMDI in some studies.[174]

Aerosol Particle Size

In mechanically ventilated patients the ventilator circuit and ETT act as baffles that trap particles with larger diameter en route to the bronchi, and hygroscopic particles might increase further in size in the ventilator circuit. Wide variability exists in the MMAD of aerosol particles produced by different brands of nebulizers. Nebulizers producing smaller aerosol particles (MMAD, less than 2 μm) are likely to produce greater deposition in the lower respiratory tract of ventilator-supported patients.[175]

Endotracheal Tube

Aerosol impaction in the ETT can reduce the efficiency of aerosol delivery in mechanically ventilated patients. The efficacy of aerosol delivery decreases when narrow ETTs are used in pediatric ventilator circuits.[175,176] The efficiency with which various nebulizers deliver aerosols beyond the ETT did not vary among tube sizes ranging in internal diameter from 7 to 9 mm.[171]

Heating and Humidification

Humidification of inhaled gas decreases aerosol deposition with pMDIs and nebulizers by approximately 40% using *in vitro* models, probably because of increased particle loss in the ventilator circuit.[175-177] More recently, evidence suggests that models that exhale humidity, more accurately simulating patient conditions, show little to no difference in delivered aerosol with passive or active humidity. This would eliminate any benefit of turning off active humidification before administration of aerosol. Absence of humidification may not pose problems during the brief period required to administer a bronchodilator with a pMDI; however, inhalation of dry gas for more than a few minutes can damage the airway.[75] In addition, the disconnection of the ventilator circuit required to bypass the humidifier interrupts ventilation and may increase the risk of ventilator-associated pneumonia. For routine bronchodilator treatment, either a pMDI or a nebulizer with a humidified ventilator circuit are ideal.

Density of Inhaled Gas

High inspiratory flow with air or oxygen produces turbulence and increased aerosol impaction. Breathing less dense gas such as helium–oxygen improves aerosol deposition. Studies in ambulatory patients with airway obstruction reveal higher aerosol retention when breathing helium–oxygen compared with air.[178,179] Studies on the effects of helium–oxygen mixtures on aerosol

deposition during mechanical ventilation demonstrated an up to 50% increase in deposition of albuterol from a pMDI or SVN during CMV of a simulated ventilator-dependent adult patient.[28]

Ventilator Mode and Settings

The ventilator mode and settings of tidal volume, flow, and respiratory rate influence the characteristics of the airflow used to deliver aerosol in mechanically ventilated patients. For optimal aerosol delivery, actuation of a pMDI into a spacer needs to be synchronized with the onset of inspiratory airflow. Actuation of a pMDI into a cylindrical spacer synchronized with inspiration results in approximately 30% greater efficiency of aerosol delivery compared with actuation during exhalation.[75] When using an elbow adapter, actuation of a pMDI that is not synchronized with inspiratory airflow achieves negligible aerosol delivery to the lower respiratory tract. Aerosol can be delivered during assisted modes of ventilation, provided that the patient is breathing in synchrony with the ventilator. Albuterol deposition may be up to 23% higher during simulated spontaneous breaths than with controlled breaths of equivalent tidal volume.[177] For efficient aerosol delivery to the lower respiratory tract, the tidal volume of the ventilator-delivered breath must be larger than the volume of the ventilator tubing and ETT. Tidal volumes of 500 mL or greater in adults are associated with adequate aerosol delivery, but the higher pressures required to deliver larger tidal volumes can be detrimental to the lungs. For infants and small children, volumes that exceed the mechanical dead space of the circuit and airway help optimize delivery.

Aerosol delivery directly correlates with longer inflation times.[175-177] Because nebulizers generate aerosol over several minutes, longer inspiratory times have a cumulative effect in improving aerosol delivery. However, pMDIs produce aerosol only over a portion of a single inspiration, and the mechanism by which longer inspiratory times increase aerosol delivery is unclear. Aerosol particles that deposit in the ventilator tubing may be swept off the walls and entrained by longer periods of inspiratory flow.

In addition, the diluent volume and the duration of treatment influence nebulizer efficiency.[174] Approximately 5% of the nominal dose of albuterol administered by a pMDI is exhaled in mechanically ventilated patients, whereas less than 1% is exhaled with the use of pMDIs in ambulatory patients.[28,180] The mean exhaled fraction (7%) with the use of nebulizers in mechanically ventilated patients is similar to that with MDIs, but considerable variability exists between patients (coefficient of variation, 74%).[181]

TECHNIQUE OF AEROSOL ADMINISTRATION IN CRITICAL CARE

Deposition of aerosol during mechanical ventilation varies with the type of aerosol generator used. During mechanical ventilation of adult patients under standard conditions (humidity on; I:E ratio, 1:2), 1% to 3% of the dose is delivered to the lungs.[182] Under similar conditions, a pMDI, with proper spacer and synchronized actuation, can deliver 11% of an emitted dose to the lungs. Both USNs and VMNs may deliver up 10% to 15% of a dose.[183,184]

In an infant, the deposition is considerably less (0.2% to 1.0%) with jet nebulizers and pMDIs, whereas the VMN appears to be an order of magnitude more efficient (9% to 12.9%).[184]

In both adults and infants, the gas driving the jet nebulizer enters the ventilator circuit, with the potential for changing delivered volumes, pressures, and parameters; this can set off alarms. Because of the relatively low flow rates used in infant ventilator circuits, the addition of 2 to 6 L/minute of gas can more than double the delivered volume. With other aerosol generators such as pMDIs and USNs and VMNs, there is no substantial increase in gas volume, and ventilator parameters remain consistent.

Specific techniques can improve the efficiency of every ventilator circuit. *In vitro,* the best delivery with a jet nebulizer during CMV (15% to 35%) was accomplished with a nebulizer (e.g., AeroTech II; Biodex Medical Systems, Shirley, NY) that produces particles with an MMAD less than 2 μm, but it can take 35 minutes to administer a 3 mL dose of medication. This dose was nebulized into a dry ventilator circuit, with a duty cycle of 0.5 at inverse-ratio ventilation.[181] Admittedly, this approach might be difficult to tolerate for a patient requiring mechanical ventilation. A common nebulizer that generates particles with an MMAD of 3.5 μm takes half the time but may reduce the dose to the lung by up to 50%, reducing total deposition to 7.5%. Keeping the humidifier on during administration reduces delivery by another 40% (decreasing total deposition to 4%), and reducing the duty cycle to a normal 0.25 reduces deposition to 2%.[174]

Studies on the dose response to bronchodilators in mechanically ventilated patients have not been done in children and infants. Thus data must be extrapolated from adult ventilated patients, in whom bronchodilator effects were observed with the administration of a 3-mL unit dose containing 2.5 mg of albuterol with a jet nebulizer or 4 actuations (400 μg) with a pMDI.[166] The pMDI was administered to stable patients through a humidified ventilator circuit, with a chamber-style adapter placed in the inspiratory limb at the Y-piece. Actuations were synchronized to inspiration, with a pause of 20 to 30 seconds between actuations. Minimal therapeutic advantage was gained by administering higher doses, but the potential for side effects was increased.[184,185] In the routine clinical setting, higher doses of bronchodilators may be needed for patients with severe airway obstruction or if the technique of administration is not optimal. Because these results were observed with humidified ventilator circuits, we do not recommend bypassing the

humidifier for routine bronchodilator therapy. In summary, when the technique of administration is carefully executed, most stable mechanically ventilated patients achieve near maximal bronchodilation after administration of four puffs of albuterol with a pMDI or 2.5 mg with a nebulizer. Dosing requirements for infants and small children during mechanical ventilation have not been established and should be titrated when there is an increase. In this case, to a decrease in airway resistance or an increase in tachycardia or tremor. Some authors have recommended that flow–volume loops be monitored before and after bronchodilator administration to quantify changes in airway resistance. In patients who are not totally sedated, these loops can change with patient inspiratory efforts and may be misleading.

Single-dose ampules of drug are preferred to multidose containers or bottles, which are more easily contaminated. Similarly, when the chamber spacer remains in the ventilator circuit between treatments, condensate collects inside. Using a heated wire circuit can reduce the formation of condensate within the spacer. Care must be taken to prevent the condensate in the spacer from being washed into the patient's respiratory tract when the spacer is pulled open during use. When a noncollapsible spacer chamber is used to actuate a pMDI, it should be removed from the ventilator circuit between treatments. No studies demonstrate contamination problems with administration of aerosol from a pMDI during CMV.

The administration of medication by pMDI to a mechanically ventilated neonate may not be well tolerated. Leaving a chamber device in-line is not practical because of the increased compressible volume incorporated into the ventilator circuit. Depending on the FiO_2 and the propellant gas volume, an in-line pMDI actuation theoretically may result in the delivery of a hypoxic gas mixture to an infant receiving a tidal volume less than 100 mL. It is possible to deliver a pMDI aerosol medication to an intubated neonate, especially for medications available only in pMDI preparations. However, it may be preferable to hand ventilate the pMDI delivery of medication to the patient. If a chamber adapter is used, the infant must be removed from the circuit, the chamber placed in-line, and the infant reattached to the circuit before the pMDI is administered. The large dead space volume caused by placing a spacer or chamber at the end of the ETT must also be considered when administering pMDI medications to an infant.

AEROSOL DRUG DELIVERY DURING HIGH-FREQUENCY OSCILLATORY VENTILATION

Until recently, efficient administration of medical aerosol during high-frequency oscillatory ventilation (HFOV) was dismissed as impractical. Several recent *in vitro* studies report circumstances in which drug delivery during HFOV was more efficient than during conventional mechanical ventilation. Using a mesh nebulizer with infant ventilation parameters, placement of the aerosol generator between the HFOV circuit and airway resulted in three times greater deposition than was best achieved with a conventional mechanical ventilator.[186]

Fang *et al.* compared aerosol delivery mesh and jet nebulizer during HFOV for infants (8.6 versus 0.1), children (17.4% versus 2.8%), and adults (22.7% versus 3.0%) with mesh and jet nebulizers, respectively, with placement proximal (at the ETT). When aerosol delivery devices were placed at the distal position, negligible drug mass was observed (less than 0.5%) regardless of the nebulizer device used.[187]

AEROSOL DRUG DELIVERY TO CHILDREN WITH A TRACHEOSTOMY

Aerosol therapy has been an important modality in the treatment of children with tracheostomy in recent years, and a recent survey reported that more than 92% of institutions use nebulizers and pMDIs for the delivery of different aerosolized medications to this patient population.[188] It is important to use nonelectrostatic valved holding chambers with pMDIs because of their high efficiency in aerosol drug delivery.[189-191] Using *in vitro* lung models, previous studies reported that aerosol deposition through tracheostomy was lower with the 3.5-mm ID tracheostomy tube than the 4.5- and 5.5-mm ID tracheostomy tubes in spontaneously breathing children with a tracheostomy.[189,192] Drug deposited in the tracheostomy tube ranges from 0.8% to 10% of the nominal dose used with the aerosol device during therapy.[189,190,192,193] Another *in vitro* study found that delivery efficiency of a breath-enhanced nebulizer was greater than the breath-actuated (AeroEclipse) and the standard jet nebulizers (UpDraft II).[192] In addition, the breath-enhanced nebulizer had a higher proximal–distal ratio in a pediatric lung model with tracheostomy and may be used to deliver antibiotics for the treatment of tracheitis.[192] Also, it is essential to turn off the high-flow oxygen delivery device before aerosol drug delivery to children so that aerosols will not be wasted to the environment as a result of additional gas flow within the system.[194-198] Although delivery technique is an important component of aerosol therapy, there is a discrepancy in results of studies evaluating the effect of assisted technique on aerosol drug delivery to children.[190,192,193] It may be related to differences in breathing patterns, lung models, and *in vitro* configurations that are used in these studies.

DEPOSITION IN INTUBATED AND NONINTUBATED INFANTS

Fok and colleagues[8] measured radioaerosol deposition of salbutamol by jet nebulizer and pMDIs with a valved holding chamber in ventilated and nonventilated

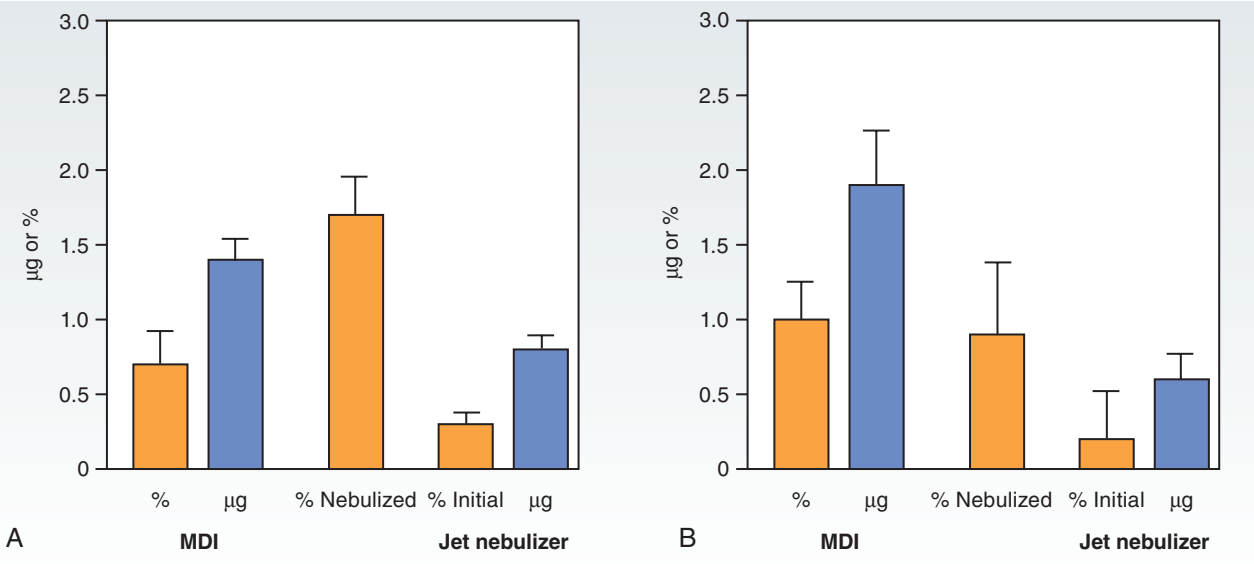


FIGURE 11-17 A dose of 200 µg of albuterol was administered by jet nebulizer or metered-dose inhaler *(MDI)* with chamber to infants with bronchopulmonary dysplasia, between 1 and 4 kg in size, and either ventilated or nonventilated. Mean (SEM) values for lung deposition are shown in **(A)** nonventilated infants (n = 13) and **(B)** ventilated infants (n = 10). Values are given as the percentage of the amount delivered to the infants and, for nebulizers, also as the percentage of the initial nebulizer dose. The absolute amount (µg) of salbutamol deposited in the lungs *(blue columns)* is given for reference. (Redrawn from Fok TF, Monkman S, Dolovich M, et al: Efficient of aerosol medication delivery from a metered dose inhaler versus jet nebulizer in infants with bronchopulmonary dysplasia. *Pediatr Pulmonol* 21(5):301–309, 1996.)

infants (1-4 kg) with bronchopulmonary dysplasia, finding less than 1% of the dose delivered to the lung in all cases (Figure 11-17). Delivery of aerosol was low for all delivery systems, and similar regardless of whether subjects were intubated, with considerable variability across patients. Lung deposition in ventilated infants was similar to that obtained from previous *in vitro, in vivo* animal, and indirect human studies.

BRONCHODILATOR ADMINISTRATION

INHALER VERSUS NEBULIZER

Nebulizers and pMDIs are equally effective in the treatment of airway obstruction in ambulatory children.[199] Similarly, nebulizers and pMDIs produce similar therapeutic effects in mechanically ventilated patients.

The use of pMDIs for routine bronchodilator therapy in ventilator-supported patients is preferred because of several problems associated with the use of jet nebulizers. The rate of aerosol production by nebulizers is highly variable, not only in nebulizers from different manufacturers, but also in different batches of the same brand. Furthermore, the nature of the aerosol produced, especially the particle size, is also highly variable among different nebulizers. The issue is further complicated because the operating efficiency of a nebulizer changes with the pressure of the driving gas and with different fill volumes. Because the pressure of the gas supplied by a ventilator to drive the nebulizer during inspiration is lower than that supplied by a tank and air compressor unit, the efficiency of some nebulizers can be drastically decreased in a ventilator circuit. The gas flow driving the nebulizer produces additional airflow in the ventilator circuit, necessitating adjustment of tidal volume and inspiratory flow when the nebulizer is in use. When patients are unable to trigger the ventilator during assisted modes of mechanical ventilation because of the additional nebulizer gas flow, hypoventilation can result.[185] Therefore, before using a jet nebulizer to treat a ventilator-supported patient, it is imperative to characterize its efficiency in a ventilator circuit under the typical clinical conditions in which it will be used.

Box 11-8 outlines a modification of the technique of aerosol administration with jet nebulizers to mechanically ventilated patients. Box 11-9 provides another strategy for bronchodilator therapy using a pMDI.[5]

CARE OF ACCESSORY DEVICES AND NEBULIZERS

For intubated infants or children with increased work of breathing or poor I:E ratios and for those in whom intubation is imminent, a nebulizer or pMDI adapted to a resuscitation bag can be used. The same FiO_2 is used with the jet nebulizer and the resuscitation bag. Flow to the nebulizer should be optimal for the nebulizer used, and flow to the bag should be reduced to compensate for the flow from the nebulizer. When using a bag and mask to deliver medication, care must be taken to avoid gastric insufflation, pulmonary hyperinflation, and hyperventilation or hypoventilation.

Box 11-8 Technique for Using Nebulizers to Treat Mechanically Ventilated Patients

- Place the drug solution in the nebulizer to the optimal fill volume (2-6 mL).*
- Place the nebulizer in the inspiratory line, about 30 cm from the patient's Y-piece.
- Ensure sufficient airflow (6-8 L/minute) to operate the nebulizer.†
- Ensure adequate tidal volume (about 500 mL in adults, 7 mg/kg for infants and children). Attempt to use a duty cycle greater than 0.3, if possible.
- Adjust the minute volume, sensitivity trigger, and alarms to compensate for additional airflow through the nebulizer if required.
- Turn off flow-by or continuous-flow mode on the ventilator and remove the heat moisture exchanger (if present) from between the nebulizer and the patient.
- Observe the nebulizer for adequate aerosol generation throughout use.
- Disconnect the nebulizer when no more aerosol is being produced.
- Rinse with sterile water or air dry between uses. Store the nebulizer under aseptic conditions.
- Reconnect the ventilator circuit, and return to original ventilator and alarm settings. Confirm proper operation with no leaks in circuit.

*The volume of solution associated with maximal efficiency varies with different nebulizers and should be determined before using any nebulizer.
†The nebulizer may be operated continuously or only during inspiration; the latter method is more efficient for aerosol delivery. Some ventilators provide inspiratory gas flow to the nebulizer. Continuous gas flow from an external source can also be used to power the nebulizer.

Box 11-9 Technique for Using Pressurized Metered-Dose Inhalers to Treat Mechanically Ventilated Patients

1. Minimize the inspiratory flow rate during administration.
2. Aim for an inspiratory/expiratory ratio (excluding the inspiratory pause) greater than 0.3 of total breath duration.
3. Ensure that the ventilator breath is synchronized with the patient's inspiration.
4. Shake the pMDI vigorously.
5. Place the canister in the actuator of a cylindrical spacer situated in the inspiratory limb of the ventilator circuit.*
6. Actuate the pMDI to synchronize with precise onset of inspiration by the ventilator.†
7. Allow passive exhalation.
8. Repeat actuations after 20–30 seconds until total dose is delivered.‡

pMDI, Pressurized metered-dose inhaler.
*With pMDIs, it is preferable to use a spacer that remains in the ventilator circuit so that disconnection of the ventilator circuit can be avoided at the time of each bronchodilator treatment. Although bypassing the humidifier can increase aerosol delivery, it prolongs the time for each treatment and requires disconnection of the ventilator circuit.
†In ambulatory patients with the pMDI placed inside the mouth, actuation is recommended briefly after initiation of inspiratory airflow. In mechanically ventilated patients in whom a pMDI and spacer combination is used, actuation should be synchronized with onset of inspiration.
‡The manufacturer recommends repeating the dose after 1 minute. However, pMDI actuation within 20–30 seconds after the prior dose does not compromise drug delivery.

The mask is used to create a good seal, and attempts must be made to time the inflation with the inspiratory effort. Care must be taken to stabilize the ETT to prevent accidental extubation with the added weight of the equipment. The patient is ventilated using the same pressures and rate as with the mechanical ventilator. It is theoretically helpful to deliver an occasional sigh by providing a slight inspiratory hold at the peak inspiratory pressure, thereby enhancing the volume and depth of medication delivered while providing additional time for deposition to occur in the airways.

OTHER MEDICATIONS FOR AEROSOL DELIVERY

ANTIBIOTICS

Aerosol systems can deliver high concentrations of antibiotics to the airway with low systemic bioavailability, thus reducing toxicity. This approach is of particular importance in patients with CF, who often require courses of antibiotic therapy.[200] In a phase 3 registration study, 468 patients with CF were enrolled in a 6-month masked, placebo-controlled trial of preservative-free, nonpyrogenic tobramycin solution for inhalation (TOBI; Novartis, Emeryville, CA), alternating between 4-week courses of tobramycin and placebo. During treatment the patients received 300 mg of tobramycin in 5 mL of quarter-strength saline. The FEV_1 increased by more than 10% by the end of 6 months, with patients receiving tobramycin 26% less likely to be hospitalized and 36% less likely to require intravenous antipseudomonal antibiotics and a greater than 10-fold reduction in sputum bacterial density.[201] Follow-up studies in CF and non-CF bronchiectasis have generally been consistent with these earlier results.[202]

Additional inhaled antibiotic products include Aztreonam (Gilead) and Tobi Podhaler (Novartis). Other antibiotics are being developed for aerosol delivery, including colistin, gentamicin, ciprofloxacin, and amikacin. Although aerosolized antibiotics may find a role in the therapy of patients with severe bronchopulmonary dysplasia or those with chronic tracheostomies, the emergence of bacterial resistance to these antibiotics is a real risk and must be closely monitored.[203]

MUCOACTIVE AGENTS

Sputum is expectorated mucus mixed with inflammatory cells, cellular debris, polymers of DNA and F-actin, and bacteria. Mucus is usually cleared by airflow and ciliary movement, and sputum is cleared by cough.[204] Dornase alfa (Pulmozyme; Genentech, South San Francisco, CA) was the first approved mucoactive agent for the treatment of CF.[9] Dornase alfa is safe and effective, even in patients with more severe pulmonary disease, defined as a forced vital capacity less than 40% of the predicted value.[205] Efficacy has not yet been demonstrated for the therapy of acute exacerbations of CF lung

disease or for the treatment of other chronic airway diseases.[206] A small phase 1 study in non-CF bronchiectasis demonstrated no efficacy in non-CF bronchiectasis, and there was a suggestion that the use of dornase worsened disease in this adult population.[207] This may be related to the fact that secretions in bronchiectasis and chronic obstructive pulmonary disease are composed primarily of mucin and related proteins, thus constituting true mucous hypersecretion,[208] whereas in the CF airway there is significantly decreased mucin and mucus, the CF secretions being almost entirely neutrophil-derived pus.[209]

Other mucoactive agents under development include mucolytics such as Nacystelyn (N-acetylcysteinate lysine),[210] thymosin β4, and low-molecular-weight dextran[211] ; mucokinetic agents such as surfactant; and P2Y2 chloride channel activators.[212] The use of hyperosmolar saline or mannitol to improve secretion clearance in CF is discussed in the section Hyperosmolar Aerosols.

SURFACTANT

There is profound loss of surfactant in the inflamed airway with bronchitis or CF.[213] Randomized, masked, placebo-controlled studies demonstrate that surfactant aerosol improves pulmonary function and sputum transportability in patients with chronic bronchitis and that this effect is dose dependent with no significant side effects.[214] As a wetting and spreading agent, the surfactant also has the ability to increase the lower airway deposition of other aerosol medications, such as dornase alfa or gene therapy vectors, and may increase small particle translocation through the mucous layer.[20]

HYPEROSMOLAR AEROSOLS

For many years, sputum induction by hyperosmolar saline inhalation has been used to obtain specimens for the diagnosis of pneumonia. In a pilot study, 58 patients with CF were randomly assigned to receive 10 mL of either 0.9% normal saline or 6% hypertonic saline twice daily by ultrasonic nebulization.[215] Spirometry was measured for 2 weeks during therapy and for 2 weeks after therapy. At 2 weeks there was a significant increase in the FEV_1 in the hypertonic saline group, with a return to baseline by 28 days. Despite pretreatment with 600 μg of inhaled albuterol, several patients had an acute decrease in FEV_1 after inhaling hypertonic saline. Similarly, hyperosmolar dry powder mannitol improves quality of life and pulmonary function in adult subjects with non-CF bronchiectasis and significantly improves the surface adhesiveness and cough clearance of expectorated sputum.[216]

Subsequent studies, as reviewed in the Cochrane Database of Systematic Reviews, tend to confirm that the long-term use of inhaled hyperosmolar saline improves pulmonary function in patients with CF[217] and that inhaled hyperosmolar saline or mannitol is beneficial in non-CF bronchiectasis.[218] Although this therapy is readily available and inexpensive, it has been reported that hypertonic saline aerosol is not as effective as dornase alfa in the therapy of CF lung disease.[219]

GENE TRANSFER THERAPY

Gene transfer therapy represents a novel use for aerosols. Efforts in this arena have centered largely on complementary (copy) DNA transfer of the normal CF transmembrane regulator (CFTR) gene to patients with CF. Gene transfer was first attempted by inserting the normal CFTR gene into a replication-defective adenovirus vector with bolus bronchoscopic delivery of the vector. An unanticipated host immune response to the vector led to reevaluation of this strategy.[220]

For gene transfer to be effective, the vector and its package must be nonimmunogenic, stable to shear forces during aerosolization, and safe to transfected cells. The vector should not increase cell turnover. It should either stably integrate into the progenitor (basal) cell genome or be safe and effective with repeated administration and should be able to reach the cellular target of relevance. Part of the difficulty with CF is that this cellular target has not been clearly identified as epithelial cell, goblet cell, submucous gland, or all of these. The amount of gene and vector and persistence in the airway must also be determined for each vector and delivery system.[221]

Viral vectors that have been studied include adenovirus, adeno-associated virus, and lentivirus. Adenovirus naturally targets the airway epithelium. Adeno-associated virus is a small organism that requires a "helper" virus to replicate. These viruses are capable of site-directed insertion into DNA, reducing the risk of insertional mutagenesis (initiating cancer by activation of an oncogene or inactivation of an oncogene suppressor). Gene therapy with adeno-associated virus appears to be especially promising.[222] Lentiviruses are retroviruses such as human immunodeficiency virus. They are able to transfect cells that are not terminally differentiated, such as the basal or airway progenitor cell, but insertional mutagenesis is a substantial risk.

The primary nonviral vectors studied to date have been cationic liposomes. These lipid capsules are able to form complexes with DNA and then enter cells. With the first generation of liposome vectors, the efficiency of gene transfer was poor; however, this has improved dramatically with newer systems.[223] The development of this technology will result in revolutionary aerosol generators.[224]

AEROSOLS FOR SYSTEMIC ADMINISTRATION

Aerosols can be targeted to different sites in the airway. Depending on the intrapulmonary behavior of each molecule, the aerosol mode of administration allows airway secretion delivery, cellular delivery, or systemic delivery. Most medications are targeted to

the airway epithelium, including the neuromuscular plexus (bronchodilators) and inflammatory cells (corticosteroids). Epithelial agents such as the P2Y2 ion channel activators are targeted directly to the ciliated epithelium. Mucolytics, proteases, and antibiotics are targeted to secretions in the airway rather than to the epithelial cells.

Small particles targeted to the alveolus can be effective for systemic delivery of macromolecules through the extensive pulmonary vascular bed. Insulin is likely to be the first such medication introduced for systemic administration through aerosol administration, but other peptides and macromolecules are under development. Considerations for systemic administration include cost, convenience, efficacy, and safety. The pulmonary behavior of an inhaled molecule is not predictable and must be studied individually.[225]

INSULIN

Insulin was one of the first medications to be administered by aerosol. Because of the nebulizer and insulin formulation available at that time, absorption and efficacy were highly unpredictable. This has changed dramatically with the development of ultrafine particles and aerosol devices that can efficiently and reliably target the alveolar space.

With a rapid and smooth onset of action and elimination of the necessity for injections with their attendant risks and discomfort, inhaled insulin has great potential for clinical use. Intrapulmonary insulin administration to healthy subjects can induce significant hypoglycemia and a clinically relevant increase in serum insulin concentrations.[226] Once plasma glucose levels are normalized, postprandial glucose levels can be maintained below diabetic levels by delivering insulin into the lungs 5 minutes before ingestion of a meal.[227,228]

Studies have confirmed that inhaled insulin is safe and effective for the therapy of type 2 diabetes even when this is not controlled by diet[229,230] and that the addition of inhaled insulin or oral therapy with hypoglycemic agents improves glycemic control.[231]

With the success of inhaled insulin demonstrating the safe and effective systemic administration of complex peptides via the pulmonary bed, it is highly probable that other aerosol therapies will be developed that could revolutionize fields as diverse as endocrinology, critical care, immunology, and genetics.[232,233] Because the respiratory therapist will be at the front line for teaching and administering these novel therapies, this will greatly expand the role of the respiratory therapist in the future.

The use of therapeutic aerosol medications is evolving from a basis of optimizing the delivery of asthma medications to the airway to understanding how the extensive pulmonary vascular bed can be used for the systemic administration of a variety of macromolecules. Evolving and novel uses of therapeutic aerosols will require an understanding of aerosol generation, deposition, and translocation, and will likely target organ physiology and pharmacology.

HOME CARE AND MONITORING COMPLIANCE

With most therapeutic aerosols being administered in the home, patient education and adherence with written medicine and action plans are critical. To improve compliance, aerosol therapy should be administered along with some easily remembered activity of daily living. For twice-daily administration, medications can be kept with the toothbrush and inhaled just before brushing the teeth. This approach also reduces aerosol corticosteroid deposition in the oral pharynx. It is always best to avoid the regular use of medication at school, because the inconvenience can significantly reduce compliance and may embarrass some children. However, the availability of rescue medication at school (or day care or other caregiver's home) must be ensured. It helps to prepare written guidelines for medication use. These guidelines should be distributed to all the places where the child stays, such as home, school, or the residence of each parent if divorced or separated.[77]

It is helpful, at least initially, to keep a diary of medication use. Lack of response to inhaled asthma medication can be related to a number of factors, including incorrect technique of inhalation; inhalation from depleted canisters of medications, thinking that they still contain active drug; not taking preventive medications as prescribed; change in the child's environment; or misdiagnosis. For example, children with aspirated foreign body, gastroesophageal reflux disease, or psychogenic wheeze will have a poor response to asthma therapy. Infants with tracheomalacia or bronchopulmonary dysplasia may even become much worse after inhaling a bronchodilator aerosol because of increased dynamic airway collapse.[78,234]

Standard nebulizers and pMDIs have no intrinsic mechanism for tracking use or compliance. The pMDI also has no mechanism to track how many doses remain in the canister. If accurately completed, medication diaries can help track medication use and the use of rescue medications while monitoring prescription refill records.

Several aerosol delivery devices entering the market can directly track use and monitor compliance. These devices range from electronic models integrated with the nebulizer that track number of breaths taken, size of breaths, and duration and frequency of treatment, to simple counting devices attached to the pMDI actuator boot. More sophisticated devices allow monitoring of both pMDI use and expiratory maneuvers for later transmission to the care provider's office. Some newer DPI devices contain a built-in counter that advances each time a dose is loaded. These devices also give a visual signal when only a few doses remain in the device.

Key Points

- Infants are obligate nose breathers up to 6 to 9 months.
- With growth, lung volumes increase, airways get larger, and respiratory rates decrease.
- Smaller airways filter out more aerosol, reducing lung doses compared with larger children and adults.
- From ages 3 to 13 years, pulmonary deposition increases but dose per kilogram is similar.
- Nebulizers vary in method of operation and delivered dose.
- BANs can increase inhaled dose and dosing time by threefold compared with continuous nebulizers.
- Infants and toddlers may not be able to use BANs.
- Jet nebulizers and USNs have residual medication volumes of 0.5 to 1.4 mL.
- Nebulizers with medication cups that directly connect to a vent circuit or mouthpiece are prone to contamination from drool and contaminated condensate.
- DPIs typically require highly sustained inspiratory flows to disaggregate drug and may not be suitable for children younger than 5 years of age.
- No aerosol devices were specifically designed for infants and toddlers.
- A DPI or pMDI alone are not suitable for children younger than 4 to 5 years.
- A pMDI with VHC and nebulizers (continuous) are suitable for children younger than 4 years.
- The interface of the aerosol device to the patient is critical.
- The mask must be tightly fitted for optimal delivery with a jet nebulizer or pMDI.
- Blow-by has not been shown to be effective.
- A mask with jet nebulizer more than 2 cm from an infant's face is not effective.
- Agitated and crying infants do not receive much, if any, aerosol to the lungs.
- Nasal delivery of aerosol via a high-flow nasal cannula may be a solution.
- As flow decreases, aerosol delivery increases in infants and small children.
- Heliox appears to improve aerosol delivery when inspiratory flow rates are higher.
- Very few inhaled medications have been approved based on studies in infants and small children, making administration to this population "off label."
- Caution should be exercised during administration of any aerosol to neonates and infants.
- New and developing medications are showing great promise for use with children.

Assessment Questions

See Evolve Resources for answers.

1. Which of the following is true when a standard unit dose is nebulized to patients of different sizes and ages?
   - **A.** A smaller percentage of dose is delivered to bigger patients.
   - **B.** A larger percentage of dose is delivered to smaller patients.
   - **C.** Similar inhaled doses per kilogram of body weight are delivered.
   - **D.** Similar total inhaled doses are delivered.
   - **E.** No dose is delivered to infants.
2. In infants between 1 and 4 kg, deposition of aerosol with a pressurized metered-dose inhalers (pMDI) or jet nebulizer is:
   - **A.** Similar whether intubated and mechanically ventilated or spontaneously breathing with a normal airway
   - **B.** Less than 1% in all cases
   - **C.** Slightly greater with a pMDI than with a jet nebulizer
   - **D.** All of the above
   - **E.** None of the above
3. What should the operator do when operating a jet nebulizer with a mixture of helium and oxygen?
   - **A.** Provide the same total flow of gas to the nebulizer as with air or oxygen.
   - **B.** Increase the flow of gas to the nebulizer by twofold or threefold.
   - **C.** Reduce the flow of gas to the nebulizer by one-half.
   - **D.** Never use heliox to drive a nebulizer.
   - **E.** Never use an air- or oxygen-flow meter.
4. Which of the following statements is true about the small-particle aerosol generator (SPAG)?
   - **A.** It makes very small particles.
   - **B.** It uses a secondary chamber to dry particles.
   - **C.** It is used to administer ribavirin.
   - **D.** It is often used with double containment systems.
   - **E.** All of the above.
5. What is the most reliable way to determine how many actuations are left in a pMDI?
   - **A.** Float the canister in water.
   - **B.** Count the number of doses used.
   - **C.** Actuate until it is empty.
   - **D.** Use it for only 1 month.
   - **E.** All of the above.
6. What limits use of dry powder inhalers (DPIs) for children younger than 5 years of age?
   - **A.** They are not big enough to generate sufficient inspiratory flow.
   - **B.** They cannot use a mouthpiece.
   - **C.** DPIs make them cough.
   - **D.** They cannot coordinate actuation with inspiration.
   - **E.** None of the above.
7. Which of the following statements is/are true about a large proportion of patients and their caregivers?
   - **A.** They do not know how to properly use a DPI.
   - **B.** They do not know how to properly use a pMDI.
   - **C.** They do not know how to properly clean and assemble a nebulizer.
   - **D.** They misuse their inhaler to the point of not benefiting from their medication.
   - **E.** All of the above.
8. During bronchodilator administration in severe airway obstruction:
   - **A.** An increased dose may be more effective than increased frequency.
   - **B.** Undiluted bronchodilator may be substituted for diluted bronchodilator.
   - **C.** Continuous nebulization may work better than intermittent nebulization.
   - **D.** Patients who do not respond to initial high doses are more often admitted to hospital.
   - **E.** All of the above.

9. What is the most practical way to improve aerosol deposition during mechanical ventilation?
- **A.** Use a nebulizer with a small particle size.
- **B.** Use a ramp versus square-wave pattern.
- **C.** Minimize inspiratory flow rates.
- **D.** Use a pMDI instead of a nebulizer.
- **E.** All of the above.

10. Which drug was one of the first to be administered by aerosol?
- **A.** Mucolytics
- **B.** Antibiotics
- **C.** Gene therapy
- **D.** Surfactant
- **E.** Insulin

REFERENCES

1. Newhouse MT, Dolovich MB. Control of asthma by aerosols. *N Engl J Med*. 1986;315:870.
2. Janson C. Plasma levels and effects of salbutamol after inhaled or i.v. administration in stable asthma. *Eur Repir J*. 1991;4:544.
3. Brain JD, Valberg PA. Deposition of aerosol in the respiratory tract. *Am Rev Respir Dis*. 1979;120:1325.
4. Gross NJ, Jenne J, Hess D. Bronchodilator therapy. In: Tobin MJ, ed. *Principles and Practice of Mechanical Ventilation*. New York: McGraw-Hill; 1994:1077-1123.
5. Rubin B, Fink J. Aerosol therapy for children. *Respir Care Clin N Am*. 2001;7(2):100-108.
6. Wildhaber JH, Janssens HM, Piérart F, Dore ND, Devadason SG, LeSouëf PN. High-percentage lung delivery in children from detergent-treated spacers. *Pediatr Pulmonol*. 2000;29(5):389-393.
7. Dolovich MB. Assessing nebulizer performance. *Respir Care*. 2002;47:1290.
8. Fok TF, Monkman S, Dolovich M, et al. Efficiency of aerosol medication delivery from a metered dose inhaler versus jet nebulizer in infants with bronchopulmonary dysplasia. *Pediatr Pulmonol*. 1996;21(5):301-309.
9. Wildhaber JH, Dore ND, Wilson JM, Devadason SG, LeSouëf PN. Inhalation therapy in asthma: nebulizer or pressurized metered-dose inhaler with holding chamber? In vivo comparison of lung deposition in children. *J Pediatr*. 1999;135(1):28-33.
10. Fink J, Dhand R. Aerosol therapy. In: Fink J, Hunt G, eds. *Clinical practice in respiratorycare*. Philadelphia: Lippincott-Raven; 1998:307-336.
11. Dolovich M. Physical principles underlying aerosol therapy. *J Aerosol Med*. 1989;2:171.
12. Pedersen S. Delivery systems in children. In: Barnes P, Grunstein M, Leff A, Woolcock A, eds. *Asthma*. Philadelphia: Lippincott-Raven; 1997:1925-1929.
13. Desai MA, Mutlu M, Vadgama P. A study of macro-molecular diffusion through native porcine mucus. *Experientia*. 1992;48:22.
14. Bolister N, Basker M, Hodges NA, Marriott C. The diffusion of beta-lactam antibiotics through mixed gels of cystic fibrosis-derived mucin and Pseudomonas aeruginosa alginate. *J Antimicrob Chemother*. 1991;27(3):285-293.
15. King M, Kelly S, Cosio M. Alteration of airway reactivity by mucus. *Respir Physiol*. 1985;62(1):47-59.
16. De Sanctis GT, Kelly SM, Saetta MP, et al. Hyporesponsiveness to aerosolized but not to infused methacholine in cigarette-smoking dogs. *Am Rev Respir Dis*. 1987;135(2):338-344.
17. Bataillon V, Lhermitte M, Lafitte JJ, Pommery J, Roussel P. The binding of amikacin to macromolecules from the sputum of patients suffering from respiratory diseases. *J Antimicrob Chemother*. 1992;29(5):499-508.
18. Taskar VS, Sharma RR, Goswami R, John PJ, Mahashur AA. Effect of bromhexeine on sputum amoxycillin levels in lower respiratory infections. *Respir Med*. 1992;86(2):157-160.
19. Stern M, Caplen NJ, Browning JE, et al. The effect of mucolytic agents on gene transfer across a CF sputum barrier in vitro. *Gene Ther*. 1998;5(1):91-98.
20. Schürch S, Gehr P, Im Hof V, Geiser M, Green F. Surfactant displaces particles toward the epithelium in airways and alveoli. *Respir Physiol*. 1990;80(1):17-32.
21. Kharasch VS, Sweeney TD, Fredberg J, et al. Pulmonary surfactant as a vehicle for intratracheal delivery of technetium sulfur colloid and pentamidine in hamster lungs. *Am Rev Respir Dis*. 1991;144(4):909-913.
22. Newhouse M, Kennedy A. Rapid temperature change from 25 C to 15 C impairs powder deaggregation in Bricanyl Turbuhaler. *J Aerosol Med*. 1999;12:113.
23. Hess D, Fisher D, Williams P, Pooler S, Kacmarek RM. Medication nebulizer performance. Effects of diluent volume, nebulizer flow, and nebulizer brand. *Chest*. 1996;110(2):498-505.
24. Johnson MA, Newman SP, Bloom R, Talaee N, Clarke SW. Delivery of albuterol and ipratropium bromide from two nebulizer systems in chronic stable asthma: efficacy and pulmonary deposition. *Chest*. 1989;96:6.
25. Hadfield JW, Windebank WJ, Bateman JR. Is driving gas flow rate clinically important for nebulizer therapy? *Br J Dis Chest*. 1986;80(1):50-54.
26. Douglas JG, Leslie MJ, Crompton GK, Grant IW. A comparative study of two doses of salbutamol nebulized at 4 and 8 litres per minute in patients with chronic asthma. *Br J Dis Chest*. 1986;80(1):55-58.
27. Hess DR, Acosta FL, Ritz RH, Kacmarek RM, Camargo Jr CA. The effect of heliox on nebulizer function using a beta-agonist bronchodilator. *Chest*. 1999;115(1):184-189.
28. Goode ML, Fink JB, Dhand R, Tobin MJ. Improvement in aerosol delivery with helium-oxygen mixtures during mechanical ventilation. *Am J Respir Crit Care Med*. 2001;163(1):109-114.
29. Malone RA, Hollie MC, Glynn-Barnhart A, Nelson HS. Optimal duration of nebulized albuterol therapy. *Chest*. 1993;104(4):1114-1118.
30. Thomas SH, Lanford JA, George RD, Geddes DM. Improving the efficiency of drug administration with jet nebulisers. *Lancet*. 1988;1:126.
31. Rau JL, Ari A, Restrepo RD. Performance comparison of nebulizer designs: constant-output, breath-enhanced, and dosimetric. *Respir Care*. 2004;49(2):174-179.
32. Ari A, Hess D, Myers TR, Rau JL. *A Guide to Aerosol Delivery Devices for Respiratory Therapists*. Dallas, Texas: American Association for Respiratory Care; 2009.
33. Newnham DM, Lipworth BJ. Nebuliser performance, pharmacokinetics, airways and systemic effects of salbutamol given via a novel nebuliser delivery system ("Ventstream"). *Thorax*. 1994;49(8):762-770.
34. Sangwan S, Condos R, Smaldone GC. Lung deposition and respirable mass during wet nebulization. *J Aerosol Med*. 2003;16(4):379-386.

35. Sabato MK, Ward P, Hawk W, Gildengorin G, Asselin JM. Randomized controlled trial comparing a breath actuated nebulizer to a hospital's standard therapy to treat pediatric asthma in the emergency department. *Respir Care*. 2011;56(6):761-770.
36. Lin YZ, Huang FY. Comparison of breath-actuated and conventional constant-flow jet nebulizers in treating acute asthmatic children. *Acta Paediatr Taiwan*. 2004;45(2):73-76.
37. Lin HL, Wan GH, Chen YH, Fink JB, Liu WQ, Liu KY. Influence of nebulizer type with different pediatric aerosol masks on drug deposition in a model of a spontaneously breathing small child. *Respir Care*. 2012;57(11):1894-1900.
38. Ari A, Fink JB. Effective bronchodilator resuscitation of children in the emergency room: device or interface? *Respir Care*. 2011;56(6):882-885.
39. Ari A, Fink JB. Breath-actuated nebulizer versus small-volume nebulizer: efficacy, safety, and satisfaction. *Respir Care*. 2012;57(8):1351-1353.
40. The Nebulizer Project Group of the British Thoracic Society Standards of Care Committee. Current best practice for nebuliser treatment. *Thorax*. 1997;52(suppl 2):S4.
41. Standaert T, Morlin GL, Williams-Warren J, et al. Effects of repetitive use and cleaning techniques of disposable jet nebulizers on aerosol generation. *Chest*. 1998;114:577-586.
42. Guideline for prevention of nosocomial pneumonia. Centers for Disease Control and Prevention. *Respir Care*. 1994;39(12):1191-1236.
43. Oie S, Kamiya A. Bacterial contamination of aerosol solutions containing antibiotics. *Microbios*. 1995;82:109.
44. Kelly HW, Keim KA, McWilliams BC. Comparison of two methods of delivering continuously nebulized albuterol. *Ann Pharmacotherapy*. 2003;37(1):23-26.
45. Papo MC, Frank J, Thompson AE. A prospective, randomized study of continuous versus intermittent nebulized albuterol for severe status asthmaticus in children. *Crit Care Med*. 1993;21(10):1479-1486.
46. Khine H, Fuchs SM, Saville AL. Continuous vs intermittent nebulized albuterol for emergency management of asthma. *Acad Emerg Med*. 1996;3(11):1019-1024.
47. Berlinski A, Willis JR, Leisenring T. In-vitro comparison of 4 large-volume nebulizers in 8 hours of continuous nebulization. *Respir Care*. 2010;55(12):1671-1679.
48. Kacmarek RM, Kratohvil J. Evaluation of a double-enclosure double-vacuum unit scavenging system for ribavirin administration. *Respir Care*. 1992;37:37.
49. Adderley RJ. Safety of ribavirin with mechanical ventilation. *Pediatr Infect Dis J*. 1990;9(suppl 9):S112-114.
50. Committee on Infectious Diseases, American Academy of Pediatrics. Reassessment of the indications for ribavirin therapy in respiratory syncytial virus infections. *Pediatrics*. 1996;97:137.

50a. Walsh BK, Betit P, Fink JBArnold J., Pereira LM, Arnold J. Characterization of ribavirin aerosol with small particle aerosol generatory and vibrating mesh micropump aerosol technologies. *Respir Care* 2016;61(5):577–585.

51. Phillips GD, Millard FJ. The therapeutic use of ultrasonic nebulizers in acute asthma. *Respir Med*. 1994;88:387-389.
52. Ari A. Nebulizers: An evaluation of nebulizers for better clinical practice. *Eurasian Journal of Pulmonology*. 2014;16(1-7).
53. Summer W, Elston R, Tharpe L, Nelson S, Haponik EF. Aerosol bronchodilator delivery methods. Relative impact on pulmonary function and cost of respiratory care. *Arch Intern Med*. 1989;149(3):618-623.
54. Yuksel B, Greenough A. Comparison of the effects on lung function of two methods of bronchodilator administration. *Respir Med*. 1994;88(3):229-233.
55. Nakanishi AK, Lamb BM, Foster C, Rubin BK. Ultrasonic nebulization of albuterol is no more effective than jet nebulization for the treatment of acute asthma in children. *Chest*. 1997;111(6):1505-1508.
56. Doershuk CF, Matthews LW, Gillespie CT, Lough MD, Spector S. Evaluation of jet-type and ultrasonic nebulizers in mist tent therapy for cystic fibrosis. *Pediatrics*. 1968;41(4):723-732.
57. Boucher RM, Kreuter J. The fundamentals of the ultrasonic atomization of medicated solutions. *Ann Allergy*. 1968;26(11):591-600.
58. Thomas SH, O'Doherty MJ, Page CJ, Treacher DF, Nunan TO. Delivery of ultrasonic nebulized aerosols to a lung model during mechanical ventilation. *Am Rev Respir Dis*. 1993;148(4):872-877.
59. Ari A, Restrepo RD. Aerosol delivery device selection for spontaneously breathing patients: 2012. *Respir Care*. 2012;57(4):613-626.
60. Boe J, Dennis JH, O'Driscoll BR, et al. European Respiratory Society Guidelines on the use of nebulizers. *Eur Respir J*. 2001;18(1):228-242.
61. Tablan O, Anderson L, Besser R, Bridges C, Hajjeh R. Guidelines for Preventing Health Care—Associated Pneumonia. Recommendations of the CDC and the Healthcare Infection Control Practices Advisory Committee. *MMWR Recommendations & Reports*. 2004; http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5303a1.htm. Accessed January 19, 2009.
62. Saiman L, Siegel J. Infection control recommendations for patients with cystic fibrosis: microbiology, important pathogens, and infection control practices to prevent patient-to-patient transmission. *Am J Infect Control*. 2003;31(3):S1-62.
63. O'Malley CA, VandenBranden SL, Zheng XT, Polito AM, McColley SA. A day in the life of a nebulizer: surveillance for bacterial growth in nebulizer equipment of children with cystic fibrosis in the hospital setting. *Respir Care*. 2007;52(3):258-262.
64. Lin YZ, Hsieh KH. Metered dose inhaler and nebuliser in acute asthma. *Arch Dis Child*. 1995;72:214.
65. Newhouse M, Dolovich M. Aerosol therapy in children. In: Chermick V, Mellins R, eds. *Basic Mechanisms of Pediatric Respiratory Disease: Cellular and Integrative*. Toronto: BC Decker; 1991.
66. Svartengren K, Lindestad P, Svartengren M, Philipson K, Bylin G, Camner P. Added external resistance reduces oropharyngeal deposition and increases lung deposition of aerosol particles in asthmatics. *Am J Respir Crit Care Med*. 1995;152(1):32-37.
67. Hill LS, Slater AL. A comparison of the performance of two modern multidose dry powder asthma inhalers. *Respir Med*. 1998;92(1):105-110.
68. Rajkumari N, Byron PR, Dalby RN. Testing of dry powder aerosol formulations in different environmental conditions. *Int J Pharm*. 1995;113(1):123-130.
69. Larsen JS, Hahn M, Ekholm B, Wick KA. Evaluation of conventional press-and-breathe metered-dose inhaler technique in 501 patients. *J Asthma*. 1994;31(3):193-199.
70. Guidry GG, Brown WD, Stogner SW, George RB. Incorrect use of metered dose inhalers by medical personnel. *Chest*. 1992;101:31-33.
71. Fink JB, Rubin BK. Problems with inhaler use: a call for improved clinician and patient education. *Respir Care*. 2005;50(10):1360-1374.
72. Newman SP, Pavia D, Clarke SW. Simple instructions for using pressurized aerosol bronchodilators. *J R Soc Med*. 1980;73(11):776-779.
73. Hampson NB, Mueller MP. Reduction in patient timing errors using a breath-activated metered dose inhaler. *Chest*. 1994;106:462.
74. Toogood JH, Baskerville J, Jennings B, Lefcoe NM, Johansson SA. Use of spacers to facilitate inhaled corticosteroid treatment of asthma. *Am Rev Respir Dis*. 1984;129(5):723-729.
75. Diot P, Morra L, Smaldone GC. Albuterol delivery in a model of mechanical ventilation. Comparison of metered-dose inhaler and nebulizer efficiency. *Am J Respir Crit Care Med*. 1995;152(4 Pt 1):1391-1394.

76. Salzman GA, Pyszczynski DR. Oropharyngeal candidiasis in patients treated with beclomethasone dipropionate delivered by metered-dose inhaler alone and with Aerochamber. *J Allergy Clin Immunol*. 1988;81(2):424-428.
77. Rubin BK. Pressurized metered-dose inhalers and holding chambers for inhaled glucocorticoid therapy in childhood asthma. *J Allergy Clin Immunol*. 1999;103(6):1224-1225.
78. Closa RM, Ceballos JM, Gómez-Papí A, Galiana AS, Gutiérrez C, Martí-Henneber C. Efficacy of bronchodilators administered by nebulizers versus spacer devices in infants with acute wheezing. *Pediatr Pulmonol*. 1998;26(5):344-348.
79. Williams JR, Bothner JP, Swanton RD. Delivery of albuterol in a pediatric emergency department. *Pediatr Emerg Care*. 1996;12(4):263-267.
80. Cunningham SJ, Crain EF. Reduction of morbidity in asthmatic children given a spacer device. *Chest*. 1994;106(3):753-757.
81. Ganderton D. The generation of respirable clouds from coarse powder aggregates. *J Biopharm Sci*. 1994;3:101.
82. Dolovich M. Measurement of the particle size and dosing characteristics of a radiolabelled albuterol sulphate lactose blend used in the SPIROS dry powder inhaler. In: Dalby R, Byron PR, Farr S, eds. *Respiratory Drug Delivery*. Buffalo, Grove, NY: Interpharm Press; 1996:332-335.
83. Engel T, Heinig JH, Madsen F, Nikander K. Peak inspiratory flow and inspiratory vital capacity of patients with asthma measured with and without a new dry-powder inhaler device (Turbuhaler). *Eur Respir J*. 1990;3(9):1037-1041.
84. Pedersen S, Hansen OR, Fuglsang G. Influence of inspiratory flow rate upon the effect of a Turbuhaler. *Arch Dis Child*. 1990;65:308.
85. Thorsson L, Edsbäcker S, Conradson TB. Lung deposition of budesonide from Turbuhaler is twice that from a pressurized metered-dose inhaler P-MDI. *Eur Respir J*. 1994;7(10):1839-1844.
86. Hindle M, Byron PR. Dose emissions from marketed dry powder inhalers. *Int J Pharm*. 1992;116(2):169-177.
87. Bisgaard H, Klug B, Skamstrup K, Sumby B. Inspiratory flow rate through the discus/accuhaler inhaler and turbuhaler inhaler in children with asthma. *J Aerosol Med*. 1996;116:169.
88. Smith KJ, Chan HK, Brown KF. Influence of flow rate on aerosol particle size distributions from pressurized and breath-actuated inhalers. *J Aerosol Med*. 1998;11(4):231-245.
89. Pedersen S. Delivery options for inhaled therapy in children over the age of 6 years. *J Aerosol Med*. 1997;10(suppl 1):S41-44.
90. Ari A. Patient education and adherence in aerosol therapy. *Respir Care*. 2015;60(6):941-957.
91. Ari A, Fink JB. Aerosol therapy in children: challenges and solutions. *Expert Rev Respir Med*. 2013;7(6):665-672.
92. Fok TF, Lam K, Chan CK, et al. Aerosol delivery to nonventilated infants by metered dose inhaler: should a valved spacer be used? *Pediatr Pulmonol*. 1997;24(3):204-212.
93. Kesten S, Elias M, Cartier A, Chapman KR. Patient handling of a multidose dry powder inhalation device for albuterol. *Chest*. 1994;105(4):1077-1081.
94. Ari A, Fink JB. Guidelines to aerosol devices in infants, children and adults: which to choose, why and how to achieve effective aerosol therapy? *Expert Rev Respir Med*. 2011;5(4):561-572.
95. Everard ML. Guidelines for devices and choices. *J Aerosol Med*. 2001;14(suppl 1):S59-S64.
96. Everard ML. Aerosol delivery to children. *Pediatr Ann*. 2006;35(9):630-636.
97. Everard ML. Inhalation therapy for infants. *Adv Drug Deliv Rev*. 2003;55(7):869-878.
98. Ari A. Drug delivery interfaces: A way to optimize inhalation therapy in spontaneously breathing children. *World J Clin Pediatr*. 2016;5(3):281-287.
99. Mansour MM, Smaldone GC. Blow-by as potential therapy for uncooperative children: an in-vitro study. *Respiratory Care*. 2012;57(12):2004-2011.
100. Lin HL, Restrepo RD, Gardenhire DS, Rau JL. Effect of face mask design on inhaled mass of nebulized albuterol, using a pediatric breathing model. *Respiratory Care*. 2007;52(8):1021-1026.
101. Restrepo RD, Dickson SK, Rau JL, Gardenhire DS. An investigation of nebulized bronchodilator delivery using a pediatric lung model of spontaneous breathing. *Respir Care*. 2006;51(1):56-61.
102. Amirav I, Shakked T, Broday DM, Katoshevski D. Numerical investigation of aerosol deposition at the eyes when using a hood inhaler for infants–a 3D simulation. *J Aerosol Med Pulm Drug Deliv*. 2008;21(2):207-214.
103. Kugelman A, Amirav I, Mor F, Riskin A, Bader D. Hood versus mask nebulization in infants with evolving bronchopulmonary dysplasia in the neonatal intensive care unit. *J Perinatol*. 2006;26(1):31-36.
104. Amirav I, Oron A, Tal G, et al. Aerosol delivery in respiratory syncytial virus bronchiolitis: hood or face mask? *J Pediatr*. 2005;147(5):627-631.
105. Amirav I, Balanov I, Gorenberg M, Groshar D, Luder AS. Nebuliser hood compared to mask in wheezy infants: aerosol therapy without tears! *Arch Dis Child*. 2003;88(8):719-723.
106. Ari A, Harwood R, Sheard M, Dailey P, Fink JB. In vitro comparison of heliox and oxygen in aerosol delivery using pediatric high flow nasal cannula. *Pediatr Pulmonol*. 2011;46(8):795-801.
107. Bhashyam AR, Wolf MT, Marcinkowski AL, et al. Aerosol delivery through nasal cannulas: an in vitro study. *J Aerosol Med Pulm Drug Deliv*. 2008;21(2):181-188.
108. Ari A, de Andrade AD, Sheard M, AlHamad B, Fink JB. Performance comparisons of jet and mesh nebulizers using different interfaces in simulated spontaneously breathing adults and children. *J Aerosol Med Pulm Drug Deliv*. 2015;28(4):281-289.
109. Ditcham W, Murdzoska J, Zhang G, et al. Lung deposition of 99mTc-radiolabeled albuterol delivered through a pressurized metered dose inhaler and spacer with facemask or mouthpiece in children with asthma. *J Aerosol Med*. 2014;27(suppl 1):S63-S75.
110. Amirav I, Newhouse MT. Aerosol therapy in infants and toddlers: past, present and future. *Expert Rev Respir Med*. 2008;2(5):597-605.
111. DiBlasi RM. Clinical controversies in aerosol therapy for infants and children. *Respir Care*. 2015;60(6):894-916.
112. Amirav I, Mandelberg A. Face masks for aerosols-there is more science. *Pediatr Pulmonol*. 2010;45(3):221-223.
113. Amirav I, Newhouse MT. Review of optimal characteristics of face-masks for valved-holding chambers (VHCs). *Pediatr Pulmonol*. 2008;43(3):268-274.
114. Sangwan S, Gurses BK, Smaldone GC. Facemasks and facial deposition of aerosols. *Pediatr Pulmonol*. 2004;37(5):447-452.
115. El Taoum KK, Xi J, Kim J, Berlinski A. In vitro evaluation of aerosols delivered via the nasal route. *Respir Care*. 2015;60(7):1015-1025.
116. Smaldone GC, Berg E, Nikander K. Variation in pediatric aerosol delivery: importance of facemask. *J Aerosol Med*. 2005;18(3):354-363.
117. Smaldone GC, Sangwan S, Shah A. Facemask design, facial deposition, and delivered dose of nebulized aerosols. *J Aerosol Med*. 2007;20(suppl 1):S66-S75.
118. Iles R, Lister P, Edmunds AT. Crying significantly reduces absorption of aerosolised drug in infants. *Arch Dis Child*. 1999;81(2):163-165.
119. Everard ML. Trying to deliver aerosols to upset children is a thankless task. *Arch Dis Child*. 2000;82(5):428.

120. Erzinger S, Schueepp KG, Brooks-Wildhaber J, Devadason SG, Wildhaber JH. Facemasks and aerosol delivery in vivo. *J Aerosol Med*. 2007;20(suppl 1):S78-S83.
121. Janssens HM, van der Wiel EC, Verbraak AF, de Jongste JC, Merkus PJ, Tiddens HA. Aerosol therapy and the fighting toddler: is administration during sleep an alternative? *J Aerosol Med*. 2003;16:395-400.
122. Esposito-Festen JE, Ijsselstjin H, Hop W, van Vliet F, de Jongste J, Tiddens H. Aerosol therapy by pMDI-spacer in sleeping young children: to do or not to do? *Chest*. 2006; 130:487-492.
123. Janssens HM, Heijnen EM, de Jong VM, et al. Aerosol delivery from spacers in wheezy infants: a daily life study. *Eur Repir J*. 2000;16(5):850-856.
124. Smaldone GC. Assessing new technologies: patient-device interactions and deposition. *Respir Care*. 2005;50(9):1151-1160.
125. Esposito-Festen JE, Ates B, van Vliet FJ, Verbraak AF, de Jongste JC, Tiddens HA. Effect of a facemask leak on aerosol delivery from a pMDI-spacer system. *J Aerosol Med*. 2004;17(1):1-6.
126. Esposito-Festen J, Ates B, van Vliet F, Hop W, Tiddens H. Aerosol delivery to young children by pMDI-spacer: is facemask design important? *Pediatr Allergy Immunol*. 2005;16(4):348-353.
127. Amirav I, Newhouse MT. Aerosol Therapy With Valved Holding Chambers in Young Children: Importance of the Facemask Seal. *Pediatrics*. 2001;108:389.
128. Hayden JT, Smith N, Woolf DA, Barry PW, O'Callaghan C. A randomised crossover trial of facemask efficacy. *Arch Dis Child*. 2004;89(1):72-73.
129. Amirav I, Luder AS, Halamish A, et al. Design of aerosol face masks for children using computerized 3D face analysis. *J Aerosol Med Pulm Drug Deliv*. 2014;27(4):272-278.
130. Amirav I, Newhouse MT, Luder A, Halamish A, Omar H, Gorenberg M. Feasibility of aerosol drug delivery to sleeping infants: a prospective observational study. *BMJ open*. 2014;4(3):e004124.
131. Amirav I, Luder A, Chleechel A, Newhouse MT, Gorenberg M. Lung aerosol deposition in suckling infants. *Arch Dis Child*. 2012;97(6):497-501.
132. Chua HL, Collis GG, Newbury AM, et al. The influence of age on aerosol deposition in children with cystic fibrosis. *Eur Respir J*. 1994;7(12):2185-2191.
133. Amirav I, Borojeni AA, Halamish A, Newhouse MT, Golshahi L. Nasal versus oral aerosol delivery to the "lungs" in infants and toddlers. *Pediatr Pulmonol*. 2015;50(3):276-283.
134. Sunbul F, Fink J, Harwood R, Ari A. Comparison of HFNC, Bubble CPAP and SiPAP on aerosol delivery in premature babies: an in-vitro study. *Pediatric Pulmonology*. 2015;50(11): 1099-1106.
135. Perry SA, Kesser KC, Geller DE, Selhorst DM, Rendle JK, Hertzog JH. Influences of cannula size and flow rate on aerosol drug delivery through the Vapotherm humidified high-flow nasal cannula system. *Pediatr Crit Care Med*. 2013;14(5):e250-256.
136. Réminiac F, Vecellio L, Loughlin RM, et al. Nasal high flow nebulization in infants and toddlers: An in vitro and in vivo scintigraphic study. *Pediatr Pulmonol*. 2017;52(3): 337-344.
137. National Asthma Education and Prevention Program. *Expert Panel III: Guidelines for the diagnosis and management of asthma*. Bethesda, MD: National Heart, Lung, and Blood Institute (NHLBI); 2007.
138. Schuh S, Parkin P, Rajan A, et al. High-versus low-dose, frequently administered, nebulized albuterol in children with severe, acute asthma. *Pediatrics*. 1989;83(4):513-518.
139. Direkwatanachai C, Teeratakulpisarn J, Suntornlohanakul S, et al. Comparison of salbutamol efficacy in children—via the metered-dose inhaler (MDI) with Volumatic spacer and via the dry powder inhaler, Easyhaler, with the nebulizer—in mild to moderate asthma exacerbation: a multicenter, randomized study. *Asian Pac J Allergy Immunol*. 2011;29(1):25-33.
140. Yilmaz O, Sogut A, Kose U, Sakinci O, Yuksel H. Influence of ambulatory inhaled treatment with different devices on the duration of acute asthma findings in children. *J Asthma*. 2009;46(2):191-193.
141. Mandelberg A, Tsehori S, Houri S, Gilad E, Morag B, Priel IE. Is nebulized aerosol treatment necessary in the pediatric emergency department? *Chest*. 2000;117(5):1309-1313.
142. Ploin D, Chapuis FR, Stamm D, et al. High-dose albuterol by metered-dose inhaler plus a spacer device versus nebulization in preschool children with recurrent wheezing: A double-blind, randomized equivalence trial. *Pediatrics*. 2000;106(2 Pt 1): 311-317.
143. Rubilar L, Castro-Rodriguez JA, Girardi G. Randomized trial of salbutamol via metered-dose inhaler with spacer versus nebulizer for acute wheezing in children less than 2 years of age. *Pediatr Pulmonol*. 2000;29(4):264-269.
144. Leversha AM, Campanella SG, Aickin RP, Asher MI. Costs and effectiveness of spacer versus nebuliser in young children with moderate and severe acute asthma (Structured abstract). *J Pediatr*. 2000(4):497-502.
145. Deerojanawong J, Manuyakorn W, Prapphal N, Harnruthakorn C, Sritippayawan S, Samransamruaikit R. Randomized controlled trial of salbutamol aerosol therapy via metered dose inhaler-spacer vs jet nebulizer in young children with wheezing. *Pediatr Pulmonol*. 2005;39(5): 466-472.
146. Delgado A, Chou KJ, Silver EJ, Crain EF. Nebulizers vs metered-dose inhalers with spacers for bronchodilator therapy to treat wheezing in children aged 2 to 24 months in a pediatric emergency department. *Arch Pediatr Adolesc Med*. January 2003;157(1):76-80.
147. Sannier N, Timsit S, Cojocaru B, et al. [Metered-dose inhaler with spacer vs nebulization for severe and potentially severe acute asthma treatment in the pediatric emergency department]. *Arch Pediatr*. 2006;13(3):238-244.
148. Chong Neto HJ, Chong-Silva DC, Marani DM, Kuroda F, Olandosky M, De Noronha L. Different inhaler devices in acute asthma attacks: a randomized, double-blind, placebo-controlled study (Structured abstract). *J Pediatr*. 2005(4): 298-304.
149. Goh AE, Tang JP, Ling H, et al. Efficacy of metered-dose inhalers for children with acute asthma exacerbations. *Pediatr Pulmonol*. 2010;46(5):421-427.
150. Hurley KF, Sargeant J, Duffy J, Sketris I, Sinclair D, Ducharme J. Perceptual reasons for resistance to change in the emergency department use of holding chambers for children with asthma. *Ann Emerg Med*. 2008;51(1):70-77.
151. Osmond MH, Gazarian M, Henry RL, Clifford TJ, Tetzlaff J. Barriers to metered-dose inhaler/spacer use in Canadian pediatric emergency departments: a national survey. *Acad Emerg Med*. 2007;14(11):1106-1113.
152. Scott SD, Osmond MH, O'Leary KA, Graham ID, Grimshaw J, Klassen T. Barriers and supports to implementation of MDI/spacer use in nine Canadian pediatric emergency departments: a qualitative study. *Implement Sci*. 2009; 4:65.
153. Mecklin M, Paassilta M, Kainulainen H, Korppi M. Emergency treatment of obstructive bronchitis: change from nebulizers to metered dose inhalers with spacers. *Acta Paediatr*. 2011;100(9):1226-1229.
154. Colacone A, Wolkove N, Stern E, Afilalo M, Rosenthal TM, Kreisman H. Continuous nebulization of albuterol (salbutamol) in acute asthma. *Chest*. 1990;97:693.
155. Portnoy J, Aggarwal J. Continuous terbutaline nebulization for the treatment of severe exacerbations of asthma in children. *Ann Allergy*. 1988;60(4):368-371.

156. Amado M, OPortnoy J. A comparison of low and high doses of continuously nebulized terbutaline for treatment of severe exacerbations of asthma [abstract]. *Ann Allergy*. 1988;60:165.
157. Rubin BK, Albers GM. Use of anticholinergic bronchodilation in children. *Am J Med*. 1996;100(1A):49S-53S.
158. Zorc JJ, Pusic MV, Ogborn CJ, Lebet R, Duggan AK. Ipratropium bromide added to asthma treatment in the pediatric emergency department. *Pediatrics*. 1999;103(4 Pt 1): 748-752.
159. Lanes SF, Garrett JE, Wentworth CE, Fitzgerald JM, Karpel JP. The effect of adding ipratropium bromide to salbutamol in the treatment of acute asthma: a pooled analysis of three trials. *Chest*. 1998;114(2):365-372.
160. Lin RY, Pesola GR, Bakalchuk L. Superiority of ipratropium plus albuterol over albuterol alone in the emergency department management of adult asthma: a randomized clinical trial. *Ann Emerg Med*. 1998;31(2):208-213.
161. Qureshi F, Pestian J, Davis P, Zaritsky A. Effect of nebulized ipratropium on the hospitalization rates of children with asthma. *N Engl J Med*. 1998;339(15):1030-1035.
162. Schuh S, Johnson DW, Callahan S, Canny G, Levison H. Efficacy of frequent nebulized ipratropium bromide added to frequent high-dose albuterol therapy in severe childhood asthma. *J Pediatr*. 1995;126(4):639-645.
163. White CC, Crotwell DN, Shen S, et al. Bronchodilator delivery during simulated pediatric noninvasive ventilation. *Respir Care*. 2013;58(9):1459-1466.
164. Fink J, Tobin M, Dhand R. Bronchodilator therapy in mechanically ventilated patients. *Respir Care*. 1999;44(1):53-69.
165. Fink JB, Dhand R, Grychowski J, Fahey PJ, Tobin MJ. Reconciling in vitro and in vivo measurements of aerosol delivery from a metered-dose inhaler during mechanical ventilation and defining efficiency-enhancing factors. *Am J Respir Crit Care Med*. 1999;159(1):63-68.
166. Fok TF, Al-Essa M, Monkman S, et al. Pulmonary deposition of salbutamol aerosol delivered by metered dose inhaler, jet nebulizer, and ultrasonic nebulizer in mechanically ventilated rabbits. *Pediatr Res*. 1997;42(5):721-727.
167. Hughes J, Saez J. Effects of nebulizer mode and position in a mechanical ventilator circuit on dose efficiency. *Respir Care*. 1987;32(12):1131-1135.
168. Harvey CJ, O'Doherty MJ, Page CJ, Thomas SH, Nunan TO, Treacher DF. Effect of a spacer on pulmonary aerosol deposition from a jet nebulizer during mechanical ventilation. *Thorax*. 1995;50(1):50-53.
169. Ari A, Areabi H, Fink JB. Evaluation of position of aerosol device in two different ventilator circuits during mechanical ventilation. *Respir Care*. 2010;55(7):837-844.
170. Ari A, Atalay OT, Harwood R, Sheard MM, Aljamhan EA, Fink JB. Influence of nebulizer type, position, and bias flow on aerosol drug delivery in simulated pediatric and adult lung models during mechanical ventilation. *Respir Care*. 2010;55(7):845-851.
171. Rau J, Harwood RJ, Groff JL. Evaluation of a reservoir device for metered-dose bronchodilator delivery to intubated adults: an in-vitro study. *Chest*. 1992;102(3):924-930.
172. Bishop MJ, Larson RP, Buschman DL. Metered dose inhaler aerosol characteristics are affected by the endotracheal tube actuator/adapter used. *Anesthesiology*. 1990;73(6):1263-1265.
173. Fuller HD, Dolovich MB, Turpie FH, Newhouse MT. Efficiency of bronchodilator aerosol delivery to the lungs from the metered dose inhaler in mechanically ventilated patients. A study comparing four different actuator devices. *Chest*. 1994;105(1):214-218.
174. Manthous CA, Hall JB, Schmidt GA, Wood LD. Metered-dose inhaler versus nebulized salbutamol in mechanically ventilated patients. *Am Rev Resp Dis*. 1993;148(6):1567-1570.
175. O'Riordan TG, Greco MJ, Perry RJ, Smaldone GC. Nebulizer function during mechanical ventilation. *Am Rev Respir Dis*. 1992;145(5):1117-1122.
176. Garner SS, Wiest DB, Bradley JW. Albuterol delivery by metered-dose inhaler with a pediatric mechanical ventilatory circuit model. *Pharmacotherapy*. 1994;14(2):210-214.
177. Fink JB, Dhand R, Duarte AG, Jenne JW, Tobin MJ. Aerosol delivery from a metered-dose inhaler during mechanical ventilation. An in-vitro model. *Am J Respir Crit Care Med*. 1996;154(2):382-387.
178. Svartengren M, Anderson M, Philipson K, Camner P. Human lung deposition of particles suspended in air or in helium/oxygen mixture. *Exp Lung Res*. 1989;15(4):575-585.
179. Anderson M, Svartengren M, Bylin G, Philipson K, Cammer P. Deposition in asthmatics of particles inhaled in air or in helium-oxygen. *Am Rev Respir Dis*. 1993;147(3): 524-528.
180. Moren F, Anderson J. Fraction of dose exhaled after administration of pressurized inhalation aerosols. *Int J Pharm*. 1980;6:295-300.
181. O'Riordan TG, Palmer LB, Smaldone GC. Aerosol deposition in mechanically ventilated patients. Optimizing nebulizer delivery. *Am J Respir Crit Care Med*. January 1994; 149(1):214-219.
182. Thomas SH, O'Doherty MJ, Fidler HM, Page CJ, Treacher DF, Nunan TO. Pulmonary deposition of a nebulised aerosol during mechanical ventilation. *Thorax*. 1993;48(2):154-159.
183. Dubus JC, Vecellio L, De Monte M, et al. Aerosol deposition in neonatal ventilation. *Pediatr Res*. 2005;58(1):10-14.
184. Fink JB. Aerosol delivery to ventilated infant and pediatric patients. *Respir Care*. 2004;49(6):653-665.
185. Dhand R, Duarte AG, Jubran A, et al. Dose response to bronchodilator delivered by metered-dose inhaler in ventilator supported patients. *Am J Respir Crit Care Med*. 1996; 154(2):388-393.
186. DiBlasi RM, Crotwell DN, Shen S, Zheng J, Fink JB, Yung D. Iloprost drug delivery during infant conventional and high-frequency oscillatory ventilation. *Pulm Circ*. 2016;6(1): 63-69.
187. Fang TP, Lin HL, Chiu SH, et al. Aerosol delivery using jet nebulizer and vibrating mesh nebulizer during high frequency oscillatory ventilation: an in vitro comparison. *J Aerosol Medicine*. 2016;29(5):447-453.
188. Willis LD, Berlinski A. Survey of aerosol delivery techniques to spontaneously breathing tracheostomized children. *Respir Care*. 2012;57(8):1234-1241.
189. Berlinski A, Chavez A. Albuterol delivery via metered dose inhaler in a spontaneously breathing pediatric tracheostomy model. *Pediatr Pulmonol*. 2013;48(10):1026-1034.
190. Cooper B, Berlinski A. Albuterol Delivery via facial and tracheostomy route in a model of a spontaneously breathing child. *Respir Care*. 2015;60(12):1749-1758.
191. Berlinski A, Cooper B. Oronasal and Tracheostomy Delivery of Soft Mist and Pressurized Metered-Dose Inhalers With Valved Holding Chamber. *Respir Care*. 2016;61(7):913-919.
192. Berlinski A. Effect of mask dead space and occlusion of mask holes on delivery of nebulized albuterol. *Respir Care*. 2014;59(8):1228-1232.
193. Alhamad BR, Fink JB, Harwood RJ, Sheard MM, Ari A. Effect of Aerosol Devices and Administration Techniques on Drug Delivery in a Simulated Spontaneously Breathing Pediatric Tracheostomy Model. *Respir Care*. 2015;60(7):1026-1032.
194. Piccuito CM, Hess DR. Albuterol delivery via tracheostomy tube. *Respir Care*. 2005;50(8):1071-1076.
195. Ari A, Harwood R, Sheard M, Alquaimi MM, Alhamad B, Fink JB. Quantifying Aerosol delivery in simulated spontaneously breathing patients with tracheostomy using different humidification systems with or without exhaled humidity. *Respir Care*. 2016;61(5):600-606.

196. Berlinski A, Ari A, Davies P, et al. Workshop report: aerosol delivery to spontaneously breathing tracheostomized patients. *J Aerosol Med Pulm Drug Deliv*. 2017;30(4):207-222.
197. Ari A. Aerosol drug delivery in critical pulmonary care. *Respir Care*. 2015;60(6):858-879.
198. Ari A, Fink JB. Inhalation therapy in patients with tracheostomy: A guide to clinicians. *Expert Rev Respir Med*. 2017;11(3):201-208.
199. Dolovich MB, Ahrens RC, Hess DR, et al. Device selection and outcomes of aerosol therapy: evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. *Chest*. 2005;127(1):335-371.
200. Rubin BK. Emerging therapies for cystic fibrosis lung disease. *Chest*. 1999;154:388.
201. Ramsey BW, Astley SJ, Aitken ML, et al. Efficacy and safety of short-term administration of aerosolized recombinant human deoxyribonuclease in patients with cystic fibrosis. *Am Rev Respir Dis*. 1993;148(1):145-151.
202. Sexauer WP, Fiel SB. Aerosolized antibiotics in cystic fibrosis. *Semin Respir Crit Care Med*. 2003;24:717.
203. Ryan G, Mukhopadhyay S, Singh M. Nebulised antipseudomonal antibiotics for cystic fibrosis. *Cochrane Database Syst Rev*. 2003;(3):CD001021.
204. Rubin BK, van der Schans C. *Lung Biology in Health and Disease*. Boca Raton, Fla: CRC Press/Taylor & Francis; 2004.
205. McCoy K, Hamilton S, Johnson C. Effects of 12-week administration of dornase alfa in patients with advanced cystic fibrosis lung disease. *Chest*. 1996;110:889.
206. Wilmott RW, Amin RS, Colin AA, et al. Aerosolized recombinant human DNase in hospitalized cystic fibrosis patients with acute pulmonary exacerbations. *Am J Respir Crit Care Med*. 1996;153(6 Pt 1):1914-1917.
207. O'Donnell AE, Barker AF, Ilowite JS, Fick RB. Treatment of idiopathic bronchiectasis with aerosolized recombinant human DNase I. rhDNase Study Group. *Chest*. 1998;113(5):1329-1334.
208. Henke MO, Shah SA, Rubin BK. The role of airway secretions in COPD–clinical applications. *COPD*. 2005;2(3):377-390.
209. Henke MO, Renner A, Huber RM, Seeds MC, Rubin BK. MUC5AC and MUC5B mucins are decreased in cystic fibrosis airway secretions. *Am J Respir Cell Mol Biol*. 2004;31(1):86-91.
210. App EM, Baran D, Dab I, et al. Dose-finding and 24-h monitoring for efficacy and safety of aerosolized Nacystelyn in cystic fibrosis. *Eur Respir J*. 2002;19(2):294-302.
211. Feng W, Garrett H, Speert DP, King M. Improved clearability of cystic fibrosis sputum with dextran treatment in vitro. *Am J Respir Crit Care Med*. 1998;157(3 Pt 1):710-714.
212. Deterding R, Retsch-Bogart G, Milgram L, et al. Safety and tolerability of denufosol tetrasodium inhalation solution, a novel P2Y2 receptor agonist: results of a phase 1/phase 2 multicenter study in mild to moderate cystic fibrosis. *Pediatr Pulmonol*. 2005;39(4):339-348.
213. Griese M, Essl R, Schmidt R, et al. Sequential analysis of surfactant, lung function and inflammation in cystic fibrosis patients. *Respir Res*. 2005;6:133.
214. Anzueto A, Jubran A, Ohar JA, et al. Effects of aerosolized surfactant in patients with stable chronic bronchitis: a prospective randomized controlled trial. *JAMA*. 1997;278(17):1426-1431.
215. Eng PA, Morton J, Douglass JA, Riedler J, Wilson J, Robertson CF. Short-term efficacy of ultrasonically nebulized hypertonic saline in cystic fibrosis. *Pediatr Pulmonol*. 1996;21(2):77-83.
216. Daviskas E, Anderson SD, Gomes K, et al. Inhaled mannitol for the treatment of mucociliary dysfunction in patients with bronchiectasis: effect on lung function, health status and sputum. *Respirology*. 2005;10(1):46-56.
217. Wark PA, McDonald V. Nebulised hypertonic saline for cystic fibrosis. *Cochrane Database Syst Rev*. 2003;2(1):CD001506.
218. Wills P, Greenstone M. Inhaled hyperosmolar agents for bronchiectasis. *Cochrane Database Syst Rev*. 2006;(2):CD002996.
219. Suri R, Metcalfe C, Lees B, et al. Comparison of hypertonic saline and alternate-day or daily recombinant human deoxyribonuclease in children with cystic fibrosis: a randomised trial. *Lancet*. 2001;358(9290):1316-1321.
220. Knowles MR, Hohneker KW, Zhou Z, et al. A controlled study of adenoviral-vector-mediated gene transfer in the nasal epithelium of patients with cystic fibrosis. *N Engl J Med*. 1995;333(13):823-831.
221. Rochat T, Morris MA. Gene therapy for cystic fibrosis by means of aerosol. *J Aerosol Med*. 2002;15(2):229-235.
222. Moss RB, Rodman D, Spencer LT, et al. Repeated adeno-associated virus serotype 2 aerosol-mediated cystic fibrosis transmembrane regulator gene transfer to the lungs of patients with cystic fibrosis: a multicenter, double-blind, placebo-controlled trial. *Chest*. 2004;125(2):509-521.
223. Eastman SJ, Scheule RK. Cationic lipid:pDNA complexes for the treatment of cystic fibrosis. *Curr Opin Mol Ther*. 1999;1(2):186-196.
224. Flotte TR, Carter BJ. In vivo gene therapy with adeno-associated virus vectors for cystic fibrosis. *Adv Pharmacol*. 1997;40:85-101.
225. Mallet JP, Diot P, Lemarié E. [Inhalation route for administration of systemic drugs]. *Rev Mal Respir*. 1997;14(4):257-267.
226. Heinemann L, Traut T, Heise T. Time-action profile of inhaled insulin. *Diabet Med*. 1997;14(1):63-72.
227. Jendle JH, Karlberg BE. Intrapulmonary administration of insulin to healthy volunteers. *J Intern Med*. 1996;240(2):93-98.
228. Laube BL, Benedict GW, Dobs AS. The lung as an alternative route of delivery for insulin in controlling postprandial glucose levels in patients with diabetes. *Chest*. 1998;114(6):1734-1739.
229. DeFronzo RA, Bergenstal RM, Cefalu WT, et al. Efficacy of inhaled insulin in patients with type 2 diabetes not controlled with diet and exercise: a 12-week, randomized, comparative trial. *Diabetes Care*. 2005;28(8):1922-1928.
230. Dawson M, Wirtz D, Hanes J. Enhanced viscoelasticity of human cystic fibrotic sputum correlates with increasing microheterogeneity in particle transport. *J Biol Chem*. 2003;278(50):50393-50401.
231. Rosenstock J, Zinman B, Murphy LJ, et al. Inhaled insulin improves glycemic control when substituted for or added to oral combination therapy in type 2 diabetes: a randomized, controlled trial. *Ann Intern Med*. 2005;143(8):549-558.
232. Laube BL. The expanding role of aerosols in systemic drug delivery, gene therapy, and vaccination. *Respir Care*. 2005;50(9):1161-1176.
233. Edwards DA, Dunbar C. Bioengineering of therapeutic aerosols. *Annu Rev Biomed Eng*. 2002;4:93-107.
234. Rubin BK. Tracheomalacia as a cause of respiratory compromise in infants. *Clin Pulm Med*. 1999;6:195.
235. Fink JB, Ari A. Humidity and aerosol therapy. In: *Mosby's Respiratory Care Equipment*. St. Louis, Missouri: Mosby-Elsevier Inc; 2013.

12 Airway Clearance Techniques and Hyperinflation Therapy

Brian K. Walsh

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. Explain the indications and risks of airway clearance techniques.
2. Apply the various techniques of airway clearance.
3. Understand how to avoid complications associated with airway clearance techniques.
4. Understand the role of hyperinflation therapy and its relationship to proper airway clearance.

Key Terms

airway clearance technique (ACT)
cough
hyperinflation therapy
positive expiratory airway pressure (PEP) therapy

Traditional **airway clearance techniques (ACTs)** are designed to remove secretions from the lungs and include postural drainage, percussion, chest wall vibration, and coughing. Newer techniques considered part of ACTs are maneuvers to improve the efficacy of cough, such as the following:

- The forced expiration technique (FET)
- **Positive expiratory airway pressure (PEP)** therapy
- High-frequency chest compression (HFCC)
- Insufflator–exsufflator (e.g., Cough Assist)
- High-frequency chest wall oscillation with Cough Assist
- Intrapulmonary percussive ventilation
- Specialized breathing techniques, such as autogenic drainage (AD)

Because all these techniques share the same goal—removal of bronchial secretions—the term *bronchial*

drainage is often employed to describe them collectively. This term may be preferable to *ACT* because it highlights the aims, rather than the means, of treatment. This chapter is devoted to describing and analyzing bronchial drainage techniques and how they should be applied to an infant or pediatric patient with lung disease or respiratory impairment.

HISTORY AND CURRENT STATUS OF AIRWAY CLEARANCE TECHNIQUES

Postural drainage was used as early as 1901 in the treatment of bronchiectasis.[1] In the 1960s and 1970s, the use of ACTs increased.[2] It was introduced in many US hospitals concurrent with a wave of mounting criticism of intermittent positive-pressure breathing (IPPB) therapy. Many institutions began replacing the routine use of IPPB with the routine use of ACTs. Beginning in the late 1970s, experts in the field began to point to the lack of evidence to support the routine use of ACTs in pulmonary disorders such as pneumonia and chronic bronchitis.[3] However, despite a steady stream of criticism, the use of ACTs appears to have increased dramatically.[4-12] The clinician must evaluate the possible usefulness of airway clearance in relation to low-level evidence and intervene only when the benefit clearly outweighs the risk.

Traditional airway maintenance, airway clearance therapy, and principles of their application are similar for neonates, children, and adults. In pediatric patients, distinct differences in physiology and pathology limit the application of adult-derived airway clearance and maintenance modalities. One of the major obstacles in device research, particularly airway clearance or maintenance modality, is proper blinding and equipoise.

The lack of scientific rigor, among other issues, has led to a deficiency of high-level evidence. Yet airway maintenance and clearance therapy take a great deal of the clinician's time. Many clinicians feel that if the patient is producing secretions, they should do something about it. Although most studies have focused on the primary outcome of sputum production, it is not clear whether sputum volume is an appropriate indication or outcome of airway clearance. There is a perception that airway clearance may not help, but it will not hurt either. This attitude can lead to inappropriate orders and inadvertent complications. Many ACTs are not benign, particularly if they are not used as intended.

PHYSIOLOGIC AND PATHOPHYSIOLOGIC CONSIDERATIONS

Airway Clearance Mechanisms

Ciliary movement and **cough** are the two primary airway clearance mechanisms. Expulsion of mucus requires turbulent flow from the peripheral airway toward the trachea. The airway undergoes compression that creates moving choke points or stenoses that catch mucus and facilitate expiratory airflow, propelling the mucus downstream[13] (Figure 12-1). This mechanism requires narrowing of the airway, but complete obstruction will inhibit this transfer. Children, particularly infants, are prone to complete airway obstruction that can lead to atelectasis and the elimination of expiratory flow. This result is particularly true for those with heterotaxy.

Infants and children have high chest wall compliance because they have less musculature, ossification, and stiffness of their rib cage than adults.[14] They also have lower pulmonary compliance and greater elasticity than adults, leading to a lower functional residual capacity (FRC) compared with their total lung capacity, which promotes premature airway closure.[15] The bronchus will collapse as pleural pressure exceeds intralumen airway pressure. This collapse is prevented by opposing forces that make up the rigidity of the airway structure, specifically smooth muscle in the peripheral airways and cartilage in the central airways. In infants, especially premature infants, the airway cartilage is less developed and more compliant than that of older children and adults.[16] This increased yield leads to greater airway collapse at lower changes in pleural and airway pressure. Common neonatal disease states reduce pulmonary compliance and produce bronchial wall edema, enhancing the risk of airway collapse. The clinical picture of airway collapse often prompts ACT or bronchodilator orders. This airway collapse can be further exaggerated when

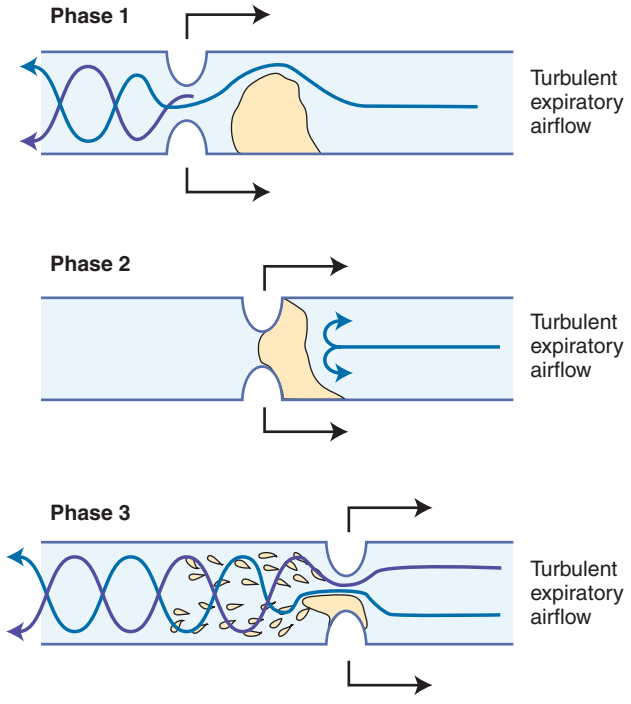


FIGURE 12-1 Compression of the airways creates moving choke points or stenoses that facilitate mucus expulsion. Narrowing of the airway is required, but complete obstruction will inhibit this transfer.

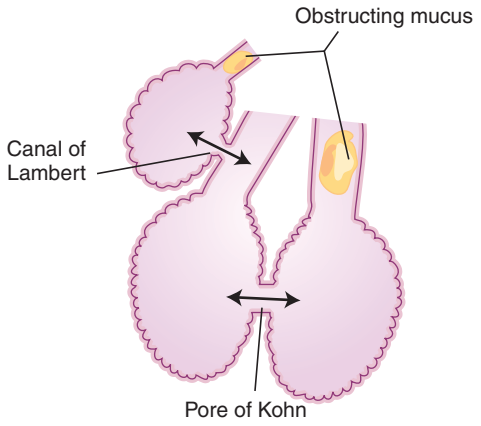


FIGURE 12-2 The location of collateral airways such as the interalveolar pores of Kohn and bronchiolar-alveolar canals of Lambert.

chest percussion is performed or bronchodilators administered. Bronchodilators cause a decrease in smooth muscle tone, leading to increased collapsibility. This is why continuous positive airway pressure (CPAP) or PEP can be therapeutic in patients with airway collapse because it tends to improve their FRC and establishes a fundamental airway clearance mechanism of producing air behind the secretions. Efforts to increase FRC can be valuable tools in the airway clearance arsenal.

Airway resistance is disproportionately high in children at baseline. Small changes in airway diameter such as that caused by edema, secretions, foreign bodies, or inflammation can lead to drastic changes in resistance. This decrease in airflow limits the child's ability to expel secretions and may contribute to the work of breathing. Furthermore, the upper airway, particularly the nose, can contribute up to 50% of the airway resistance, which is only compounded by nasal congestion.[17]

Interalveolar pores of Kohn and bronchiolar-alveolar canals of Lambert are compensatory mechanisms that contribute to the aeration of gas exchange units distal to obstructed airways in older children and adults (Figure 12-2). However, these are missing in infants, in whom these collaterals are not well developed. This can hinder airway clearance and lead to large areas of atelectasis.

TRADITIONAL AIRWAY CLEARANCE TECHNIQUES

Traditional ACT has four components: (1) postural drainage, (2) percussion, (3) vibration of the chest wall, and (4) coughing.

POSTURAL DRAINAGE

Postural drainage attempts to use gravity to move secretions from peripheral airways to the larger bronchi, from which they are more easily expectorated. The patient is placed in various positions, each designed to drain specific segments of the lung, and may be supported by rolled towels, blankets, or pillows. Figures 12-3 and 12-4 illustrate postural drainage positions used in infants and children.[13] Other versions incorporating minor variations have also been published. [2,19,20] Postural drainage can be performed with or without percussion or vibration. When accompanied by percussion or vibration, each position is maintained for 1 to 5 minutes, depending on the severity of the patient's condition. When percussion or vibration is omitted, longer periods of simple postural drainage can be performed.

PERCUSSION

Percussion is believed to loosen secretions from the bronchial walls. While the patient is in the various postural drainage positions, the clinician percusses the chest wall using a cupped hand (Figure 12-5). The areas to be percussed are illustrated in Figures 12-3 and 12-4. Clinicians should not percuss over bony prominences; over the spine, sternum, abdomen, last few ribs, sutured areas, drainage tubes, kidneys, or liver; or below the rib cage. The ideal frequency of percussion is unknown; however, some reports recommend a frequency of 5 to 6 Hz (300-360 blows per minute), whereas others recommend slow, rhythmic clapping.[19,21] Several devices can be used for percussion, including soft face masks and commercially designed devices, such as "palm cups" and mechanical percussors (Figure 12-6). Infants and children may have percussion performed in the lap of the clinician. However, if the patient is mechanically ventilated or has multiple tubes and intravenous lines in place, it may be preferable to perform therapy with the patient in the bed. Catheters, tubes, and indwelling lines are easily dislodged in infants and young children, and appropriate care must be taken.

POSTURAL DRAINAGE AND PERCUSSION

Many investigations have been conducted to determine the relative importance of percussion, vibration, and postural drainage. In a study designed to determine the contribution of these maneuvers to clearance of mucus, there was no demonstration of improvement in clearance of mucus from the lung when percussion, vibration, or breathing exercises were added to postural drainage.[22] These investigators also showed that FET was superior to simple coughing and when combined with postural drainage was the most effective form of treatment.[23] Other studies[24-26] have reported the following:

1. Percussion without postural drainage or cough produced minimal change in the clearance of mucus.
2. When compared with simple postural drainage, chest percussion actually reduced the amount of sputum mobilized.
3. Manual self-percussion did not increase the amount of sputum expectorated compared with simple postural drainage in a group of patients with cystic fibrosis (CF).

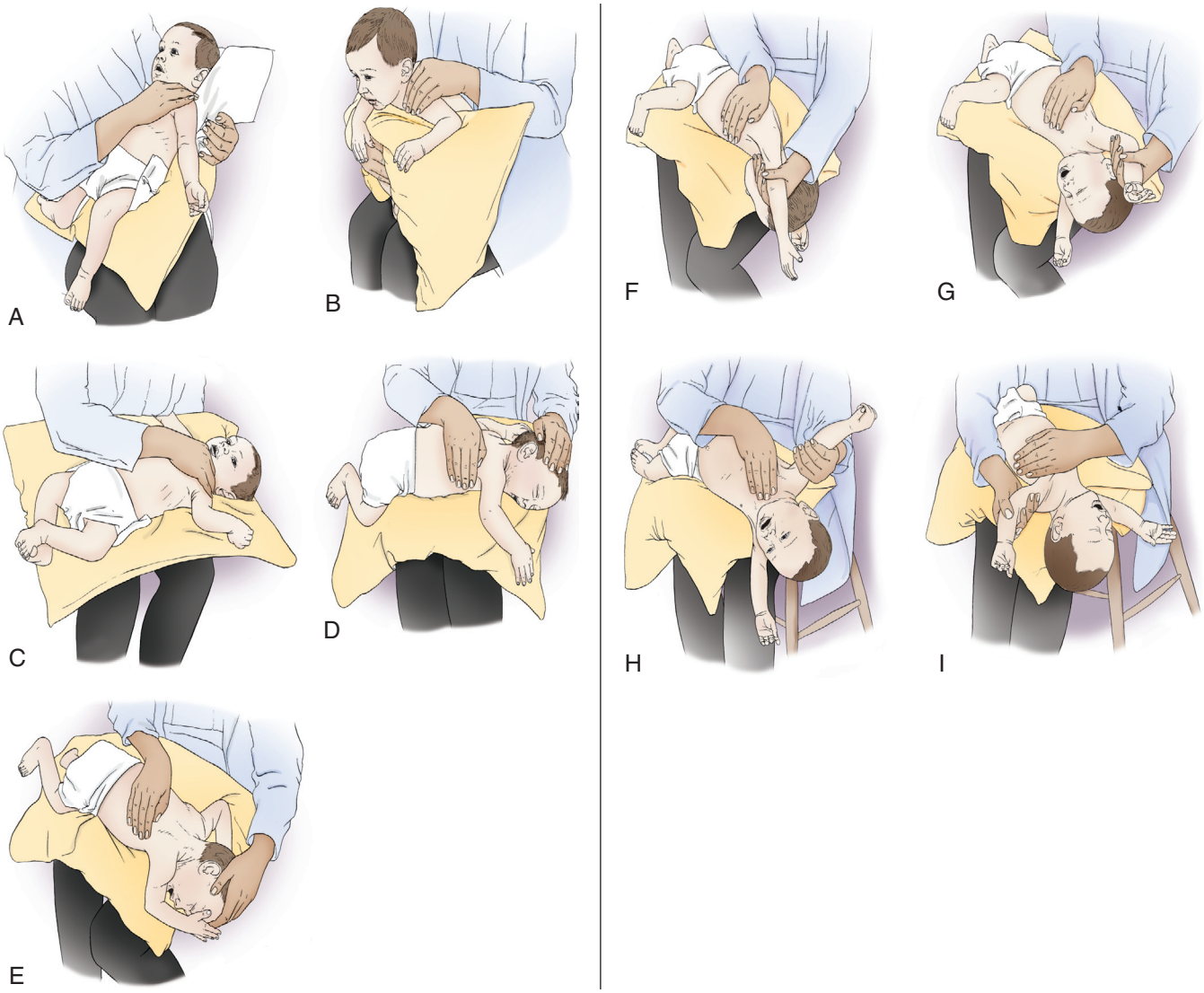


FIGURE 12-3 Postural drainage positions for infants and younger children. **A,** Apical segment of the right upper lobe and apical subsegment of the apical–posterior segment of the left upper lobe. **B,** Posterior segment of the right upper lobe and posterior subsegment of the apical–posterior segment of the left upper lobe. **C,** Anterior segments of right and left upper lobes. **D,** Superior segments of both lower lobes. **E,** Posterior basal segments of both lower lobes. Postural drainage positions for infants. **F,** Lateral basal segment of the right lower lobe. Lateral basal segment of the left lower lobe is drained in a similar fashion but with the right side down. **G,** Anterior basal segment of the right lower lobe. The segments on the left side are drained in a similar fashion but with the right side down. **H,** Right middle lobe. **I,** Left lingular segment of lower lobe. (From Waring WW: Diagnostic and therapeutic procedures. In Chernick V, editor: *Kendig's disorders of the respiratory tract in children,* ed 5, Philadelphia, 1990, WB Saunders.)

VIBRATION OF THE CHEST WALL

Vibrations represent an additional method of transmitting energy through the chest wall to loosen or move bronchial secretions. Unlike in percussion, the clinician's hand does not lose contact with the chest wall during the procedure. Vibrations are performed by placing both hands (one over the other) over the area to be vibrated and tensing and contracting the shoulder and arm muscles while the patient exhales. To prolong exhalation, the patient may be asked to breathe through pursed lips or make a "hissing" sound. As with percussion, the ideal frequency is unknown, although some recommend 10 to 15 Hz.[27]

It is unclear how well clinicians are able to perform vibrations at this frequency. Several mechanical vibrators are commercially available. Some models of mechanical percussors or vibrators are appropriate only for newborns or premature infants, whereas other models are appropriate for larger children. When evaluating such devices, the clinician should consider whether the appearance and sound of the device will be frightening and whether the amount of force is appropriate for the size of the patient. All percussion and vibration devices should be cleaned after each use and between patients if not for single-patient use.

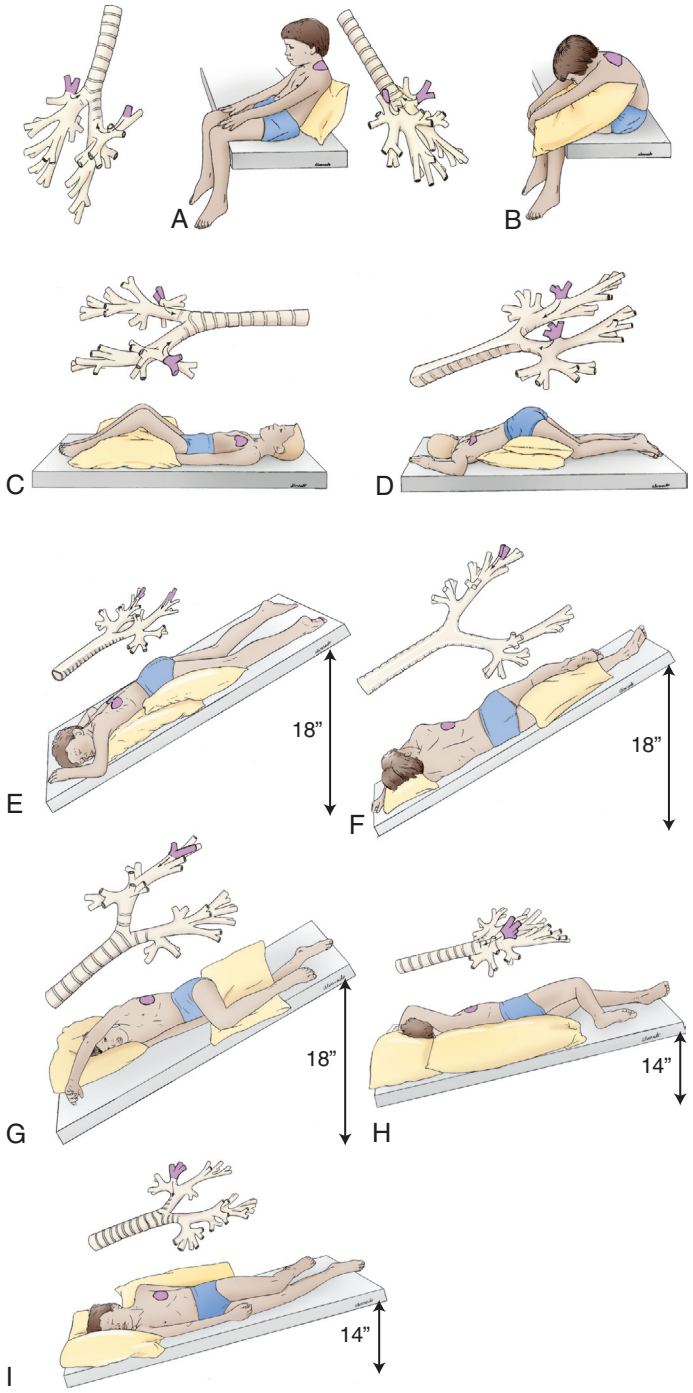


FIGURE 12-4 Postural drainage positions for a child or adult. The model of the tracheobronchial tree next to or above the child illustrates the segmental bronchi being drained. The shaded area on the child's chest illustrates the area to be percussed or vibrated. **A,** Apical segment of the right upper lobe and apical subsegment of the apical-posterior segment of the left upper lobe (area between the clavicle and top of the scapula). **B,** Posterior segment of the right upper lobe and posterior subsegment of the apical-posterior segment of the left upper lobe (area over the upper back). **C,** Anterior segments of the right and left upper lobes (area between the clavicle and nipple). **D,** Superior segments of both lower lobes (area over the middle of the back at the tip of the scapula, beside the spine). **E,** Posterior basal segments of both lower lobes (area over the lower rib cage, beside the spine). **F,** Lateral basal segment of the right lower lobe. The segment on the left is drained in a similar fashion but with the right side down (area over the middle portion of the rib cage). **G,** Anterior basal segment of the left lower lobe. The segment on the right is drained in a similar fashion but with the left side down (area over lower ribs, below the armpit). **H,** Right middle lobe (area over right nipple; below the breast in developing females). **I,** Left lingular segment of the lower lobe (area over the left nipple; below the breast in developing females). (From Waring WW: Diagnostic and therapeutic procedures. In Chernick V, editor: *Kendig's disorders of the respiratory tract in children,* ed 5, Philadelphia, 1990, WB Saunders.)

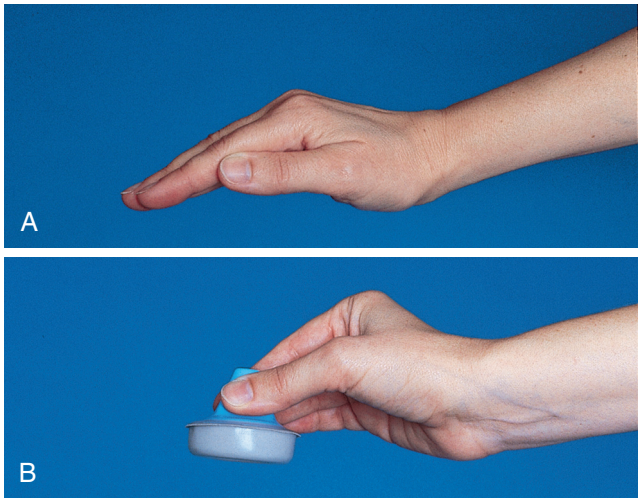


FIGURE 12-5 **A,** Cupped hand position for percussion. **B,** Device for infant percussion. (From Hockenberry M, Wilson D: *Wong's nursing care of infants and children*, ed 10, St. Louis, 2015, Mosby.)

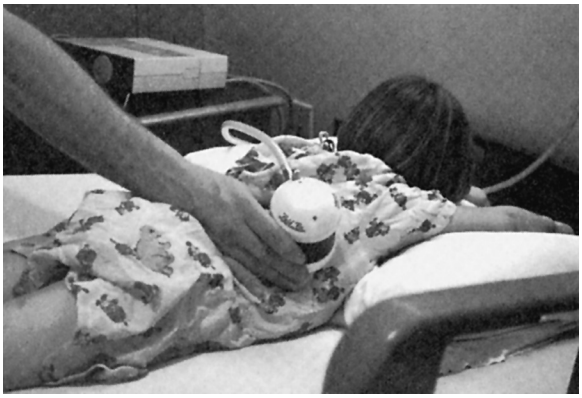


FIGURE 12-6 Percussion being performed on a child with a pneumatic percussor.

AIRWAY CLEARANCE THERAPY

Collapse of the right upper lobe after extubation is a common complication in premature infants, and routine treatment of premature infants after extubation is common.[28,29] However, most treatments are not necessary, because little respiratory compromise is seen with a single-lobe collapse. Treatment may be given to the right upper lobe only and need not be prolonged, nor does it require the routine use of percussion. A treatment length of 5 minutes is sufficient, and vibration is applied to the right upper lobe in one of the three standard drainage positions every 4 to 6 hours for 24 to 48 hours.[29] The most beneficial treatment is likely frequent position changes and weaning of sedatives to return the patient's natural sigh, movement, and cough.

Patients with esophageal atresia and tracheoesophageal fistula often require assistance with mobilizing thick secretions. Aspiration of oropharyngeal secretions, leading to atelectasis or pneumonia, is common. If surgical repair has been performed, deep endotracheal suctioning (beyond the tip of the endotracheal tube) is contraindicated, because the suction catheter may reopen the closed fistula. Likewise, nonintubated patients should rarely have the catheter advanced more than 7 cm, because this makes removal of secretions more difficult. On occasion, tracheal suction under direct vision with a laryngoscope is necessary. If the fistula has been closed, Trendelenburg (head-down) positioning may be used. This is especially helpful if the patient has difficulty clearing oral secretions by swallowing. These patients should not be routinely placed flat on their backs, because this promotes aspiration of oral secretions. If a thoracotomy has been performed to repair the defect, use of a small mechanical vibrator may be preferable to chest percussion.

The clinician must be careful to avoid excessive movement (extension or extreme turning) while treating an infant. Esophageal atresia is repaired by performing an anastomosis of the distal and proximal esophagus. Excessive head movement may result in its disruption. Many other patients in the neonatal intensive care unit require ACTs. Usually, such patients have been intubated for some time and have responded to prolonged intubation with excessive production of secretions.

BEHAVIORAL ISSUES

Without the key component of cooperation, airway clearance becomes much more difficult. The potential for harm during airway clearance modalities increases as transpulmonary pressure swings increase.[13] When forceful crying occurs during airway clearance, these swings create an environment suitable for lung damage. All efforts to decrease crying, such as facilitated tucking or modified ACT, should be incorporated. In modalities that administer pressure to aid airway clearance, less pressure should be administered to a noncooperative child. For older patients, a multidisciplinary approach can increase airway clearance quantity and quality by 50%.[30] This approach, introduced by Ernst et al., involves allowing for patient selection of airway clearance protocol, creating a reward system for the patient, and scheduling priority given to airway clearance.[30] When performing ACTs on young children, the clinician must make a special effort to secure the patient's confidence and cooperation. Spending a few moments to gain the child's trust is well worth the effort. Assigning the same clinician to treat the child as often as is practical may be useful in establishing a rapport. Likewise, allowing the child as much control over the situation as possible, such as deciding which lobes will be treated first, may increase the child's sense of control and reduce hospitalization-related anxiety. Having a parent available during therapy, especially when the child is unfamiliar with ACT, is useful as well.

ACTs may be extremely uncomfortable for postoperative patients, and routine use of ACTs in these patients may actually promote atelectasis. Some patients, however, suffer from excessive secretions or mucous plugging and atelectasis. Performing ACTs in these patients can be difficult. Adequate analgesia is essential, and attempts should be made to schedule ACT shortly after pain medication is administered. Coughing is also a considerable source of discomfort in pediatric patients postoperatively. Cough efficacy can be improved if the patient is taught to splint the wounds when coughing. Holding a pillow over the incision may also be useful in minimizing movement of the incision when coughing.

ADVERSE CONSEQUENCES

Several conditions common for full-term or preterm newborns suggest that these infants may be at risk for increased complications from ACT; therefore, modification of routine ACT procedures is advisable. Because newborns have high chest wall compliance, the loss of lung volume caused by chest wall compression (e.g., from percussion) may be greater in infants than in adults.[31] For this reason, some institutions routinely omit chest wall percussion in neonatal ACT treatments, opting instead to use small vibrators. Because an infant's chest wall is not as thick as an adult's and the infant's ribs are more cartilaginous, a gentler touch is required during therapy.[32] Hypoxemia has been reported after ACTs in newborns.[33-36] Handling infants, for whatever reason, often results in hypoxemia. It is therefore essential that oxygenation be monitored when performing ACT in infants.

Routine application of ACTs in preterm infants has been associated with an increased risk of intraventricular hemorrhage (IVH).[37] A preterm infant is unable to adequately regulate cerebral blood flow, and changes in blood pressure often lead to increased intracranial pressure and volume, with rupture of immature blood vessels. Trendelenburg positioning and chest wall percussion would seem likely to increase cerebral blood flow and reduce venous return, further increasing the risk of IVH. Therefore, these procedures should be used sparingly, if at all, in infants at risk. If possible, ACTs should be withheld from infants at high risk for IVH (i.e., very premature infants in the first few days of life).

Critically ill newborns are unable to adequately maintain body temperature and are therefore routinely placed in incubators or under radiant warmers. Caregiver interventions of any kind, including ACTs, interfere with maintaining temperature stability, especially for infants in closed incubators. Treatment time with these patients should be kept to a minimum, usually between 5 and 10 minutes. If a patient is in a temperature-regulated environment, special attention must be given to preventing heat loss during therapy.

A newborn's trachea and bronchi are especially vulnerable to damaging effects from endotracheal tubes and suction catheters. Consequences of deep endotracheal suctioning include the development of bronchial stenosis and granulomas. Avoiding deep endotracheal suctioning minimizes risks.[38] Therefore, when suctioning intubated infants after ACTs, the suction catheter should not be routinely advanced beyond the end of the endotracheal tube. If there is evidence of persistent secretion retention despite adequate suction of the endotracheal tube, the suction catheter can be carefully and slowly advanced 1 or 2 cm beyond the tip of the endotracheal tube.

Many infants in the neonatal intensive care unit are sensitive to handling. This is especially true of preterm infants and full-term infants with pulmonary hypertension, who may develop hypoxemia or bradycardia in response to excessive stimulation. Many clinicians believe that clustering as many caregiver interventions as possible can minimize the adverse consequences of handling, thereby leaving the infant undisturbed for longer periods. Minimizing excessive light and sound associated with therapy is also desirable.

COUGH

All ACT sessions should end with a period of deep breathing and coughing. Patients with minimal lung disease should be able to clear the lungs after one or two attempts. Those with severe lung disease or neuromuscular weakness may need more prolonged coughing periods or coughing assistance (e.g., tussive squeezes, insufflator–exsufflator, abdominal compression). Prolonged periods of unproductive coughing should be avoided because they may tire the patient. The clinician should emphasize effective, productive coughing. Infants may require nasopharyngeal suction to stimulate a cough, whereas patients with artificial airways may require endotracheal suctioning.

The following procedures are sometimes incorporated into ACT treatments, or used independently, with the aim of promoting bronchial drainage: (1) FET, (2) PEP therapy with Cough Assist, (3) AD, and (4) automatic high-frequency chest wall compression (HFCWC)/high-frequency chest wall oscillation (HFCWO).

FORCED EXPIRATION TECHNIQUE

FET is also known as "huff" coughing. This maneuver requires the patient to forcibly exhale, from middle to low lung volumes, with an open glottis. This is repeated several times, after which the patient coughs to remove any loosened mucus.[39] It requires extreme cooperation and cannot be performed on infants or young children. FET can be used alone

or in conjunction with other forms of therapy. It is designed to prevent dynamic airway collapse by preventing the explosive pressure changes associated with coughing.[8,39] Studies have documented that patients with long-standing lung disorders characterized by destruction or weakening of the bronchial wall, such as CF and bronchiectasis, have ineffective coughing secondary to dynamic airway compression while coughing.[40] The developers of this technique now use the term *active cycle of breathing* to refer to FET. They emphasize the importance of interspersing "huff" coughs with periods of deep, relaxed breathing. This helps prevent bronchospasm and ensures sufficient lung volume to promote an effective cough.

COUGHING AND FORCED EXPIRATION TECHNIQUE

Over the years, a number of investigators have demonstrated that the single most important component of ACT is vigorous coughing.[41-45] Simple postural drainage has been reported to improve secretion clearance, whereas the addition of percussion did not.[42] Several other studies in patients with CF and other chronic lung diseases likewise support the notion that vigorous coughing, especially when used in conjunction with FET, may be as effective as postural drainage and percussion.[43,44,46]

Many clinicians, however, are reluctant to abandon postural drainage, percussion, or vibration in favor of simple FET, especially in patients needing lifelong assistance with secretion removal, such as those with CF. A 3-year prospective study in children with CF demonstrated that conventional ACT, performed twice a day, was more effective than FET used at the same frequency.[47] Patients performing FET in this study had an average age of slightly younger than 12 years. In contrast, patients in studies that showed FET to be successful were older.[44,46] This suggests that forms of self-care may be more effective in adolescents than in younger children, who perhaps require more supervision. Likewise, a comparison of studies on the efficacy of exercise as pulmonary therapy in CF suggests that self-therapy is more effective in older patients.[48,49]

POSITIVE EXPIRATORY AIRWAY PRESSURE THERAPY

PEP therapy uses an expiratory resistor, coupled with the patient's active expiration, to generate positive airway pressure throughout expiration. This prevents dynamic airway collapse and improves clearance of mucus.[50] It is widely used in Europe, and increasingly in the United States, as an adjunct to or substitute for conventional ACTs in the treatment of CF or bronchiectasis, and to a lesser extent in postoperative patients. Various devices are available to serve as expiratory resistors: anything from a simple high-resistance 2.5 endotracheal tube (ETT) adapter attached to a mask or mouthpiece to a Flutter (Axcan Pharma, Mont-Saint-Hilaire, PQ, Canada), acapella (blue; Smiths Medical, Weston, MA), or Quake device (Thayer Medical, Tucson, AZ) that requires hand motion and breathing coordination. PEP therapy is essentially the same as the "blow bottles" that have been used to prevent postoperative atelectasis.[51] Both PEP therapy and FET are advocated as forms of simple self-treatment for patients with CF. PEP therapy is better tolerated by children than conventional IPPB.

Cough Assist

The insufflator–exsufflator, or Cough Assist, has been shown to be beneficial in patients with neuromuscular weakness by simply supporting their cough effort. This blower-driven device provides positive airflow and pressure to increase FRC and allow air distal to the mucus. The increase in FRC allows the weak muscles the best advantage possible to create a cough. Then it creates a negative flow and pressure to help simulate a cough.[52] Streigl et al. demonstrated in an infant lung model with a tracheostomy tube that an insufflation time of 1 second or more is required for the insufflator–exsufflator to achieve equilibration of alveolar pressure to insufflation pressure. They also discovered that longer exsufflation time does not significantly alter maximum expiratory flow rate.[52] Vienello et al.[53] showed that the insufflator–exsufflator in conjunction with traditional chest physiotherapy (CPT) may improve the management of airway secretions.

Manual rib cage compression. Manual rib cage compression (MRCC), sometimes called *tussive squeezes*, can be used to increase the expiratory flow rate and facilitate the expectoration of mucus. Although most studies have not shown a benefit,[54-57] a recent publication has brought to light that the procedure may be to blame.[58] For MRCC to be effective, the expiratory flow rates generated must be higher than the inspiratory flow rates. Daniel Marti and colleagues[58] were able to demonstrate in animals that hard and brief MRCC synchronized with an early expiratory phase was superior to soft and gradual rib cage compression applied late in the expiratory phase. If the goal is to mimic a cough for those who cannot cough for themselves, it must be similar. Coughs are violent bursts of flow that exceed inspiratory flow rates and are extremely effective in strong patients. The MRCC must be similar to be effective.

AUTOGENIC DRAINAGE

AD is a series of breathing exercises designed to mobilize secretions in patients with bronchiectasis or CF.[59-61] To loosen secretions from the smallest airways, the patient begins breathing in a slow, controlled manner, first at the expiratory reserve volume level. The volume

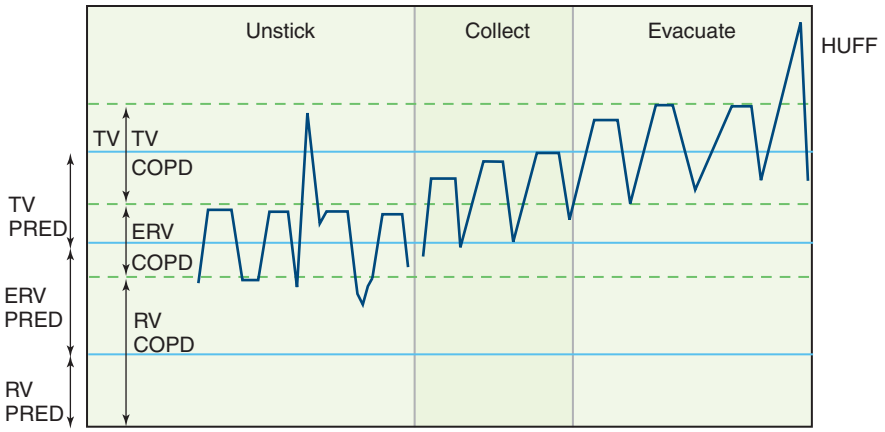


FIGURE 12-7 Graphic illustration of the depth of successive breaths by lung volume, using the autogenic drainage technique. *ERV,* Expiratory reserve volume; *HUFF,* huff maneuver; *PRED,* predicted; *RV,* residual volume; *TV,* tidal volume.

of ventilation is then increased, with the patient breathing in the normal tidal volume range but exhaling approximately halfway into the expiratory reserve volume. This moves secretions from the peripheral to the middle airways. Finally, the depth of inspiration is increased, with the patient inhaling maximally to total lung capacity and exhaling as before, about halfway into the expiratory reserve volume. Figure 12-7 graphically illustrates the autogenic drainage technique. Advocates of AD claim that its simplicity (no device or clinician is needed) and efficacy make it an ideal form of self-treatment for patients with CF.

POSITIVE EXPIRATORY AIRWAY PRESSURE THERAPY AND AUTOGENIC DRAINAGE

PEP therapy and AD have been shown to be highly effective. PEP therapy especially has been shown by a number of researchers to be beneficial in mobilizing secretions and preserving pulmonary function in patients with CF, and with FET it was marginally superior to simple FET and postural drainage.[62-69] Less information is available on AD, although a few reports indicate that it is highly effective and compliance is improved.[59-61,70]

FIGURE 12-8 Patient wearing an inflatable vest during high-frequency chest compression therapy in the hospital. (Used with permission of Electromed, Inc.)

HIGH-FREQUENCY CHEST WALL COMPRESSION

Commercially available devices have been developed that compress the entire chest wall at high frequencies by means of a snug-fitting inflatable vest connected to a high-performance air compressor (Figure 12-8). Intermittent chest wall compression produces brief periods of high expiratory airflow, which loosens and mobilizes mucus from bronchial walls.[71] The device is widely used in patients with CF.

HFCWC has also been evaluated in a long-term study. After a 22-month period of using HFCWC as the sole form of ACT, patients experienced a small but significant improvement in pulmonary function. In contrast, after a similar period on conventional manual ACT, pulmonary function declined somewhat.[71] HFCWC does not require the patient to perform postural drainage (known to be effective for sputum mobilization) and incorporates rapid percussion (generally demonstrated to be ineffective). What accounts for this seeming paradox? HFCWC compresses the chest at frequencies up to 22 Hz, which is much higher than can be generated by manual percussion (5-8 Hz). Furthermore, compression is usually applied only on exhalation. In the initial studies with HFCWC, the developers of this device measured expiratory volumes and flows and selected the frequencies that resulted in the highest values for

these variables. High expiratory airflow is maintained with HFCWC even at low lung volumes. The result is multiple brief periods of high expiratory air flow (or more precisely air velocity), similar to "huff" coughing or FET.[72]

High expiratory air velocity at low lung volumes produces the greatest air–mucus interaction and hence mucus mobilization. HFCWC does not directly dislodge mucus from the bronchial wall, as conventional percussion is thought to do, but instead simulates multiple coughs or FETs by generating high expiratory air velocities. Because the compressive phase of HFCWC is brief (as short as 0.02 second at a frequency of 22 Hz) and the glottis remains open during therapy, it is unlikely that dynamic airway collapse occurs, as happens with natural coughing in patients with bronchiectasis or CF.

Manual percussion bears little resemblance to HFCWC. In contrast to HFCWC, manual percussion is rarely, if ever, adjusted to produce optimal expiratory airflow to simulate cough or FET. In addition, it is given during inspiration as well as expiration, which may limit the deep breathing that is essential for producing high expiratory air velocities. Finally, manual percussion is applied only to a small portion of the chest wall at one time, which may be insufficient to generate adequate expiratory flows.

HIGH-FREQUENCY CHEST WALL OSCILLATION

HFCWO is similar to HFCWC, with the exception that the device provides positive pressure (compression/push) as well as negative pressure (pull) oscillations to the chest wall. It has not been well studied or compared to HFCWC, but likely has similar results.[53,73] Plioplys et al.[73] showed a reduction in pneumonias and respiratory-related hospitalizations in a study of seven quadriplegic cerebral palsy patients. This negative extrathoracic pressure swing may prove to be more beneficial in infants and toddlers, who are more prone to airway collapse.

EFFECTIVENESS OF TECHNIQUES

Proponents of conventional ACTs often describe the problem that they aim to treat as abnormal (excessive, thick, tenacious) secretions. Although this is partially correct, therapies that would seem to attack this problem directly have proved disappointing. Manual low-frequency chest percussion does not seem to jar mucus loose from the airways, nor does chest wall vibration. Of the therapies that do work—postural drainage, PEP, AD, FET, and the HFCWC system—all attempt to prevent or compensate for dynamic airway collapse. Postural drainage attempts to move mucus passively, by force of gravity, past the damaged, collapsible portions of the airways and toward less diseased, more rigid central airways. The remaining therapies attempt to prevent dynamic airway collapse while at the same time producing high expiratory air velocity at low lung volumes. This develops the shearing force required to mobilize sputum.[4] A novel explanation for the efficacy of simple postural drainage is suggested by Lannefors and Wollmer,[74] who demonstrated improved mucous clearance in the dependent lungs of patients undergoing postural drainage. For most patients, lung volumes and airway diameters are reduced in the dependent lung, but ventilation is increased. These factors result in increased air movement at high velocity, which increases turbulence and shearing in small airways and results in greater mobilization of mucus.

Deep breathing associated with vigorous exercise has also been shown to be an effective technique for mobilization of secretions in patients with CF.[75,76] To accommodate the increased ventilatory demands of exercise, rate and depth of breathing are increased and active exhalation may occur. Hence, vigorous exercise produces a ventilatory pattern that, like AD or FET, increases air velocity at low lung volumes and promotes sputum mobilization.

"Take a deep breath and you'll feel better." This is a sound piece of advice that was given long before the advent of incentive spirometry or IPPB. Taking a deep breath to total lung capacity, either by sighing or yawning, is a normal unconscious maneuver performed periodically to keep the lungs inflated and to avoid ventilation–perfusion mismatch.[77] When the breathing pattern becomes one of tidal ventilation without periodic maximal inflation, atelectasis ensues within a few hours.[78] Variations in the normal pattern of breathing may result in respiratory complications and an increase in postoperative morbidity and mortality. Changes in the breathing patterns of pediatric patients are most often caused by increased sedation, narcotics, pain, fluid overload, parenchymal lung damage, fear and anxiety, and abdominal or thoracic surgery. It has been estimated that 10% to 40% and even as many as 70% of patients undergoing abdominal or thoracic surgery experience postoperative pulmonary complications,[79,80] consisting of atelectasis, pneumonia, pulmonary embolism, and hypoxemia. These conditions are believed to be caused by reduced diaphragmatic movement (especially after upper abdominal surgery), changes in chest wall muscle tone, and secretion retention, all of which result in decreased lung volumes.[81]

The modalities and methods used to increase a child's lung volume can be classified as (1) voluntary, using the patient's own effort and initiative to sustain a deep breath (incentive spirometry); or (2) applied, providing the patient with a positive-pressure–generated breath to achieve an increase in lung volume (IPPB). In this chapter, these methods of lung volume expansion therapy are discussed as they relate to pediatric patients.

COMPLICATIONS OF AIRWAY CLEARANCE TECHNIQUES

Numerous studies have demonstrated that ACTs can be detrimental, especially for patients with little or no sputum production. Reported complications of ACTs range from rare reports of complete airway obstruction and respiratory arrest to bronchospasm and hypoxemia.

HYPOXEMIA

The most commonly cited adverse effect of ACT is hypoxemia. Several studies have reported hypoxemia in infants receiving ACT.[33-36] Hypoxemia has also been documented in studies of adolescent and adult patients receiving ACT and was reported to occur more often in patients with preexisting cardiovascular complications, with minimal sputum production, and when mucoid rather than mucopurulent secretions were present. It occurred in patients with good pulmonary function and when supplemental oxygen was being used.[82-87] Tachypnea and tachycardia may occur in patients who experience hypoxemia during ACT.

There may be a variety of reasons why ACT often causes hypoxemia. Among the proposed mechanisms are ventilation–perfusion abnormalities caused by postural changes, atelectasis, bronchospasm, alterations in cardiac output and oxygen consumption, and incomplete expectoration of mobilized secretions. In addition, each of the techniques may contribute to hypoxemia to differing degrees.

Position

Most studies of the effects of posture on oxygenation in adults would suggest that putting the diseased portion of the lung uppermost, as in postural drainage therapy, improves oxygenation.[88-90] This is a consequence of improved perfusion of the healthy dependent lung tissue at the expense of the diseased elevated lung segments. Thus, at least with localized unilateral lung disease, abnormalities secondary to postural changes are an unlikely explanation for ACT-associated hypoxemia in patients outside of infancy. Infants, however, have better oxygenation when the affected side is dependent (i.e., the good lung is up).[91] This may in part be the result of higher baseline pulmonary artery pressures, which would mitigate the effects of gravity on pulmonary blood flow. Hence, alterations in relationships as a direct result of postural changes are a possible explanation for CPT-associated hypoxemia in infants. Patients with generalized lung disease may respond differently to postural changes, however, and careful monitoring of oxygenation with position changes may be warranted. Positional changes during ACT may also result in hypotension or hypertension.

Percussion

Several studies report that chest percussion, rather than postural changes, is responsible for ACT-associated hypoxemia.[35,82-84] These studies suggest that chest percussion causes significant abnormalities, and unless counterbalanced by removal of a substantial quantity of mucus and improvement in ratios, the net change will be a deterioration in relationships and hypoxemia.

Atelectasis

Both human and animal studies have shown an increase in atelectasis when ACT was given.[81,92] Vigorous chest percussion has been noted to produce pressure swings in the chest of up to 30 cm H_2O. Such pressure generated by intermittent compression or percussion of the chest wall would seem sufficient to expel appreciable quantities of air from the lung, especially if chest wall compliance is high. Chest wall vibration, in contrast to percussion, has been associated with hypoxemia in some studies.[34-36,93,94] This reflects the fact that vibration may or may not be associated with chest wall compression, depending on the techniques or equipment used, whereas chest percussion invariably causes chest wall compression.

Bronchospasm

An additional explanation for the association of chest percussion with hypoxemia is the observation that chest percussion can cause bronchospasm in susceptible patients, especially when sputum production is minimal. Administering bronchodilators before therapy may be desirable, especially when ACTs are used for patients with reactive airway disease.

Increased Oxygen Consumption

Oxygen consumption is increased when performing an ACT.[95,96] If significant shunting is present, or if an increase in cardiac output is not produced, increased oxygen consumption can be manifested by decreased Pao_2 (partial pressure of oxygen in the arterial blood).

Gastroesophageal Reflux

Gastroesophageal reflux (GER) is a common cause of respiratory problems in infants and children, and ACT is often ordered for patients who have GER. One study found that in patients with GER, ACT resulted in a fivefold increase in reflux episodes compared with periods when ACT was not given.[97] This increase in GER was seen even though treatments were withheld up to 3.5 hours after the infant's last feeding. The study did not link the increase in reflux episodes to any particular aspect of ACT, such as head-down positioning. GER may cause severe esophagitis, bronchospasm, or pneumonia and has been linked to apnea and sudden infant death syndrome.[98] Therefore,

ACT should be given only when the benefits of treatment clearly outweigh the risks of aggravated GER. Although withholding treatment as long as possible after an infant's feeding is advisable, it clearly will not eliminate the risks involved.

AIRWAY OBSTRUCTION AND RESPIRATORY ARREST

Although ACTs can be an effective means of removing bronchial foreign bodies in children, it may also result in acute upper airway obstruction and death.[99] This is especially true when the foreign body consists of organic material, such as seeds or nuts, that may increase in size (secondary to water absorption) after a period of retention in the lung. Vomiting and aspiration may also occur during ACTs, especially if therapy is given soon after the patient has eaten. Therefore, at least 1 hour should be allowed after the last meal or feeding before beginning ACTs. Patients receiving continuous feedings through a gastric tube should have the feedings turned off at least 30 minutes before therapy. More time may be needed for patients with a history of vomiting or reflux. For patients in whom feedings cannot be interrupted, Trendelenburg (head-down) positioning should not be used.

INTRACRANIAL COMPLICATIONS

Studies in preterm infants have reported that certain positions of the infant's head may increase intracranial pressure and that routine application of ACTs, especially in the first few days of life, can significantly increase the risk of IVH.[37,100] ACT procedures in a child or adult with a recent head injury can also increase intracranial pressure.[101] Because of these concerns, many institutions do not place premature infants or patients with head injuries in the Trendelenburg position during ACT.

RIB FRACTURES AND BRUISING

Rib fractures have been reported as a complication of chest percussion in preterm infants with bronchopulmonary dysplasia.[102] The infants in this study suffered from rickets secondary to long-term parenteral nutrition. Improvement in nutritional therapy for preterm infants, however, should make rickets a rare finding in those with bronchopulmonary dysplasia. Infants with the rare condition osteogenesis imperfecta are also at high risk of rib fractures. Bruising may occur in some patients, especially in very small premature infants and children with vitamin K deficiency. Most patients are more comfortable if percussion or vibration is performed with the skin covered by a pajama top or t-shirt. If the patient is not wearing pajamas or clothing, a lightweight blanket or towel should be placed on the chest and back. Excessive padding, however, should be avoided.

AIRWAY TRAUMA

In all patients, extreme care must be taken to maintain a proper airway. Infants and children with artificial airways in place can be accidentally extubated during ACTs, especially if they are being mechanically ventilated. The ventilator tubing or endotracheal tube, or both, can be easily pulled during position changes, and extubation may result. When turning the patient, condensation in the ventilator tubing can be inadvertently drained into the patient's airway, which may result in bronchospasm and respiratory distress. Special attention should also be given to patients who receive ACTs during the first 24 hours after a tracheostomy, because hemorrhage may occur if therapy is given too vigorously.[32] Therefore, for patients in intensive care units or those with artificial airways in place, suction equipment as well as a manual resuscitator and mask should be readily available, preferably at the patient's bedside.

SELECTION OF PATIENTS FOR AIRWAY CLEARANCE TECHNIQUES

ACTs are ordered for many conditions, including acute respiratory infections, postoperative complications, CF, and asthma. Evidence is increasing, however, that ACTs are required for only a limited number of conditions, all of which are characterized by chronic excessive sputum production.

CONDITIONS IN WHICH AIRWAY CLEARANCE TECHNIQUES MAY NOT BE BENEFICIAL

Various studies in children and adults have demonstrated that ACTs may not be beneficial in certain conditions.

Asthma

In studies of the effects of ACT in children hospitalized with severe exacerbation of asthma, no difference was found in the rate of improvement of pulmonary function, even in the most severe cases.[89] Other studies in adults with reactive airway disease have shown that chest percussion can cause bronchospasm and hypoxemia.[84,103,104] Selected patients with asthma may benefit from ACTs, especially when copious secretions or obstructive atelectasis is present. However, bronchospasm and hypoxemia should be well controlled before treatment. ACT is no substitute for adequate treatment with bronchodilating agents. It is also essential that a patient with asthma be well hydrated before ACT is begun.

Bronchiolitis

Although bronchiolitis is characterized by increased secretions, studies have reported ACT to be of minimal value. CPT made no difference in the length of hospital stay or the severity or duration of symptoms

in patients with bronchiolitis, even when associated pneumonia or atelectasis was present.[105] It also produced no beneficial changes in lung mechanics or work of breathing in patients with bronchiolitis.[106] The failure of CPT to produce an effect in bronchiolitis most likely results from the fact that the disease affects the smaller peripheral airways, where ACTs are generally not effective.[8]

Pneumonia

Several studies have evaluated the role of CPT in pneumonia and have reported that CPT either had no effect or actually delayed resolution, especially in young adults.[105,107,109]

Postsurgical Patients

In a study of a group of closely matched pediatric cardiac surgery patients, Reines and colleagues[108] reported that those treated with ACTs had twice the incidence of atelectasis as did the control group (68% vs. 32%), who received deep-breathing instruction, coughing, or suction as appropriate. Moreover, atelectasis was more severe and the duration of hospitalization was prolonged in the ACT group.

Percussion to the right upper lobe every 1 to 2 hours for 24 hours after extubation is a common practice in many neonatal intensive care units. This practice is based on a report by Finer and associates[109] that claimed a dramatic reduction in the risk of right upper lobe atelectasis after extubation when an ACT was given. However, it is unclear from the study if suctioning alone or the ACT was responsible for the results.

CONDITIONS IN WHICH AIRWAY CLEARANCE TECHNIQUES MAY BE BENEFICIAL

In contrast to the reports criticizing their effectiveness, ACTs have been shown to be beneficial in patients with acute and chronic conditions characterized by excessive secretion production or mucous plugging of large airways that does not clear with coughing or suction. "Excessive secretions" usually means 30 mL of sputum per day in adults. Lesser amounts would qualify as excessive secretions in children. ACTs are also useful in the treatment of obstructive atelectasis. Figure 12-9 illustrates the process of evaluating a pediatric patient for ACTs.

Acute Lobar Atelectasis

Most patients with acute atelectasis secondary to mucous plugs respond with one ACT treatment.[28,112,113] If patients fail to respond to several ACT treatments, the atelectasis most likely is caused by conditions not amenable to ACTs, and therapy should be discontinued. The presence of an air bronchogram, suggesting no mucous obstruction of the airways, has been shown to predict a poor response to ACT.[28,113] Although a period of ACT after resolution of the atelectasis may be warranted, prolonged ACT should not be necessary. As discussed earlier, ACT is not useful in preventing the return of atelectasis, except in patients with large amounts of secretions.

Cystic Fibrosis

ACT has been widely used as a mainstay of treatment for the pulmonary complications of CF. In fact, much of the available knowledge of ACTs comes from studies conducted in patients with CF.[47,111,113] Current issues in the application of ACTs in these patients include the following questions:

1. Which techniques are most effective?
2. How can self-care be promoted?
3. How can compliance with therapy be improved?

Effective techniques are those that foster high expiratory air velocity at low lung volume, such as FET, PEP therapy, HFCWC, vigorous exercise, and AD. Postural drainage is also a useful adjunct to PEP therapy or FET. Although little evidence is available to support the routine use of manual chest percussion in the treatment of CF, and although some CF centers (especially in Europe) have abandoned the routine use of manual chest percussion, most CF treatment centers in the United States still consider it an integral component of ACTs. Many patients expect percussion to be a part of their ACT treatments, especially when hospitalized. Therefore, elimination of chest percussion from routine ACT treatments should not be carried out arbitrarily. Radical changes in ACT practice for patients facing a lifelong battle with excessive pulmonary secretions should be made only after careful deliberation and consultation with the pulmonary physicians responsible for their care.

The issue of promoting self-care is especially important when dealing with patients with CF and their families. Patients with CF differ from most patients using ACTs in that they need to employ one or more techniques for removal of bronchial secretions on a daily basis for the rest of their lives. Current practices, especially those that require the routine application of chest percussion by a second person, often give the message that ACTs are passive techniques, that they are done "to" rather than "by" the patient. This may promote passivity and dependence on parents or other caregivers. As a result, compliance is often poor and treatments become a frequent source of arguments in families of patients with CF, with difficulties increasing as the patients grow older.[46,114] Also, because ACTs must be administered by a parent two or more times a day, they may interfere with normal adolescent developmental processes, such as increasing autonomy and separation from parents. Therefore, increasing the patient's ability to perform self-care is essential. All patients with CF, especially as they approach adolescence, should be well instructed in one of the forms of self-care, such as PEP, AD, FET with or without postural drainage, or

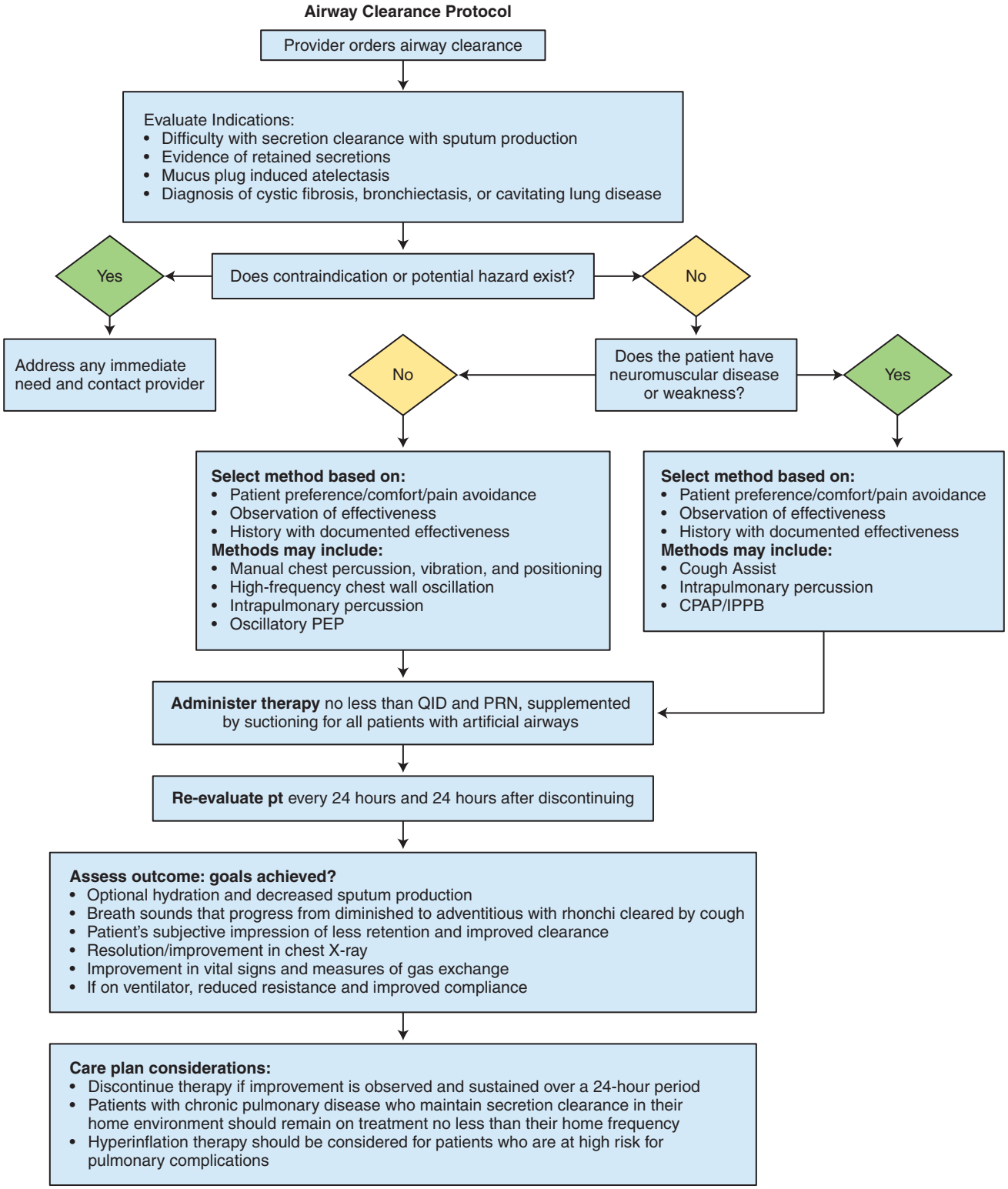


FIGURE 12-9 Algorithm for evaluating and providing airway clearance. *CPAP,* Continuous positive airway pressure; *IPPB,* intermittent positive-pressure breathing; *PEP,* positive expiratory airway pressure.

HFCWC. Vigorous exercise, such as running or swimming, is also an effective form of self-therapy in well-motivated patients. The techniques selected will depend on patient preference and learning ability, the preferences of the attending physician, and, in the case of certain technologies, the ability to arrange financing. Patients and their families often report improved compliance with self-care over parent-administered ACTs, and treatment-related conflicts are minimized.[46]

Follow-up and consistency are essential when teaching bronchial drainage techniques. Reteaching

may be necessary at intervals, and most patients with CF and their families are interested in learning new developments in ACT. Families often need assistance in adapting ACT practices to changing life circumstances, such as the patient entering school, traveling, entering college, or leaving home. Figure 12-8 demonstrates the use of HFCWC while the child continues daily activities of life. Having a younger child play a game or continue some type of fun activity can be vitally important to ensure compliance.

Patients with advanced CF often have hemoptysis. ACT therapy is usually withheld until the bleeding is controlled, because vigorous coughing may aggravate the bleeding or dislodge clots. Likewise, ACTs may need to be withheld in patients with pneumothorax, another common complication of advanced CF. Patients with end-stage disease may be especially reluctant to cooperate with ACTs, especially the Trendelenburg positioning that is required. Supplemental oxygen may allow some patients with advanced disease to tolerate postural drainage. Withholding percussion may also improve the patient's ability to maintain the Trendelenburg position. Some investigators have reported that PEP therapy is better tolerated than postural drainage and percussion in patients with end-stage disease.[50]

EXERCISE

Physical activity has been proposed to be as good as some of the traditional airway clearance techniques mentioned previously. In fact, some have intermittently substituted airway clearance sessions with physical exercise. Although there is no evidence to refute this practice, there are some common principles that apply. For example, both aerobic and anaerobic exercise require an increase in minute ventilation with often large and turbulent flow breaths, allowing air to get around and behind secretions in an effort to immobilize. In addition, there are positive effects on the cardiovascular system and overall health. There is some evidence to support the inclusion of physical training in the care management of a patient with CF, for example,[115-117] and therefore it should be encouraged for anyone capable of performing physical activity.

Clinical Highlight

- In patients who have CF, compliance with ACT is low.[118] Therefore, the clinician should work hard to ensure training and education of the ACT that is most likely to be used.
- Short- and longer-term trials show a benefit of physical training compared with no physical training.
- There is no evidence to support or refute the substitution of airway clearance sessions with physical training.

Neuromuscular Disease or Injury

ACT is commonly used in patients with neuromuscular injury or disease, and survival is often improved when ACT, coughing, turning, and deep breathing are incorporated into routine care (see Chapter 33).[10,119-121] The goal is to return a patient with neuromuscular disease or injury to airway clearance that is as normal as possible. This may require hyperinflation therapies to return FRC levels to normal or assist with the patient's natural cough. Prolonged postural drainage is often especially helpful. However, patients with acute head injury should have well-controlled intracranial pressures before ACT is initiated.

Lung Abscess

Some patients with lung abscesses, especially older children, may be successfully treated with ACTs.[122] Fearing that discharge of large amounts of infected material may spread the infection and lead to acute respiratory distress, some clinicians are reluctant to use ACTs in the treatment of lung abscesses.[27] Likewise, hemoptysis is a common complication in patients with lung abscesses, and ACTs may increase this risk. These concerns must be balanced against the knowledge that alternative treatments for lung abscesses, such as lung resections, are also risky.

Though there is not enough evidence to definitively evaluate the role of ACTs in many acute childhood diseases, it has become routine care for CF patients. ACTs appear likely to be of benefit in the maintenance or prevention of respiratory-related neuromuscular disease complications and are probably of benefit in treating atelectasis in mechanically ventilated children. ACTs appear to be of minimal to no benefit in the treatment of acute asthma, bronchiolitis, or neonatal respiratory distress, or for those requiring mechanical ventilation for acute respiratory failure, and this therapy is not effective in preventing atelectasis in the immediate postoperative period. Caution should be used, given that the conclusions are based on very limited data (Figure 12-10).

Proven	Possible
Cystic fibrosis - no one specific ACT superior	Reduction in reintubation rates post-extubation in neonates CPT
Probable	**Minimal to no benefit**
Neuromuscular disease - hyperinflation therapy (Cough Assist, IPV) Atelectasis during mechanical ventilation IPV	Asthma Bronchiolitis Neonatal RDS Acute resp. failure Post-op atelectasis

FIGURE 12-10 Effectiveness of airway clearance techniques. *ACT,* Airway clearance technique; *CPT,* chest physiotherapy; *IPV,* intrapulmonary percussive ventilation; *RDS,* respiratory distress syndrome.

CONTRAINDICATIONS

Frank hemoptysis, empyema, foreign body aspiration, and untreated pneumothorax are often considered contraindications to all components of ACTs. Withholding ACTs, especially percussion, is sometimes recommended when the platelet count is low (less than 50,000 cells/mm^3). ACTs are also usually withheld in the immediate postoperative period after tracheostomy, tracheobronchial reconstruction, and selected other conditions in which postoperative movement is extremely dangerous. Chest percussion should not be performed directly over fractured ribs, areas of subcutaneous emphysema, or recently burned or grafted skin. Some conditions may require modification of therapy or omission of certain components of ACT.

LENGTH AND FREQUENCY OF THERAPY

Treatments for patients with CF or bronchiectasis should be performed for at least 30 minutes, and many patients benefit from therapy lasting 45 minutes or longer. Patients with severe dyspnea may require rest periods, which will further prolong therapy. Most pediatric respiratory care departments limit routine ACT treatments to 15 to 20 minutes.[123] ACT therapy is rarely needed more than every 4 hours, although selected patients may benefit from more frequent suctioning or coughing. ACT orders should be evaluated at least every 48 hours for patients in intensive care units, at least every 72 hours for acute care patients, or whenever there is a change in a patient's status.[124]

Clinical Highlight

Regardless of the approach, standardization supported by clinical practice guidelines or protocols may be of assistance. Figure 12-9 is an example of a protocol used to guide therapy.

THERAPY MODIFICATION

Many patients require modification of therapy because of medical or surgical procedures. Percussion may be extremely painful for patients postoperatively, and the use of manual vibration or mechanical vibrators is sometimes better tolerated. Also, clinicians should be careful to avoid percussion over implanted devices, such as ventricular–peritoneal shunts or implantable venous access devices (often used in patients with CF). Percussion is also omitted in patients with brittle bones—for example, in those with rickets or osteogenesis imperfecta.

Many patients may not tolerate Trendelenburg positioning. Included in this group are those with severe GER, recent intracranial trauma or surgery, increased intracranial pressure, abdominal distention or ascites, compromised diaphragm movement, uncontrolled hypertension, or severe cardiopulmonary failure.[124] With careful monitoring, simple side-to-side positioning may be attempted in these patients. Patients with a gastrostomy tube or chest tube, or both, may also require modifications in drainage positions.

Patients receiving ACT therapy often have a disorder affecting only one lobe. These patients do not need ACTs in all 11 positions, but rather an abbreviated ACT treatment that uses postural drainage positions for the affected lobe only.

Infants and small children are unable to perform maneuvers such as FET and AD. Some clinicians have attempted to mimic these techniques with gentle chest wall compression during the expiratory phase, allowing the child to exhale to less than functional residual capacity. Like AD or FET performed in cooperative older patients, this technique results in increased expiratory air velocity at low lung volumes, improving mucus mobilization.

MONITORING DURING THERAPY

Patients in an intensive care unit who require ACTs should have continuous monitoring of arterial oxygen saturation (Sao_2), heart rate, and respiratory rate. Breathing pattern, skin color, and breath sounds should also be noted.[124] Patients not in an intensive care unit who require high oxygen concentration or who have a condition presenting a high risk of respiratory or cardiac failure should also have these variables monitored. Other patients with mild respiratory distress should have pulse and respiratory rate as well as breathing pattern, skin color, and breath sounds measured before and after therapy. This is especially true for younger patients who cannot verbalize complaints of distress. Routine monitoring of heart rate and respiratory rate for patients with chronic respiratory disorders, such as CF, is probably not warranted and may inadvertently give the message that ACTs are harmful. When performing percussion or vibration on patients who are connected to cardiopulmonary monitors, the alarm on the monitor may become activated because of interference from the percussion or vibration. It is best to refrain from turning monitor alarms completely off.

EVALUATION OF THERAPY

Because the goal of ACTs is to promote the removal of excessive bronchial secretions, the single most important variable in evaluating the effectiveness of ACTs is the amount of secretions expectorated with therapy; however, this cannot be done in a vacuum, and the basics should not be forgotten. The hydration status of

the patient and whether the patient's lungs are acidic can play a huge role in the success of airway clearance.[125,126] Mucus changes from sol to gel if the lungs are acidic. Changes in sputum production, breath sounds, vital signs, chest radiographic findings, blood gas values, or lung mechanics may indicate a positive response to the therapy.[124] The removal of excessive bronchial secretions is not always associated with an immediate change in blood gases, breath sounds, or lung mechanics. Patients with advanced CF, for example, almost always have audible rales before and after therapy, whereas pulmonary function and blood gas determinations change little.

Patients undergoing mechanical ventilation may have measurements of lung mechanics as well as noninvasive blood gas monitoring data readily available. If so, the clinician should note any changes associated with therapy. Deterioration in these variables, especially if unaccompanied by removal of secretions, suggests that therapy should be modified or discontinued.

DOCUMENTATION OF THERAPY

When charting ACT treatments, the clinician should describe the techniques used (e.g., postural drainage, percussion, and AD), which lobes were treated, and what positions the patient was placed in. If certain segments or positions are omitted, this should be documented, along with the reason why this was done. The clinician should also note whether suctioning was performed. To document the response to therapy, pretreatment and posttreatment breath sounds, vital signs, and the amount and quality of sputum expectorated should be noted.

HYPERINFLATION THERAPY

INCENTIVE SPIROMETRY

Incentive spirometry, also referred to as *sustained maximal inspiration*, was introduced in the early 1970s in an effort to prevent postoperative pulmonary complications.[92,127] It was designed to encourage patients to improve their inspiratory volume while visualizing their inspiratory effort. Forced expiratory maneuvers using devices such as blow bottles, blow gloves, and balloons were prescribed in the past to prevent postoperative complications; however, they have been associated with the development of atelectasis and do not result in the same physiological effects as incentive spirometry.[128-130] The objectives of incentive spirometry are to prevent or reverse atelectasis, improve lung volume, and improve inspiratory muscle performance (including use of the diaphragm), but it should no longer be routinely recommended[131,132] over early mobilization or deep breathing and coughing.[128]

INTERMITTENT POSITIVE-PRESSURE BREATHING

IPPB is the intermittent short-term delivery of positive pressure to a patient for the purpose of improving lung expansion, delivering aerosolized medications, and assisting ventilation.[133] Since its inception in 1947 and its introduction into the medical arena in 1948, IPPB has been one of the most controversial topics in respiratory care.[134] It was one of the most popular therapeutic modalities prescribed in the 1960s and 1970s and was regarded as a panacea for all pulmonary ailments. Not until the American College of Chest Physicians conference on oxygen therapy in September 1983, when both its overuse and its doubtful efficacy were discussed, did IPPB decline as a treatment modality.[135] Today newly practiced modalities, such as bilevel positive airway pressure and incentive spirometry, have rendered IPPB obsolete.[136,137] In fact, most institutions do not own an IPPB device.

INTRAPULMONARY PERCUSSIVE VENTILATION

Intrapulmonary percussive ventilation (IPV) is a technique that uses **hyperinflation therapy** and airway clearance therapy in one. The IPV device uses high-frequency oscillatory ventilation to produce percussion. The percussions are high-flow jets of gas that are delivered to the airways by a flow interrupter called a *Phasitron.* Activation of the Venturi system within the Phasitron creates bursts of gas at frequencies of 100 to 300 bursts per minute within a tightly controlled ratio of gas delivery and passive exhalation. The relationship between the gas bursts and exhalations determines the intrapulmonary "wedge" pressure. It is this wedge pressure that may provide mobilization and clearance of pulmonary secretions.

INDICATIONS, CONTRAINDICATIONS, AND COMPLICATIONS

IPV is designed to both treat active pulmonary disease and prevent the development of disease caused by secretion retention. Specific goals of therapy include promoting the mobilization of bronchial secretions, improving the efficiency and distribution of ventilation, providing an alternative delivery system for bronchodilator therapy, providing intrathoracic percussion and vibration, and providing an alternative system for the delivery of positive pressure to the lungs. The Phasitron may be manually triggered during IPV therapy in nonintubated, spontaneously breathing patients or may be set to continuous percussion for use in intubated patients. IPV may be applied via mouthpiece, mask, artificial airway, or ventilator.

When taking a least-aggressive to most-aggressive approach, the primary indication for a combination therapy like IPV is a patient refractory to traditional bronchial hygiene methods. Other indications are similar to those for other airway clearance procedures, such as patients with atelectasis, bronchitis, bronchiectasis, or bronchopneumonia. Patients who

have aggressive secretion-producing disease coupled with muscle weakness are likely the best candidates.

Contraindications are not that different from those for positive pressure and airway clearance and include untreated pneumothorax, hemoptysis, active tuberculosis, and fractured ribs or unstable chest.

Monitoring

The patient and the equipment should be monitored closely during therapy. The heart rate and respiratory rate should be obtained before, during, and after each treatment. Breath sounds should be assessed before and after each treatment and any time the patient complains of respiratory difficulty or chest pain, with the goal of therapy being to clear secretions and improve the efficiency of breathing.

ASSESSMENT OF THERAPY

The following must be documented with each IPV treatment:

- Heart rate
- Respiratory rate
- Breath sounds
- Pressure used (beginning and end of therapy)
- Machine controls used
- Medication aerosolized
- Peak flow (if applicable)
- Description of sputum production
- Patient cooperation and tolerance
- Duration of therapy
- Any patient complaints or adverse reactions and the corrective action taken

IPV therapy is believed to be effective if the therapeutic goals are met, including the following:

- Secretion clearance
- Improved breath sounds
- Improved gas exchange
- Medication delivery
- An improved chest radiograph

Clinical Highlight

- Acute and chronically ill patients who are bedridden or require mechanical ventilation for a prolonged period of time will develop some type of muscle weakness that can impair their natural airway defenses and clearance.
- Hyperinflation therapy may be the only assistance a patient needs to clear the airway.
- The most effective hyperinflation techniques apply positive pressure to the airways to help increase FRC and dilate the distal airways.

SUMMARY OF AIRWAY CLEARANCE TECHNIQUES

Irrespective of the exact mechanisms, ACTs promote mucociliary clearance by altering airflow and/or mucous viscosity. There is little evidence that one ACT is better than another. However, a specific ACT may be more effective in some situations in which the ACT counterbalances the reason for retained secretions. ACTs that center on normalization of physiological airway clearance mechanisms will likely produce the best results. This may be accomplished by new and novel drug and device therapies such as hypertonic saline or simple devices as the Cough Assist (Emerson), which helps neuromuscular patients mimic a stronger cough. Because of the understood benefits of deep breathing and coughing, the use of paralytics in acute lung injury is no longer common practice. Gene therapy for CF is just around the corner. Advances in technology will continue to give us tools that allow us to accomplish the basics while reducing overall physical size and power consumption. Many of these new devices will provide a user-friendly interface that can be used by non–health care providers in the home care setting. This allows practitioners to customize therapy for the best outcome depending on the social, economic, and educational needs of the patient and family.

Case Study

You are assigned to treat a 10-year-old child with CF who is struggling with secretion management. You are requested by the physician to assess and treat the patient with what you feel is the most appropriate ACT. After further assessment, you determine that the patient is hypoxic, requiring a dry high-flow oxygen device; has inspissated secretions and adventitious breath sounds; and is fatiguing. What should be your first actions, in order?

1. Provide humidity as soon as possible.
2. Determine the patient's home regimen and what has worked in the past.
3. Consider an ACT with hyperinflation therapy to support fatiguing muscles.
4. Call the physician to report fatigue.

A. 4, 2, 1, 3
B. 4 only and wait for direction
C. 1, 2, 3, 4
D. 2, 3

See Evolve Resources for answers.

Key Points

- The primary use of ACTs should be limited to those who cannot clear their airway secretions.
- The most effective ACT is that which mimics or supports normal physiology.
- ACTs should target symptoms. See the table here for a list of ACTs to best target various symptoms.

SYMPTOM	POSSIBLE CAUSE	INITIAL AIRWAY CLEARANCE TECHNIQUE
Weak or poor cough	• Neuromuscular disease	Combination airway clearance technique (ACT) and hyperinflation therapy. Clinician choice as to which therapy creates the highest expiratory flow rate. This requires increasing the functional residual capacity (FRC).
	• Oversedation	Wean sedation if possible and support with hyperinflation therapy.
	• Pain	Support pain management and encourage deep breathing and coughing with mobilization if possible.
Inspissated secretions	• Poor humidification	Hydration and chest physical therapy.
Airway collapse that leads to retained secretions	• External forces or defects within the airway	Solve external force issues if possible. Positive expiratory airway pressure (PEP) for obstructions that lead to atelectasis. Chest physiotherapy (CPT) for obstructed secretions that lead to distal hyperinflation.
Expectorating a large volume of secretions	• Infection	Treat infection or possible cause of sputum production and support with chest physical therapy.

- All ACTs should have an objective outcome to determine effectiveness and be reevaluated frequently.

Assessment Questions

See Evolve Resources for answers.

1. Many institutions replaced the routine use of IPPB with routine use of ACTs in which two decades?
   - **A.** 1900s and 1910s
   - **B.** 1920s and 1930s
   - **C.** 1960s and 1970s
   - **D.** 1980s and 1990s
2. Postural drainage was used as early as:
   - **A.** 1901
   - **B.** 1911
   - **C.** 1940
   - **D.** 1953
3. When doing percussion therapy, what is the recommended frequency?
   - **A.** 1 to 2 Hz
   - **B.** 3 to 4 Hz
   - **C.** 5 to 6 Hz
   - **D.** 7 to 8 Hz
4. When providing vibration chest physiotherapy, what is the recommended frequency?
   - **A.** 6 to 7 Hz
   - **B.** 8 to 9 Hz
   - **C.** 10 to 15 Hz
   - **D.** >20 Hz
5. The four components of *traditional*[159] ACT therapy are:
   - **A.** Postural drainage, percussion, vibration, and coughing
   - **B.** FET, IS, IPPB, and HFFC
   - **C.** PEP, position, AD, and resistance
   - **D.** Hydration, percussion, deep breathing, and FET
6. Premature infants may be at risk for increased complications from ACT. Why?
   - **A.** The high chest wall compliance of premature infants can cause loss of lung volume.
   - **B.** ACT is associated with IVH.
   - **C.** Prolonged handling can interfere with the temperature-regulated environment of these patients.
   - **D.** A, B, and C are correct.
7. What hyperinflation therapy was introduced in the 1970s to prevent postoperative pulmonary complications?
   - **A.** Deep breath and cough
   - **B.** Incentive spirometry
   - **C.** CPT
   - **D.** PEP
8. ACTs are required in only a limited number of conditions, all of which are characterized by which of the following?
   - **A.** Chronic excessive sputum production
   - **B.** Disease state
   - **C.** Patient age and disease state
   - **D.** None of the above
9. Treatments for patients with CF or bronchiectasis should be performed for at least _____ and reevaluated every _____ for acute care.
   - **A.** 10 minutes, 24 hours
   - **B.** 15 minutes, 48 hours
   - **C.** 20 minutes, 96 hours
   - **D.** 30 minutes, 72 hours
10. What are the contraindications for ACT?
    - **A.** Frank hemoptysis
    - **B.** Empyema
    - **C.** Foreign body aspiration
    - **D.** All of the above

REFERENCES

1. Ewart W. The treatment of bronchiectasis and of chronic bronchial infections by posture and respiratory exercises. *Lancet*. 1901;2:70.
2. Gaskell DV, Webber BA. *The Brompton Hospital guide to chest physiotherapy*. Oxford: Blackwell Scientific Publications; 1973.
3. Murray JF. The ketchup-bottle method. *N Engl J Med*. 1979;300:1155.
4. Sutton PP, Pavia D, Bateman JR, Clarke SW. Chest physiotherapy: a review. *Eur J Respir Dis*. 1982;63:188.
5. Kirilloff LH, Owens GR, Rogers RM, Mazzocco MC. Does chest physical therapy work? *Chest*. 1985;88:436.
6. Sutton P. Chest physiotherapy: time for a reappraisal. *Br J Dis Chest*. 1988;82:127.
7. Selsby D, Jones JG. Chest physiotherapy may be harmful in some patients. *BMJ*. 1989;298:541.
8. Selsby D, Jones JG. Chest physiotherapy: physiological and clinical aspects. *Br J Anaesth*. 1990;64:621.
9. Pavia D. The role of chest physiotherapy in mucus hypersecretion. *Lung*. 1990;168(suppl 1):614.
10. Stiller KR, McEvoy RD. Chest physiotherapy for the medical patient: are current practices effective? *Aust N Z J Med*. 1990;20:183.
11. Eid N, Buchheit JQ, Neuling M, Phelps H. Chest physiotherapy in review. *Respir Care*. 1991;36:270.
12. Lewis RM. Chest physical therapy: time for a redefinition and a renaming. *Respir Care*. 1992;37:419.
13. Oberwaldner B. Physiotherapy for airway clearance in paediatrics. *Eur Respir J*. 2000;15(1):196-204.
14. Papastamelos C, Panitch HB, England SE, Allen JL. Developmental changes in chest wall compliance in infancy and early childhood. *J Appl Physiol*. 1995;78(1):179-184.
15. Lai-Fook SJ, Hyatt RE. Effects of age on elastic moduli of human lungs. *J Appl Physiol*. 2000;89(1):163-168.
16. Penn RB, Wolfson MR, Shaffer TH. Developmental differences in tracheal cartilage mechanics. *Pediatr Res*. 1989; 26(5):429-433.
17. Hall GL, Hantos Z, Wildhaber JH, Sly PD. Contribution of nasal pathways to low frequency respiratory impedance in infants. *Thorax*. 2002;57(5):396-399.
18. Hough A. *Physiotherapy in Respiratory Care: A Problem Solving Approach*. London: Chapman & Hall; 1991.
19. Cystic Fibrosis Foundation. *Consumer Fact Sheet: An Introduction to Chest Physical Therapy*. Bethesda, MD: Cystic Fibrosis Foundation; 1992.
20. Mellins RB. Pulmonary physiotherapy in the pediatric age group. *Am Rev Respir Dis*. 1974;110(suppl 2):137.
21. Sutton PP, Lopez-Vidriero MT, Pavia D, et al. Assessment of percussion, vibratory shaking, and breathing exercises in chest physiotherapy. *Eur J Respir Dis*. 1985;66:147.
22. Sutton PP, Parker RA, Webber BA, et al. Assessment of the forced expiration technique, postural drainage and directed coughing in chest physiotherapy. *Eur J Respir Dis*. 1983;64:62.
23. van der Schans CP, Piers DA, Postma DS. Effect of manual percussion on tracheobronchial clearance in patients with chronic airflow obstruction and excessive tracheobronchial secretion. *Thorax*. 1986;41:448.
24. Murphy MB, Concannon D, FitzGerald MX. Chest percussion: help or hindrance to postural drainage. *Ir Med J*. 1983;76:189.
25. Webber, Parker R, Hofmeyr J, Hodson M. Evaluation of self-percussion during postural drainage using the forced expiration technique. *Physiother Pract*. 1985;1:42.
26. Faling LJ. Chest physical therapy. In: Burton GG, Gee GN, Hodgkin JE, editors. *Respiratory Care: A Guide to Clinical Practice*. 3rd ed. Philadelphia: JB Lippincott; 1991:625-654.
27. Marini JJ, Pierson DJ, Hudson LD. Acute lobar atelectasis: a prospective comparison of fiberoptic bronchoscopy and respiratory therapy. *Am Rev Respir Dis*. 1979;119:971.
28. Finer NN, Boyd J. Chest physiotherapy in the neonate: a controlled study. *Pediatrics*. 1978;61:282.
29. Ernst MM, Wooldridge JL, Conway E, et al. Using quality improvement science to implement a multidisciplinary behavioral intervention targeting pediatric inpatient airway clearance. *J Pediatr Psychol*. 2010;35(1):14-24. doi:10.1093/jpepsy/jsp013.
30. O'Bradovich HM, Chernick V. The functional basis of respiratory pathology. In: Chernick V, ed. *Kendig's Disorders of the Respiratory Tract in Children*. 5th ed. Philadelphia: WB Saunders; 1990:3-47.
31. Walters P. Chest physiotherapy. In: Levin DL, Morris FC, Moore GC, eds. *A Practical Guide to Pediatric Intensive Care*. St. Louis: Mosby; 1979:395-403.
32. Holloway R, Adams EB, Desai SD, Thambiran AK. Effect of chest physiotherapy on blood gases of neonates treated by intermittent positive pressure respiration. *Thorax*. 1969;24:421.
33. Fox WW, Schwartz JG, Shaffer TH. Pulmonary physiotherapy in neonates: physiologic changes and respiratory management. *J Pediatr*. 1978;92:977.
34. Curran CL, Kachoyeanos MK. The effects on neonates of two methods of chest physical therapy. *MCN Am J Matern Child Nurs*. 1979;4:309.
35. Walsh CM, Bada HS, Korones SB, Carter MA, Wong SP, Arheart K. Controlled supplemental oxygenation during tracheobronchial hygiene. *Nurs Res*. 1987;36:211.
36. Raval D, Yeh TF, Mora A, Cuevas D, Pyati S, Pildes RS. Chest physiotherapy in preterm infants with RDS in the first 24 hours of life. *J Perinatol*. 1987;7:301.
37. Green CG. Assessment of the pediatric airway by flexible bronchoscopy. *Respir Care*. 1991;36:555.
38. Pryor JA. The forced expiration technique. In: Pryor JA, ed. *International Perspectives in Physical Therapy*. Vol 7. Edinburgh: Churchill Livingstone; 1991:79-100.
39. Zapletal A, Stefanová J, Horák J, Vávrová V, Samánek M. Chest physiotherapy and airway obstruction in patients with cystic fibrosis: a negative report. *Eur J Respir Dis*. 1983;64:426.
40. Oldenburg Jr FA, Dolovich MB, Montgomery JM, Newhouse MT. Effects of postural drainage, exercise, and cough on mucus clearance in chronic bronchitis. *Am Rev Respir Dis*. 1979;120:739.
41. Rossman CM, Waldes R, Sampson D, Newhouse MT. Effect of chest physiotherapy on the removal of mucus in patients with cystic fibrosis. *Am Rev Respir Dis*. 1982;126:131.
42. De Boeck C, Zinman R. Cough versus chest physiotherapy. *Am Rev Respir Dis*. 1984;129:182.
43. Bain J, Bishop J, Olinsky A. Evaluation of directed coughing in cystic fibrosis. *Br J Dis Chest*. 1988;82:138.
44. van Hengstum M, Festen J, Beurskens C, Hankel M, Beekman F, Corstens F. Conventional physiotherapy and forced expiratory manoeuvres have similar effects on tracheobronchial clearance. *Eur Respir J*. 1988;1:758.
45. Denning C, Jacoby J, Xia F, et al. A biopsychosocial examination of two methods of pulmonary therapy [abstract]. *Pediatr Pulmonol*. 1989;4(suppl):145.
46. Reisman J, Rivington-Law B, Corey M, et al. Role of conventional physiotherapy in cystic fibrosis. *J Pediatr*. 1988; 113:632.
47. Holzer FJ, Schnall R, Landau LI. The effect of a home exercise programme in children with cystic fibrosis. *Aust Paediatr J*. 1984;20:297.
48. Blomquist M, Freyschuss U, Wiman LG, Strandvik B. Physical activity and self treatment in cystic fibrosis. *Arch Dis Child*. 1986;61:362.
49. Mahlmeister MJ, Fink JB, Hoffman GL, et al. Positive-expiratory-pressure mask therapy: theoretical and practical considerations and a review of the literature. *Respir Care*. 1991;36:1218.
50. Iverson LIG, Ecker RR, Fox HE, May IA. Comparative study of IPPB, the incentive spirometer and blow bottles: the

prevention of atelectasis following cardiac surgery. *Ann Thorac Surg*. 1978;25:197.
51. Striegl AM, Redding GJ, Diblasi R, Crotwell D, Salyer J, Carter ER. Use of a lung model to assess mechanical in-exsufflator therapy in infants with tracheostomy. *Pediatr Pulmonol*. 2011;46(3):211-217. doi:10.1002/ppul.21353.
52. Vianello A, Ragazzi R, Mirri L, Arcaro G, Cutrone C, Fittà C. Tracheoinnominate fistula in a Duchenne muscular dystrophy patient: successful management with an endovascular stent. *Neuromuscul Disord*. 2005;15(8):569-571. doi:10.1016/j.nmd.2005.04.010.
53. Avena Kde M, Duarte AC, Cravo SL, Sologuren MJ, Gastaldi AC. [Effects of manually assisted coughing on respiratory mechanics in patients requiring full ventilatory support]. *J Bras Pneumol*. 2008;34(6):380-386.
54. Unoki T, Kawasaki Y, Mizutani T, et al. Effects of expiratory rib-cage compression on oxygenation, ventilation, and airway-secretion removal in patients receiving mechanical ventilation. *Respir Care*. 2005;50(11):1430-1437.
55. Unoki T, Mizutani T, Toyooka H. Effects of expiratory rib cage compression and/or prone position on oxygenation and ventilation in mechanically ventilated rabbits with induced atelectasis. *Respir Care*. 2003;48(8):754-762.
56. Unoki T, Mizutani T, Toyooka H. Effects of expiratory rib cage compression combined with endotracheal suctioning on gas exchange in mechanically ventilated rabbits with induced atelectasis. *Respir Care*. 2004;49(8):896-901.
57. Martí JD, Li Bassi G, Rigol M, et al. Effects of manual rib cage compressions on expiratory flow and mucus clearance during mechanical ventilation. *Crit Care Med*. 2013;41(3):850-856. doi:10.1097/CCM.0b013e3182711b52.
58. Schöni MH. Autogenic drainage: a modern approach to physiotherapy in cystic fibrosis. *J R Soc Med*. 1989;82(suppl 16):32.
59. David A. Autogenic drainage—the German approach. In: Pryor JA, ed. *International Perspectives in Physical Therapy*. Vol 7. Edinburgh: Churchill Livingstone; 1991:65-78.
60. Davidson AGF, et al. Long-term comparison of conventional percussion and drainage physiotherapy versus autogenic drainage in cystic fibrosis [abstract]. *Pediatr Pulmonol*. 1992;8(suppl 8):298.
61. Falk M, Kelstrup M, Andersen JB, et al. Improving the ketchup bottle method with positive expiratory pressure, PEP, in cystic fibrosis. *Eur J Respir Dis*. 1984;65:423.
62. Tønnesen P, Støvring S. Positive expiratory pressure (PEP) as lung physiotherapy in cystic fibrosis: a pilot study. *Eur J Respir Dis*. 1984;65:419.
63. Tyrell JC, Hiller EJ, Martin J. Face mask physiotherapy in cystic fibrosis. *Arch Dis Child*. 1986;61:598.
64. Oberwaldner B, Evans JC, Zach MS. Forced expirations against a variable resistance: a new chest physiotherapy method in cystic fibrosis. *Pediatr Pulmonol*. 1986;2:358.
65. Van Asperen PP, Jackson L, Hennessy P, Brown J. Comparison of a positive expiratory pressure (PEP) mask with postural drainage in patients with cystic fibrosis. *Aust Paediatr J*. 1987;23:283.
66. Falk M, Andersen JB. Positive expiratory pressure (PEP) mask. In: Pryor JA, ed. *International Perspectives in Physical Therapy*. Vol 7. Edinburgh: Churchill Livingstone; 1991:51-63.
67. Oberwaldner B, Theissl B, Rucker A, Zach MS. Chest physiotherapy in hospitalized patients with cystic fibrosis: a study of lung function effects and sputum production. *Eur Respir J*. 1991;4:152.
68. Mortensen J, Falk M, Groth S, Jensen C. The effects of postural drainage and positive expiratory pressure physiotherapy on tracheobronchial clearance in cystic fibrosis. *Chest*. 1991;100:1350.
69. Lindemann H, Boldt A, Kieselmann R. Autogenic drainage: efficacy of a simplified method. *Acta Univ Carol Med (Praha)*. 1990;36:210.
70. Warwick WJ, Hansen LG. The long-term efficacy of high-frequency chest compression on pulmonary complications of cystic fibrosis. *Pediatr Pulmonol*. 1991;11:265.
71. Warwick WJ. High frequency chest compression moves mucus by means of sustained staccato coughs [abstract]. *Pediatr Pulmonol*. 1991;6(suppl 6):283.
72. Plioplys AV. Correspondence on "safety, tolerability, and efficacy of high-frequency chest wall oscillation in pediatric patients with cerebral palsy and neuromuscular diseases: an exploratory randomized controlled trial." *J Child Neurol*. 2010;25(12):1598. doi:10.1177/0883073810384614.
73. Lannefors L, Wollmer P. Mucus clearance with three chest physiotherapy regimes in cystic fibrosis: a comparison between postural drainage, PEP, and physical exercise. *Eur Respir J*. 1992;5:748.
74. Zach M, Oberwaldner B, Häusler F. Cystic fibrosis: physical exercise versus chest physiotherapy. *Arch Dis Child*. 1982;57:587.
75. Andréasson B, Jonson B, Kornfält R, Nordmark E, Sandström S. Long-term effects of physical exercise on working capacity and pulmonary function in cystic fibrosis. *Acta Paediatr Scand*. 1987;76:70.
76. Bartlett RH, Krop P, Hanson EL, Moore FD. Physiology of yawning and its application to postoperative care. *Surg Forum*. 1970;21:222.
77. Bartlett RH. Incentive spirometry. In: Kacmarek R, Stoller J, eds. *Current Respiratory Care: Techniques and Therapy*. St. Louis: Mosby; 1988.
78. Bartlett RH. Post-traumatic pulmonary insufficiency. In: Cooper P, Nyhus L, eds. *Surgery Annual*. New York: Appleton-Century-Crofts; 1971.
79. Ali J, Weisel RD, Layug AB, Kripke BJ, Hechtman HB. Consequences of postoperative alterations in respiratory mechanics. *Am J Surg*. 1974;128:376.
80. Meyers JR, Lembeck L, O'Kane H, Baue AE. Changes in functional residual capacity of the lung after operation. *Arch Surg*. 1975;110:576.
81. McDonnell T, McNicholas WT, Fitzgerald MX. Hypoxaemia during chest physiotherapy in patients with cystic fibrosis. *Ir J Med Sci*. 1986;155:345.
82. Gormezano J, Branthwaite MA. Pulmonary physiotherapy with assisted ventilation. *Anaesthesia*. 1972;27:249.
83. Gormezano J, Branthwaite MA. Effects of physiotherapy during intermittent positive pressure ventilation. *Anaesthesia*. 1972;27:258.
84. Huseby J, et al. Oxygenation during chest physiotherapy [abstract]. *Chest*. 1976;70:430.
85. Tyler ML, et al. Prediction of oxygenation during chest physiotherapy in critically ill patients [abstract]. *Am Rev Respir Dis*. 1980;121:218.
86. Dhainaut JF, Bons J, Bricard C, Monsallier JF. Improved oxygenation in patients with extensive unilateral pneumonia using the lateral decubitus position. *Thorax*. 1980;35:792.
87. Remolina C, Khan AU, Santiago TV, Edelman NH. Positional hypoxemia in unilateral lung disease. *N Engl J Med*. 1981;304:523.
88. Rivara D, Artucio H, Arcos J, Hiriart C. Positional hypoxemia during artificial ventilation. *Crit Care Med*. 1984;12:436.
89. Heaf DP, Helms P, Gordon I, Turner HM. Postural effects on gas exchange in infants. *N Engl J Med*. 1983;308:1505.
90. Holody B, Goldberg HS. The effect of mechanical vibration physiotherapy on arterial oxygenation in acutely ill patients with atelectasis or pneumonia. *Am Rev Respir Dis*. 1981;124:372.
91. Mohsenifar Z, Rosenberg N, Goldberg HS, Koerner SK. Mechanical vibration and conventional chest physiotherapy in outpatients with stable chronic obstructive lung disease. *Chest*. 1985;87:483.

92. Weissman C, Kemper M, Damask MC, Askanazi J, Hyman AI, Kinney JM. Effect of routine intensive care interactions on metabolic rate. *Chest*. 1984;86:815.
93. Weissman C, Kemper M. The oxygen uptake–oxygen delivery relationship during ICU interventions. *Chest*. 1991;99:430.
94. Vandenplas Y, Diericx A, Blecker U, Lanciers S, Deneyer M. Esophageal pH monitoring data during chest physiotherapy. *J Pediatr Gastroenterol Nutr*. 1991;13:23.
95. Orenstein SR, Orenstein DM. Gastroesophageal reflux and respiratory disease in children. *J Pediatr*. 1988;112:847.
96. Kosloske AM. Tracheobronchial foreign bodies in children: back to the bronchoscope and a balloon. *Pediatrics*. 1980;66:321.
97. Emery JR, Peabody JL. Head position affects intracranial pressure in newborn infants. *J Pediatr*. 1983;103:950.
98. Ersson U, Carlson H, Mellström A, Pontén U, Hedstrand U, Jakobsson S. Observations on intracranial dynamics during respiratory physiotherapy in unconscious neurosurgical patients. *Acta Anaesthesiol Scand*. 1990;34:99.
99. Purohit DM, Caldwell C, Levkoff AH. Multiple rib fractures due to physiotherapy in a neonate with hyaline membrane disease. *Am J Dis Child*. 1975;129:1103.
100. Asher MI, Douglas C, Airy M, Andrews D, Trenholme A. Effects of chest physical therapy on lung function in children recovering from acute severe asthma. *Pediatr Pulmonol*. 1990;9:146.
101. Campbell AH, O'Connell JM, Wilson F. The effects of chest physiotherapy upon the FEV1 in chronic bronchitis. *Med J Aust*. 1975;1:33.
102. Wollmer P, Ursing K, Midgren B, Eriksson L. Inefficiency of chest percussion in the physical therapy of chronic bronchitis. *Eur J Respir Dis*. 1985;66:233.
103. Webb MSC, Martin JA, Cartlidge PH, Ng YK, Wright NA. Chest physiotherapy in acute bronchio-litis. *Arch Dis Child*. 1985;60:1078.
104. Quittell LM, et al. The effectiveness of chest physical therapy (CPT) in infants with bronchiolitis [abstract]. *Am Rev Respir Dis*. 1988;137:406.
105. Graham WGB, Bradley DA. Efficacy of chest physiotherapy and intermittent positive-pressure breathing in the resolution of pneumonia. *N Engl J Med*. 1978;299:624.
106. Britton S, Bejstedt M, Vedin L. Chest physiotherapy in primary pneumonia. *BMJ*. 1985;290:1703.
107. Reines HD, Sade RM, Bradford BF, Marshall J. Chest physiotherapy fails to prevent postoperative atelectasis in children after cardiac surgery. *Ann Surg*. 1982;195:451.
108. Finer NN, Moriartey RR, Boyd J, Phillips HJ, Stewart AR, Ulan O. Postextubation atelectasis: a retrospective review and a prospective controlled study. *J Pediatr*. 1979;94:110.
109. Stiller K, Geake T, Taylor J, Grant R, Hall B. Acute lobar atelectasis: a comparison of two chest physiotherapy regimens. *Chest*. 1990;98:1336.
110. Currie DC, Munro C, Gaskell D, Cole PJ. Practice, problems and compliance with postural drainage: a survey of chronic sputum producers. *Br J Dis Chest*. 1986;80:249.
111. Hammon WE, Martin RJ. Chest physiotherapy for acute ate-lectasis. *Phys Ther*. 1981;61:217.
112. MacKenzie CF, Shin B, McAslan TC. Chest physiotherapy: the effect on arterial oxygenation. *Anesth Analg*. 1978;57:28.
113. Connors Jr AF, Hammon WE, Martin RJ, Rogers RM. Chest physical therapy: the immediate effect on oxygenation in acutely ill patients. *Chest*. 1980;78:559.
114. McMichan JC, Michel L, Westbrook PR. Pulmonary dysfunction following traumatic quadriplegia. *JAMA*. 1980;243:528.
115. Selvadurai HC, Blimkie CJ, Meyers N, Mellis CM, Cooper PJ, Van Asperen PP. Randomized controlled study of in-hospital exercise training programs in children with cystic fibrosis. *Pediatr Pulmonol*. 2002;33(3):194-200.
116. Klijn PH, Oudshoorn A, van der Ent CK, van der Net J, Kimpen JL, Helders PJ. Effects of anaerobic training in children with cystic fibrosis: a randomized controlled study. *Chest*. 2004;125(4):1299-1305.
117. Schneiderman-Walker J, Pollock SL, Corey M, et al. A randomized controlled trial of a 3-year home exercise program in cystic fibrosis. *J Pediatr*. 2000;136(3):304-310.
118. Kettler LJ, Sawyer SM, Winefield HR, Greville HW. Determinants of adherence in adults with cystic fibrosis. *Thorax*. 2002;57(5):459-464.
119. Kosloske AM, Ball Jr WS, Butler C, Musemeche CA. Drainage of pediatric lung abscess by cough, catheter, or complete resection. *J Pediatr Surg*. 1986;21:596.
120. Lewis R. Chest physical therapy in pediatrics: a national survey [abstract]. *Respir Care*. 1991;36:1307.
121. American Association for Respiratory Care: Clinical practice guideline: postural drainage therapy. *Respir Care*. 1991;36:1418.
122. Holma B, Hegg PO. pH- and protein-dependent buffer capacity and viscosity of respiratory mucus: their interrelationships and influence on health. *Sci Total Environ*. 1989;84:71.
123. Zelenina M, Bondar AA, Zelenin S, Aperia A. Nickel and extracellular acidification inhibit the water permeability of human aquaporin-3 in lung epithelial cells. *J Biol Chem*. 2003;278:30037.
124. Bartlett RH, Gazzaniga AB, Geraghty TR. Respiratory maneuvers to prevent postoperative pulmonary complications: a critical review. *JAMA*. 1973;224:1017.
125. Bakow ED. Sustained maximal inspiration: a rationale for its use. *Respir Care*. 1977;22:379.
126. American Association for Respiratory Care: Clinical practice guideline: incentive spirometry. *Respir Care*. 1991;36:1402.
127. Harken DE. A review of the activities of the thoracic center for the III and IV hospital groups, 160th general hospital European theater of operations, June 10, 1944 to Jan 1, 1945. *J Thorac Surg*. 1946;15:31.
128. Iverson LIG, Ecker RR, Fox HE, May IA. A comparative study of IPPB, the incentive spirometer and blow bottles: the prevention of atelectasis following cardiac surgery. *Ann Thoracic Surg*. 1978;25:197.
129. O'Donohue Jr WJ. National survey of the usage of lung expansion modalities for the prevention and treatment of postoperative atelectasis following abdominal and thoracic surgery. *Chest*. 1985;87:76.
130. Oikkonen M, Karjalainen K, Kähärä V, Kuosa R, Schavikin L. Comparison of incentive spirometry and intermittent positive pressure breathing after coronary artery bypass graft. *Chest*. 1991;99:60.
131. Strickland SL, Rubin BK, Drescher GS, et al. AARC clinical practice guideline: effectiveness of nonpharmacologic airway clearance therapies in hospitalized patients. *Respir Care*. 2013;58(12):2187-2193.
132. Restrepo RD, Wettstein R, Wittnebel L, Tracy M. Incentive spirometry: 2011. *Respir Care*. 2011;56(10):1600-1604.
133. Motley HL, Lang LP, Gordon B. Use of intermittent positive pressure breathing combined with nebulization in pulmonary disease. *Am J Med*. 1948;5:853.
134. Eubank DH, Bone RC. Intermittent positive pressure breathing. In: Eubank DH, Bone RC, eds. *Comprehensive Respiratory Care: A Learning System Module*. St. Louis: Mosby; 1985:430-450.
135. Chang N, Levison H. The effect of nebulized bronchodilator administration with or without IPPB on ventilatory function in children with cystic fibrosis and asthma. *Am Rev Respir Dis*. 1972;106:867.
136. Baker JP. Magnitude of usage of intermittent positive pressure breathing. *Am Rev Respir Dis*. 1974;110:S170.
137. Handelsman H. Agency for Health Care Policy and Research. *Health Technology Reports: Intermittent Positive Pressure Breathing (IPPB) Therapy*, AHCPR Pub. No. 92-0013. Rockville, Md: Office of Health Technology, U.S. Department of Health and Human Services, Public Health Service; 1991.

13 Airway Management

Karen Watters, Thomas Mancuso

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. Identify indications for intubation.
2. Explain how to perform orotracheal intubation.
3. Explain how to perform nasotracheal intubation.
4. Select the correct size endotracheal tube for patients of different ages.
5. Describe the complications of intubation.
6. Explain the criteria for extubation.
7. Appraise the reasons for failed extubation and treatment strategies.
8. List the indications for tracheostomy.
9. Describe the major complications of tracheostomy.
10. List the criteria for decannulation.
11. Describe the setup and list the equipment needed for tracheostomy tube changes.

Key Term

Suctioning

Recognizing that a child is in respiratory distress or failure is an integral step in caring for a critically ill child. Ensuring adequate oxygenation, ventilation, and airway protection is a major goal in managing any ill child. Bag–mask ventilation ensures adequate oxygenation and ventilation. Endotracheal intubation ensures airway protection and the prevention of aspiration of either gastric contents or oral secretions. Establishing a secure airway is one of the unique and challenging procedures associated with neonatal and pediatric critical care that has a profound impact on life and death.

In all intubations, preparations for an unanticipated difficult airway should be made. References that provide details for this eventuality are widely available. Reviewing and being familiar with one or more is essential.[1,2,3] There are certain characteristics of patients that should alert the laryngoscopist to the increased chance that airway management will be difficult.[4]

INTUBATION

Rapid and unencumbered intubation of the trachea depends on knowledge of upper airway anatomy, the indications for intubation, and the appropriate use of both airway equipment and medications available to facilitate intubation. In addition to these considerations, it is important to ascertain the NPO (*nil per os*/nothing by mouth) status of the patient. For all emergent intubations, it should be assumed that the patient is not appropriately NPO and should be considered to be at risk for aspiration during the intubation. Before attempting to intubate any patient, the patient's history

and physical appearance must be assessed. In addition to reviewing the current state of the cardiovascular and respiratory systems, the patient's airway must be carefully assessed. The child's parents may have information about airway difficulties. The electronic medical record (EMR) may also have information about prior airway management, either in anesthesiology records or possibly notes from intensivists or otolaryngology (ORL) surgeons. If airway manipulation is expected to be difficult, airway techniques other than direct laryngoscopy may be needed (see Approaches to the Difficult Airway).

INDICATIONS

There are many specific indications for endotracheal intubation. Common reasons are listed here:

1. Respiratory failure
   - Hypoxemia/hypercarbia
   - Neuromuscular disease
2. Upper airway disorders
   - Obstructive sleep apnea
   - Structural upper airway anomaly
   - Airway protection against aspiration risk
3. Hemodynamic instability
4. Other
   - Planned elective hyperventilation
   - Pulmonary toilet

The need for intubation because of respiratory failure results from deficits in oxygenation or ventilation, or both, taken in concert with the patient's clinical condition. Although clinical judgment may suffice to diagnose respiratory failure, there are laboratory parameters that can also be used, if they can be obtained. Ventilatory failure can be defined as an acute elevation of arterial partial pressure of carbon dioxide ($Paco_2$) to greater than 50 to 60 mm Hg with a pH less than 7.3. If this is not responsive to other interventions, in most cases intubation and ventilation are indicated. Hypoxemic respiratory failure is defined as an arterial partial pressure of oxygen (Pao2) less than 60 mm Hg while breathing an Fio_2 greater than or equal to 0.60. These definitions assume that there is no intracardiac right-to-left shunt resulting from a congenital cardiac defect.

It is difficult to reliably administer an Fio_2 greater than 0.8 using traditional devices for the administration of supplemental oxygen. Therefore, a patient with decreasing oxygen saturation who is unresponsive to increases in oxygen concentration is a candidate for an escalation of care that may include both noninvasive and invasive methods of providing support, such as noninvasive positive pressure or intubation and mechanical ventilation.

Hypoxemic respiratory failure in children is most commonly caused by pneumonia or bronchiolitis; however, upper airway obstruction may also cause respiratory failure. Examples in this category include diseases such as laryngotracheobronchitis (i.e., croup), epiglottitis, laryngeal papillomatosis, and severe subglottic stenosis. Protection from aspiration is another indication for intubation. This can occur in patients with severe weakness from Guillain-Barré syndrome of botulism, patients who have experienced central nervous system (CNS) damage from trauma or cerebrovascular accident, or patients who have had a drug or ethanol (ETOH) overdose.

Some patients are best managed in the operating room (OR) with both an anesthesiologist and ORL surgeon present. These include patients who have a penetrating or crush injury to the midface, tongue, maxilla, or mandible or patients who have infection of the anterior neck (Ludwig's angina) or hematoma of the neck (as may occur in patients with bleeding disorders) with accompanying airway deviation.

EQUIPMENT

Anticipating and preparing for intubation by collecting the proper equipment are essential components of successful endotracheal intubation. The equipment necessary for intubation is listed in Table 13-1. Using the anesthesiology mnemonic MSMAID is a very useful aid in preparation for elective intubation.

MSMAID

M: Machine, which refers to an anesthesia machine; here it can refer to a mechanical ventilator to be used once the intubation is completed.

S: Suction, essential for any airway manipulations.

M: Monitors, also crucial. The laryngoscopist must, of course, never take her or his eyes from the airway but can hear changes in the tone of the oximeter and the heart rate.

A: Airway, which indicates that all possible needed equipment is available: face masks, oropharyngeal airway (OPA), laryngeal mask airway (LMA), laryngoscopes, and endotracheal tubes (ETTs). If an emergency tracheostomy is considered a possibility, strong consideration should be given to performing the intubation in the OR as described previously.

Table 13-1 Essential Equipment for Intubation

MNEMONIC STEP	EQUIPMENT
Monitors	ECG, pulse oximeter, BP, end-tidal CO_2 detector, stethoscope
Suction	Yankauer suction catheter, ETT suction catheters
Machine	Oxygen source, functioning bag and mask
Airway	Masks, oral airways, nasal trumpets, endotracheal tubes, appropriate stylet, laryngoscopes (handles, curved and straight blades, bulbs, batteries), McGill forceps, tape, benzoin
Intravenous	One patent intravenous line
Drugs	Anesthetic and resuscitative agents

BP, Blood pressure; *ECG,* electrocardiogram; *ETT,* endotracheal tube.

I: Intravenous (IV) access; an elective intubation should not be undertaken without secure IV access.
D: Drugs; medication to facilitate laryngoscopy and intubation as well as resuscitation medications should be immediately available.

Endotracheal Tubes

Once a decision has been made to perform intubation, the appropriate size and type of ETT (as well as one size larger and one size smaller) should be obtained. The ETTs most commonly used are sterile, disposable, and made of clear nontoxic plastic or polyvinyl chloride. The tubes have markings placed longitudinally 1 cm apart that can be used as reference points for proper placement once endotracheal intubation is accomplished (Figure 13-1). The distal end of the ETT may contain a side hole, a Murphy eye, to prevent complete obstruction if mucoid secretions occlude the distal end of the ETT. Microcuff ETTs have a small, very thin cuff located more distal on the tube than the cuffs on other types of ETTs. Microcuff ETTs do not have a Murphy eye. The appropriate ETT size is determined by the patient's age and size. The appropriate ETT for any child 1 year of age or older may be determined by the following formula:

$$\text{Internal diameter (mm)} = (\text{age [yr]} \div 4) + 4$$

Using this formula, a 4-year-old child would need a 5.0-mm ETT, an 8-year-old child would need a 6.0-mm ETT, and so on.

Accurate selection of an ETT takes into consideration the child's weight (Table 13-2), size, and length.[5-6] Comparing the size of the patient's pinky with the size of the ETT is a method to approximate the appropriate size for a child. An ETT one-half size smaller and one-half size larger than the estimated or calculated size should always be available. The appropriate adult ETT size for an adult female is 7.0 mm and for an adult male is 8.0 mm.

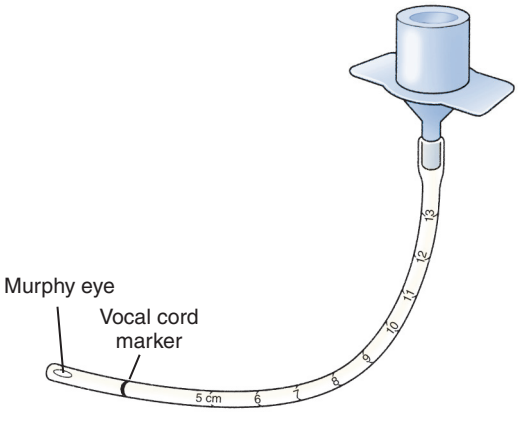


FIGURE 13-1 Endotracheal tube with distance markings.

Table 13-2 Neonatal Resuscitation Program Guidelines for Pediatric Endotracheal Tube Size

CHILD'S WEIGHT OR AGE	INTERNAL DIAMETER (mm)
Premature	
Less than 1000 g	2.5
1000-2000 g	3.0
2000-3000 g	3.5
Normal Newborns	
3000-4000 g	3.5-4.0
Infants and Children Younger than 12 Years	
6-12 mo	4.0-4.5
1-2 years	4.5
4 years	5.0
6 years	5.5
8 years	6.0
10 years	6.5
Children 12 Years of Age and Older	
Female	7.0-8.5
Male	8.0-10.0

Cuffed and Uncuffed Tubes

Because the cricoid cartilage is the narrowest portion of the pediatric airway until about 8 years of age, use of an uncuffed ETT had been recommended. In 2005 the American Heart Association's Pediatric Advance Life Support (PALS) program stopped recommending uncuffed tubes because there was no evidence to support one over the other. Today it is left up to the clinician to determine whether a cuff is needed for patients younger than 8 years. As a child grows, the airway becomes more tube shaped, with the vocal cords, not the subglottic space, becoming the smallest cross-sectional area of the airway.[7] A cuffed ETT helps create a seal to occlude unwanted air leaks during positive-pressure ventilation. The cuff also reduces the likelihood of pulmonary aspiration, although this is not guaranteed. However, with the advent of low-profile cuffs in smaller ETTs (as low as 3.0 mm), more anesthesiologists at children's hospitals are using them in the operating room in small children and infants.[8] The deflated cuff on the distal end of the ETT increases the outer diameter of the tube by approximately 0.5 mm compared with uncuffed tubes. To compensate for the increased diameter of the cuff, a smaller tube, 0.5 to 1 mm, is inserted when the cuff is present.

Laryngoscope Blades and Handles

The laryngoscope is the instrument used to expose the glottic opening during intubation. It consists of two parts: a handle and a blade. The handle is available in two sizes: large and small. The handle also contains batteries that power a light source incorporated into the blade. The large handle is recommended for an

adult, but it may also be suitable for an infant, child, or adolescent depending on operator preference and patient characteristics. Because of its size and ease of manipulation, the small handle should be used for a premature infant or newborn. Before commencing the process of intubation, the blade and handle should be tested to ensure that they fit together properly and lock in place. The light bulb should be functional and screwed in place securely.

Many types of laryngoscope blades are available. The Miller blade is a straight blade that is available in multiple sizes. The Philips blade comes in sizes 1 and 2 and is a straight blade that has the advantages of being wider than the Miller blade and having a small curve at its tip. The Philips blade is especially useful in children who have laryngomalacia, because the floppy epiglottis can be lifted out of the way. Macintosh blades are curved and wide. The Macintosh 2 blade can be used in children weighing approximately 17 kg. The Macintosh 3 blade can be used in patients who weigh more than 25 kg. Each blade requires a different technique for exposing the glottis. When a straight blade is used, the epiglottis may be lifted with the tip of the blade and pressed against the base of the tongue (Figure 13-2). In contrast, the tip of the curved blade is placed in the vallecula, the space between the epiglottis and the base of the tongue. As the laryngoscope is pulled forward, it elevates the epiglottis and exposes the glottis (Figure 13-3). Multiple blade types and sizes should be immediately available during any intubation procedure.

A video laryngoscope allows visualization of the larynx without requiring a direct line of sight to align the oral, pharyngeal, and tracheal axes. This may be very helpful in cases of a difficult airway but has not been shown to facilitate routine intubation.[9] Video laryngoscopes should be considered in cases in which precautions are necessary for the possibility of cervical spine instability.

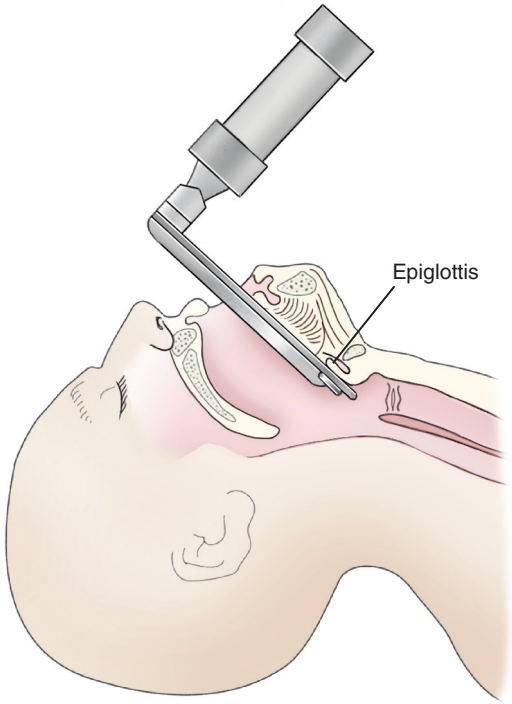


FIGURE 13-2 Direct laryngoscopy using a straight (Miller) blade.

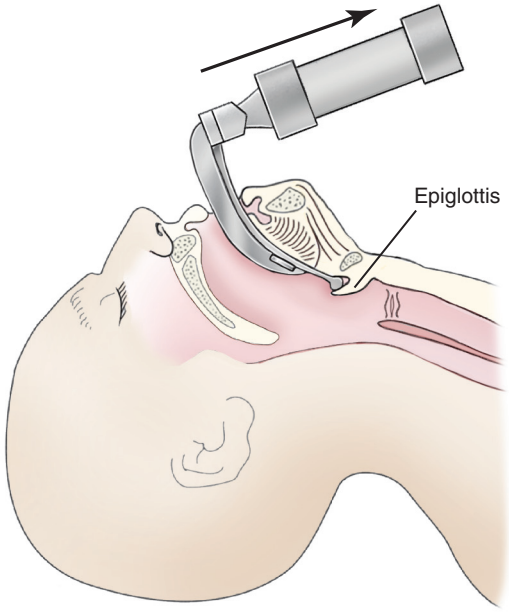


FIGURE 13-3 Direct laryngoscopy using a curved (MacIntosh) blade and demonstrating proper lifting technique. Note the upward and forward lift while the wrist is held straight.

Laryngeal Mask Airway

The LMA (Figure 13-4) is a useful alternative to a bag–mask apparatus.[10] If ETT placement is unsuccessful, an LMA can be used as a temporizing measure. The American Society of Anesthesiologists (ASA) Practice Guideline for Management of the Difficult Airway includes the use of supraglottic airways, of which an LMA is the most commonly used. Supraglottic airways such as an LMA do not provide a secure airway and may permit aspiration of gastric or oral secretions.

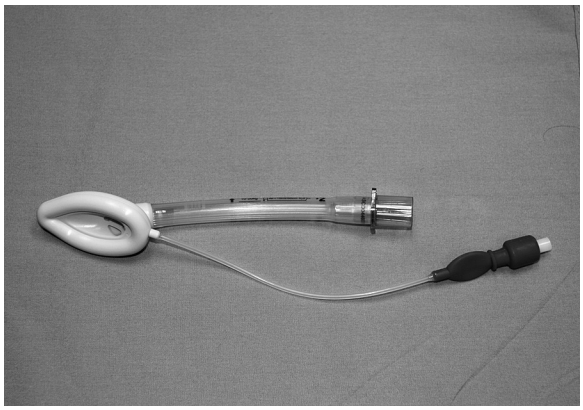


FIGURE 13-4 A laryngeal mask airway (LMA).

Table 13-3 Suggested Laryngeal Mask Airway Size Based on Weight

SIZE	WEIGHT (KG)
0.5	Infants up to 2.5
1	2.5-5
1.5	5-10
2	10-20
2.5	20-30
3	30-50
4	>50

The lubricated LMA is placed by itself into the pharynx above the epiglottis and can be used for positive-pressure ventilation using a peak inflating pressure (PIO) of less than 20 cm H_20. The deflated mask is manually inserted into the patient's mouth and guided blindly along the hard palate. It is advanced until resistance is encountered. (The distal tip of the LMA rests against the upper esophageal sphincter at this point.) The balloon is inflated to form a seal in the pharynx. There are several types of LMAs, but there is little evidence to endorse one type over the others. LMAs come in different sizes, with recommendations based on the weight of the patient for the appropriate size to use. Every emergency airway cart should have all sizes of LMAs available (Table 13-3).

Suction Equipment

Suctioning of the mouth and posterior pharynx before direct laryngoscopy facilitates viewing of the vocal cords if secretions are present. Suctioning of the ETT after it is placed clears the lower airway of secretions. Suction equipment should include a tonsil-tip suction catheter (e.g., Yankauer); several standard sterile suction catheters; and, for use in smaller children, soft-tipped smaller catheters.

INTUBATION PROCEDURE

The indication for endotracheal intubation will determine the most appropriate technique to use during the process of securing the airway for the patient. The options available to the bedside clinician include intubation after administration of medications (such as hypnotics, anxiolytics, analgesics, or neuromuscular blocking agents) to facilitate laryngoscopy and intubation, awake intubation, or scheduling the intubation procedure in the operating room with a pediatric anesthesiologist and pediatric ORL surgeon. This last option should be strongly considered in cases of a known difficult airway. Discussion of the medications used to facilitate laryngoscopy and intubation is beyond the scope of this chapter; however, the laryngoscopist must be very familiar with whatever medications she or he plans to use in his context. In addition to laryngoscopy, the laryngoscopist must be an expert in airway management, including ventilation via face mask and correct use of supraglottic airway devices such as an LMA, before administration of medications that will eliminate the child's own spontaneous respirations. The ETT can be placed through the oropharynx or nose based on the clinical situation. Universal precautions (i.e., the use of gloves, a mask, and eye protection) should be observed with all intubation procedures to reduce the risk of transmitting infectious diseases.

OROTRACHEAL INTUBATION

Proper positioning of both the patient and the laryngoscopist should be optimized before starting orotracheal intubation. The height of the bed should be such that the patient's head is level with the laryngoscopist's xiphoid process. This will allow direct visualization of the airway without putting undue physical stress or strain on the clinician. The occiput of an infant is larger than that of an older child. A small roll placed under the shoulders of a younger patient facilitates viewing of the vocal cords during laryngoscopy. Direct laryngoscopy may be facilitated by placing a roll under the shoulders of any patient lying on a soft mattress.

If the patient is breathing spontaneously, the application of 100% oxygen for 5 minutes with a bag and mask with 5 cm H_2O of positive end-expiratory pressure (PEEP) is sufficient to fully oxygenate the lungs in the absence of lung disease. If measurement of end-tidal exhaled oxygen concentration is available, it can be used to determine the adequacy of preoxygenation (or denitrogenation). For a patient who is not breathing, the laryngoscopist should *carefully* administer 100% oxygen for several minutes via face mask. Air should go in and out of the lungs and not into the stomach. Such patients may be deeply sedated or unconscious but must be considered to be at risk for aspiration. Medications administered to facilitate intubation include oxygen (first and foremost), hypnotic agents, amnestic agents, analgesic agents, and neuromuscular blocking agents. The use of external cricoid pressure by a qualified assistant to decrease the chances of aspiration of gastric contents is controversial.[11] Properly held pressure over the cricoid cartilage may or may not occlude the esophagus and minimize passive flow of gastric contents into the pharynx and may or may not prevent the aspiration of gastric contents.[12] Improperly held cricoid pressure may lead to distortion of the larynx and thus make visualization of the larynx more difficult.

After the patient has been adequately preoxygenated and the neuromuscular blocking agents, along with appropriate doses of hypnotics, analgesics, opioids, and other adjuncts, have been administered, a

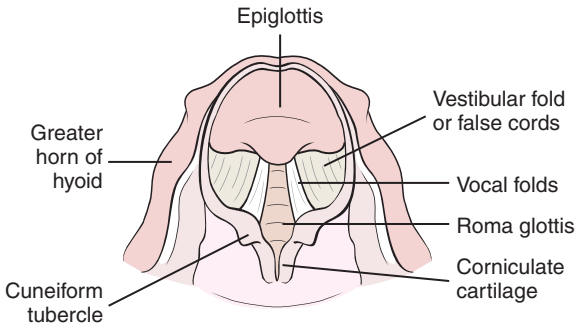


FIGURE 13-5 Glottic structures viewed through the laryngoscope. (From Cairo JM, Pilbeam SP: *Mosby's respiratory care equipment*, ed 8, St. Louis, 2010, Mosby.)

nerve stimulator must be used to ascertain the degree of muscle relaxation before attempting laryngoscopy. Inserting a laryngoscope into a partially paralyzed patient may result in the patient vomiting or biting on the laryngoscope and will not allow passage of the ETT into the trachea. Positive-pressure ventilation while waiting for the relaxant to have full effect must be administered carefully to minimize insufflation of the stomach, which in turn may lead to regurgitation and aspiration. Cricoid pressure should be applied in the appropriate manner; the mouth and oropharynx are suctioned as needed, and laryngoscopy is then performed.

Figure 13-5 illustrates the glottic structures as viewed through the laryngoscope. After visualizing the glottic opening, the appropriate size ETT is held in the right hand and is introduced into the right side of the patient's mouth to avoid obstructing the view of the glottic opening while placing it. The tip of the ETT is advanced through the glottic opening so that the single black ring is just distal to the opening of the glottis. If the ETT is marked with three rings, the ETT should be inserted until the double black ring is distal to the glottic opening. When inserting a cuffed ETT, the tube is advanced until the cuff is distal to the vocal cords. Any single attempt at intubation should not exceed 30 seconds. If intubation cannot be readily performed, the patient's airway should be reestablished by bag–mask ventilation to ensure adequate oxygenation. If needed, an oral airway should be used to facilitate bag–mask ventilation.

After intubation, it is essential that proper positioning of the ETT be quickly determined. The presence of vapor in the ETT is not an accurate test for proper placement. Proper endotracheal, and not esophageal, placement of the ETT is confirmed with sustained presence of end-tidal CO_2. Capnography via a monitor is preferred over a single-use end-tidal device (Pedi-Cap; Nellcor, Boulder, CO). End-tidal CO_2 should be monitored for at least five breaths after intubation. Even an ETT placed in the esophagus may have transient detection of CO_2 as a result of the presence of CO_2 in the stomach (which can occur because of bag–mask ventilation). The chest is auscultated after intubation as a method for assessing whether the ETT is in the trachea. Unless there is known unilateral pulmonary pathology such as a pleural effusion or pneumothorax, breath sounds should be heard over the lateral aspect of the chest wall on both the right and left sides. It should be noted that auscultation is not the most accurate method of assessing proper ETT placement.

The proper ETT position is in the midtrachea, below the clavicle and 1 to 2 cm above the carina. The proper depth of the ETT can be estimated based on the size of the ETT used. The internal diameter of the ETT is multiplied by 3, and the ETT is taped at that centimeter mark at the lip (e.g., a 4.0-mm ETT should be taped at 12 cm at the lip). The proper length of the ETT can be estimated in premature infants according to their weight: add 6 to the infant's weight in kg (e.g., in a 1-kg baby the ETT should be taped at 7 cm). This formula cannot be used in children greater than 3 kg. Confirmation of the proper position of the ETT should be confirmed radiographically. ETT depth formulas may not be accurate in patients with micrognathia or midface hypoplasia.

The necessary equipment (Box 13-1) for securing the ETT is assembled before attempting intubation. The ETT is secured by preparing the skin with benzoin. Two strips of tape are cut long enough to reach from the lateral aspect of the right eye to the lateral aspect of the left eye. Each piece is split into a Y shape, with the arms of the Y two-thirds the length of the tape. The tape should have a width that will easily fit on the upper lip and around the ETT. One end of the tape is secured to the cheek and wrapped around the tube in "candy cane" fashion (Figure 13-6). Other taping methods may be used to secure the ETT, as long as the method can be performed by all personnel involved in airway care and is fast and secure. The centimeter mark where the ETT is secured must be recorded to allow assessment of proper position at a later time if needed.

Various devices are available to secure the ETT as an alternative to using tape. Figure 13-7 illustrates an example of one of these devices. When selecting a device to secure the tube, it is important that it does not occlude access to the mouth, provides minimal tube movement when the head moves, and secures without creating ulcers at pressure points. In addition, the same rules apply as with taping methods: fast, easy,

Box 13-1 Equipment for Endotracheal Tube Stabilization

- Alcohol
- Tincture of benzoin
- Scissors
- Adhesive tape
- Two precut Y-shaped pieces of tape

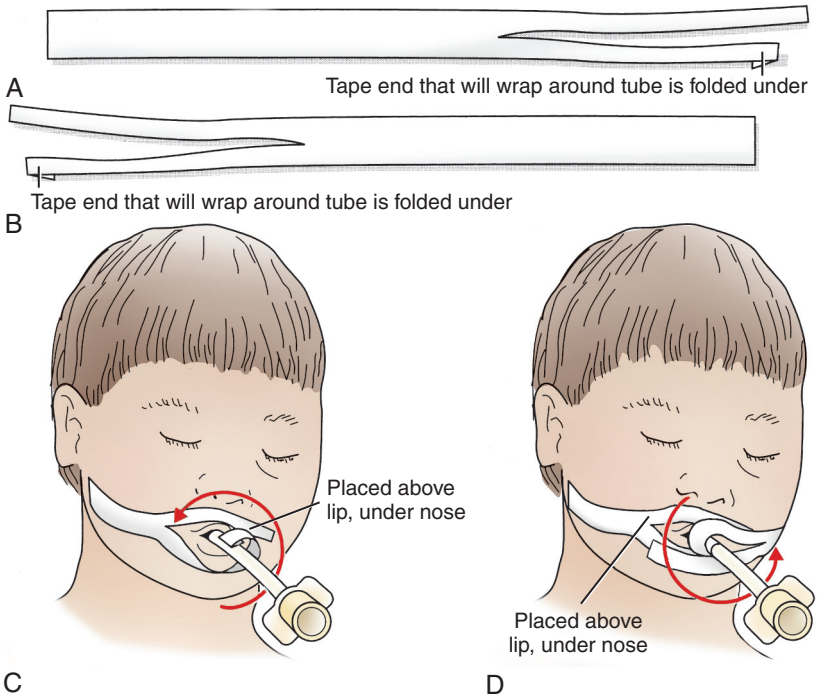


FIGURE 13-6 Steps used to secure an endotracheal tube (ETT) with tape. **A** and **B**, Slit two pieces of tape, making a Y on one end of each piece (as shown). Turn under the end of the tape that will be wrapped around the ETT. This will make tape removal easier. **C**, Apply benzoin to the area below the nose and across the cheeks (where tape will be placed). Attach one piece of tape to the cheek and below the nose, wrapping the bottom of the Y around the ETT. The tape should be placed under the tube (chin side) first, and then wrapped around the top of the tube. **D,** Repeat step C on the other side of the face.

FIGURE 13-7 The NeoBar. A commercial adaptation of the Logan bow for stabilizing an infant endotracheal tube. (Courtesy Neotech Products, Inc., Valencia, CA.)

and able to be applied by all personnel. Evidence that these devices help reduce the incidence of accidental extubation is inconclusive. However, it does suggest that the devices may be more effective on a small infant than on a larger infant or child.[13,14]

NASOTRACHEAL INTUBATION

Once a patent and stable airway has been established by the orotracheal route, if indicated, switching to a nasal tube can follow. The patient's nares are prepared by spraying a vasoconstrictive agent, such as oxymetazoline, into the opening to decrease the size of the mucosa and edema that results from passing a nasotracheal tube. Phenylephrine should not be used because of the systemic absorption and resultant effects on blood pressure and heart rate. An ETT of a size that will pass easily through the nares is used. Depending on the patient's anatomy, this may either be the same size as the tube selected for orotracheal intubation or 0.5 mm smaller.

The tube is lubricated with either petroleum jelly or 2% lidocaine jelly. The tube is then inserted into the nares until approximately one-half of it has passed through the nose. While an assistant holds the existing oral ETT in the left corner of the mouth, the glottis is exposed in the same manner as for orotracheal intubation. Once the nasal tube is visualized in the hypopharynx, the tip of the tube is grabbed with McGill forceps held in the right hand and the nasal tube is lifted up and in front of the opening to the larynx. When using a cuffed ETT, the practitioner must be sure that the McGill forceps do not damage the cuff. When direct visualization of the glottic opening is ensured, the assistant is asked to remove the orotracheal

tube while the nasotracheal tube is simultaneously advanced into the trachea. The centimeter mark at the nares is noted and the ETT is taped securely in place. The major contraindications to nasotracheal intubation are a risk of hemorrhage such as thrombocytopenia and abnormal clotting times. Other situations when nasotracheal intubation should be avoided are the presence of facial trauma, suspected basilar skull fracture, and abnormal anatomy such as choanal atresia.

ORAL VERSUS NASAL INTUBATION

Disadvantages of nasal intubation include a predisposition to sinusitis, pressure necrosis of the nares, and bleeding complications associated with passing the ETT through the nares and upper airway.

APPROACHES TO THE DIFFICULT AIRWAY[1,2,3]

Some children may present challenging anatomic or physiological problems that may make intubation difficult or impossible. Congenital causes of a difficult airway include the presence of micrognathia, retrognathia, midface hypoplasia, limited mouth opening, space-occupying lesion of the mouth, and limited cervical spine mobility (e.g., as a result of Klippel-Feil syndrome). Patients with a storage disease, such as mucopolysaccharidosis (Hunter's syndrome or Hurler's syndrome), may have several sites of airway obstruction and be extremely difficult to intubate. Children with craniofacial syndromes (e.g., Treacher Collins syndrome or Pierre Robin syndrome) are assumed to have a difficult airway, even if they have undergone jaw advancement. Acquired causes of a difficult airway include limited mouth opening as a result of decreased temporomandibular joint mobility (as may occur in rheumatoid arthritis or muscular dystrophy), orofacial trauma, trauma to the neck, hematoma of the neck, and infections of either the anterior neck or the epiglottis. Patients with a history of burns or radiation to the face or neck are very difficult to intubate. The clinician should always have additional options available to secure the airway in case orotracheal intubation is not successful. An LMA should be readily available during intubation attempts. A fiberoptic laryngoscope greatly facilitates intubation of patients with a difficult airway.[15] Clinicians should first learn how to use the fiberoptic laryngoscope on patients with a normal airway before using this device on patients with an abnormal airway. *If a fiberoptic bronchoscope is to be used in the intubation of a child with a difficult airway, the operator of the bronchoscope must be not simply familiar with its use, but an expert in its use.* This is true for any difficult airway adjunct device. If it is known that a patient will be difficult to intubate, medications that take away the patient's own spontaneous respiratory effort should *not* be administered. Patients with such difficult airways are best managed in the OR with management by experienced pediatric ORL surgeons and pediatric anesthesiologists. In general, it is important that no more than three attempts be made at direct laryngoscopy of any patient. A "cannot intubate" scenario can devolve into a "cannot ventilate" (i.e., cannot bag–mask ventilate) scenario if the airway is traumatized by multiple intubation attempts. As mentioned, flexible fiberoptic intubation, retrograde intubation, and cricothyroidotomy require the advanced airway skills of either an experienced pediatric anesthesiologist or pediatric ORL surgeon.

Emergency Tracheostomy

For infants and small children, a tracheotomy is best performed after the airway has been secured. Circumstances in which endotracheal intubation may be difficult or impossible include severe trauma or hemorrhage, craniofacial problems, and a newborn with complete laryngeal obstruction. Alternative approaches to securing the airway are dictated by the urgency of the clinical situation and the age of the patient. These include tracheotomy under local anesthesia, mask ventilation, or cricothyroidotomy.

ARTIFICIAL AIRWAY CUFF MANAGEMENT

If a cuffed ETT or tracheostomy is used, the cuff is inflated once proper placement of the artificial airway is ensured. If the patient has a large leak with the cuff deflated, then the cuff is inflated to minimal leak (see the next paragraph). To inflate the cuff, a 5- or 10-mL syringe is attached to the pilot balloon and air is added gradually to the cuff. Positive pressure applied through the ETT should produce an audible escape of air, or leak, at less than or equal to 15 to 20 cm H_2O. The larynx should be auscultated to confirm the leak. Pressures exceeding 20 to 25 cm H_2O, particularly if maintained for extended periods of time, are associated with ischemia and necrosis of the tracheal mucosa, which can result in the development of subglottic stenosis. Cuff inflation may cause vocal cord necrosis if the cuff is positioned at the level of the vocal cords instead of within the subglottic trachea.

Cuff pressure should be checked approximately every 8 hours to guarantee that it does not exceed the recommended levels. If large amounts of air are required in the cuff and a leak persists, one of two possibilities exists: (1) the cuff is damaged or (2) it has not been completely advanced through the cords. The latter problem can be identified by direct laryngoscopy.

PATIENT MONITORING

Continuously evaluating a patient undergoing intubation is essential to ensure a safe and effective outcome. Before the airway is manipulated, the heart rate, blood pressure, and oxygen saturation should be monitored and recorded; these values should then be monitored continuously. A continuous electrocardiogram monitors the heart for arrhythmias. A single individual should be made responsible for the task of monitoring

the patient continuously during the procedure. If, at any time, acceptable values or rhythms are breached, the clinician should be warned and attempts at intubation stopped. The airway should be reestablished using a bag and mask.

COMPLICATIONS

Serious complications from endotracheal intubation may occur at any time during or after the intubation procedure. The most serious complication is loss of the airway (i.e., cannot intubate, cannot ventilate). Even if intubation is successful, other complications are common, including hypoxia caused by prolonged intubation attempts and mainstem intubation (very often in the right mainstem bronchus). Bronchospasm may occur during attempts at intubation because of the stimulus of laryngoscopy and the ETT. More serious airway trauma may occur during multiple attempts at intubation. An ORL surgeon should be called to evaluate any patient for whom there is a suspicion of perforation or laceration of the pharynx or larynx. Vital sign instability may occur during laryngoscopy and intubation. Although the complete assessment and treatment of abnormal vital signs that occur during an intubation are beyond the scope of this chapter, the following brief remarks summarize common occurrences: Bradycardia or tachycardia may occur. Although bradycardia may be a vagal response to laryngoscopy, hypoxia must be considered and ruled out before attributing bradycardia to a vagal response. Tachycardia and hypertension generally result from the stimulus of the procedure itself and, depending on the details of the clinical situation, may be treated with additional hypnotics or analgesics. If hypotension occurs, it is often a result of the medications used to render the patient unconscious or unaware of the procedure. Depending on the details of the clinical situation, treatment may be with either IV fluid or a vasoactive agent.

EXTUBATION

The most important question to consider when evaluating a patient for extubation is whether there has been improvement in or reversal of the disease process that initially mandated the intubation. Before extubation, the patient must be able to breathe spontaneously with an adequate tidal volume and respiratory pattern and must have adequate neurologic integrity to protect the airway. The presence of a strong cough and gag reflex and the ability to swallow are indications that a child will protect her or his airway after extubation. The patient should also have a stable heart rate and blood pressure before extubation. However, depending on the details of the clinical situation, the requirement for modest pharmacologic support of these hemodynamic variables is not an absolute contraindication to extubation.

EQUIPMENT

As with the intubation procedure, anticipation and preparation are essential in accomplishing a smooth extubation. The equipment necessary for extubation includes a bag–mask setup, suction equipment, adhesive remover, and all the items previously listed for intubation (see Table 13-1). This ensures a proactive approach to patient care in the event that the patient does not tolerate extubation and requires reintubation.

PROCEDURE

Before extubation, unless contraindicated by the details of the patient's condition, the Fio_2 should be increased to 1.0 for several minutes to fully preoxygenate the patient. If needed, aerosolized β-agonists can be administered before extubation. The oropharynx and trachea must be suctioned before extubation. After tracheal suctioning, it is important to reestablish the functional residual capacity (FRC) with several manual or ventilator breaths and an Fio_2 of 1.0, as described previously. If the patient has been receiving enteral feedings, the feedings are discontinued for at least 6 hours before the planned extubation.

If a cuffed tube is in place, the cuff should be deflated. While the ETT is held in place, the tape is removed from the face and tube with an adhesive remover. One large breath is administered, and the ETT is withdrawn from the trachea near peak inflation. Most patients will then cough and begin to breathe spontaneously. It is not unusual, especially in small children, for a short interval of breath holding to occur. Oxygen is administered by the most appropriate delivery device, such as a nasal cannula, face tent, face mask, or oxyhood. The oxygen concentration is titrated to maintain an oxygen saturation level that is clinically indicated.

COMPLICATIONS

Sore throat and hoarseness are common complaints after extubation. The presence of an ETT may cause edema of the laryngeal structures. Once extubation is successfully accomplished, if it is going to occur, postextubation stridor develops within minutes and usually peaks within 8 hours. This condition has been well described and occurs often in the pediatric population. Corticosteroids, aerosolized racemic epinephrine, and helium-oxygen mixtures (heliox) have all been used to treat this complication.[16,17] A metaanalysis of the use of corticosteroids in the prevention of reintubation and postextubation stridor did not show any statistically significant difference in reintubation rates, but there was a significant decrease in stridor.[16]

ACCIDENTAL EXTUBATION

Risk factors associated with accidental extubation include failure to secure the ETT properly, lack of adequate sedation, failure to provide adequate restraint,

and performance of a procedure such as chest radiography.

Nasal Mask Ventilation and Heliox

To ease the transition to spontaneous ventilation or when there is residual upper airway obstruction, noninvasive positive-pressure mask ventilation may be helpful. A nasal face mask that fits over the nose and mouth is used to deliver both inspiratory and expiratory pressure. The bilevel positive airway pressure (BiPAP) system may be a useful method to transition the patient to spontaneous respiration after extubation. If a fixed narrow opening, such as in subglottic stenosis, is the cause of difficulty, heliox may be beneficial.[17] Its lower density may reduce the viscosity of airflow and decrease airway resistance. Mixtures of helium to oxygen are available as 80% helium to 20% oxygen and 70% helium to 30% oxygen. Additional oxygen can be titrated into the mixture; however, as the concentration of oxygen increases, the density of the gas decreases, and so does the agent's efficacy. When the upper airway obstruction has resolved, the patient can be gradually weaned from the heliox [by definition, weaning is a process experienced by a person, not an action done to an object].

Extubation Failure

The best predictor of successful extubation is a clinical assessment by the team who has been involved in the child's care. Factors to consider include the ease with which the child has tolerated decreases in ventilatory support to "minimal pressure support," or the degree of pressure support that corrects for the increased resistance to gas flow from the ETT and breathing circuit. This minimal degree of support should reproduce the condition of the child after extubation. Successful extubation appears to be inversely related to the duration of intubation.[18,19] A child who fails extubation should be thoroughly evaluated for cause of failure. An air leak is often checked before extubation to assess for airway edema but may not predict successful extubation.[20] Use of dexamethasone is often recommended, particularly when no air leak is audible at a pressure of 25 cm H_2O before extubation, and may have some benefit in children, but the studies are inconclusive.[21,22] Consultation with a pediatric otolaryngologist may be indicated.

Evaluation of stridor after extubation may include examination of the airway in the OR with direct laryngoscopy and bronchoscopy. The most common cause of extubation failure is soft tissue swelling of the larynx and subglottis or more chronic inflammation such as vocal cord granuloma. Often these can be managed with conservative medical therapy and reintubation with a smaller tube followed by a repeat bronchoscopy. Persistent lesions can be managed with excision or balloon dilation in cases of isolated soft tissue edema.[23] In some cases, it may be beneficial to perform an awake examination at the bedside before reintubation. This will allow for diagnosis of dynamic airway lesions such as laryngomalacia or vocal cord mobility problems. When injury or inflammation progresses to a more mature stage, stenosis ensues. In the diagnosis of lower airway lesions such as subglottic narrowing caused by edema, subglottic cysts, or subglottic stenosis, bronchoscopy is necessary.

The degree of subglottic stenosis is determined in the OR by using ETTs to estimate the size of the larynx. This is performed under general anesthesia at laryngoscopy or can be estimated if the patient is intubated with an uncuffed ETT. The appropriate size tube for a child will leak at less than 25 cm of H_2O pressure. The Cotton-Myer grading chart estimates percentage of airway obstruction. It is subdivided into grades I to IV, with IV representing no detectable lumen. The degree of obstruction helps direct therapy and can predict the success or failure of different treatment regimens. It also provides a framework to allow clinicians to compare data and outcomes.[24] In the specific case of neonates with isolated subglottic stenosis, an anterior cricoid split, performed by a pediatric ORL surgeon, can be effective at achieving extubation.[25] In cases of airway obstruction caused by subglottic stenosis and other critical airway obstructions, tracheostomy or laryngotracheal reconstruction may be indicated.

TRACHEOSTOMY

A child who is not a candidate for extubation and requires prolonged ventilatory support or upper airway reconstruction may require a tracheostomy. Previously there has been confusion over the terms *tracheotomy* and *tracheostomy.* **Tracheotomy** describes the actual incision into the trachea, whereas **tracheostomy** defines a mature opening in the neck and is more commonly used currently.[26]

INDICATIONS FOR TRACHEOSTOMY

Over the past 4 to 5 decades, the indications for tracheostomy in children have changed significantly. This primarily reflects improvements in the management of premature infants and critically ill children. Most tracheostomies are performed in the first year of life.[27-29] There are three main indications for **tracheostomy** in children: upper airway obstruction, prolonged ventilatory support, and pulmonary toilet.[30,31]

Upper Airway Obstruction

Children with congenital or acquired upper airway obstruction may require a tracheostomy in the first few months of life if extubation cannot be accomplished. In the case of congenital laryngeal stenosis, which varies in severity, tracheostomy may be required emergently after birth if the airway cannot be intubated or safely maintained. However, laryngotracheal stenosis (subglottic stenosis) is more often acquired after prolonged intubation, especially in neonates.[32] The

incidence of acquired subglottic stenosis has increased since the 1970s as a result of the increasing incidence of prolonged intubation of neonates.[33] An ETT can cause glottic and subglottic edema and erosion after 72 hours.

Bilateral vocal cord paralysis can cause stridor, airway obstruction, and failure to extubate. Congenital bilateral vocal cord paralysis may be idiopathic, but it is very important to rule out identifiable causes such as an Arnold-Chiari malformation or a neuromuscular disorder.[34] These children commonly experience severe airway obstruction and require tracheostomy. Decompression of the malformation may result in an improvement in symptoms. In idiopathic cases, vocal cord recovery has been reported as long as 5 years after diagnosis.[35,36] In cases associated with a neurologic disorder, the prognosis depends on the nature of the underlying cause.[37]

Less commonly, tracheostomy is required in patients with severe airway obstruction leading to obstructive sleep apnea that cannot be relieved surgically or managed with noninvasive ventilation, such as BiPAP or continuous positive airway pressure (CPAP).

In rare cases, critically ill children or children requiring multiple surgical procedures who are difficult to intubate because of complex airway anatomy may require tracheostomy. This is most common in children with complex craniofacial anomalies or severe craniofacial trauma.[38,39]

Prolonged Ventilatory Support

Children requiring tracheostomy for prolonged ventilatory support are typically very medically complex with multiple comorbidities. The need for prolonged intubation may be secondary to prematurity (bronchopulmonary dysplasia), central nervous system disorder, or poor pulmonary reserve. As medical advances have prolonged the lives of premature infants and medically complex children, this group has also significantly increased.[38]

Pulmonary Toilet

Children with severe dysphagia and neuromuscular disease who have trouble managing secretions may be prone to chronic aspiration and recurrent pneumonia. These children may benefit from tracheostomy for pulmonary toilet and improved quality of life.

MULTIDISCIPLINARY APPROACH

Tracheostomy is being performed increasingly in children with very complex chronic medical conditions.[40] In a large proportion of these patients, the tracheostomy will be necessary for a number of years, and possibly for their lifetime in those children requiring chronic ventilatory support.[40,41] Such children will require ongoing care and caregiver support, and it is paramount that these needs are completely addressed before tracheostomy placement. Guidance and counseling for patients and caregivers on whether to initially place a tracheostomy and what to expect over the long term after tracheostomy remain challenging.[40] The decision to perform a tracheostomy is based on the child's future prognosis, as well as on the family's ability to care for a child with a tracheostomy. Communication with the caregivers and patient, when appropriate, is important early in the decision-making process. Early education, even before placement of the tracheostomy, is paramount. It is essential to provide information about tracheostomy tubes, their care, possible complications, and any alternatives that may exist to allow for informed decision-making. A patient- and family-centered approach has shown great success. Whenever possible, it is important to assess the caregivers' ability to communicate and comprehend the implications of this life-changing event.[42] They should be given the opportunity to participate in the process whenever time and the patient's health status permits.[43-45]

This can be best addressed by a multidisciplinary approach with input from multiple specialties (e.g., pediatric intensive care medicine, otolaryngology, pulmonology, sleep medicine, anesthesia, feeding specialists, speech and language, and social work) and also, most importantly, from the caregivers. The use of multidisciplinary tracheostomy care teams with the promotion and implementation of standardized tracheostomy protocols and models of care has been shown to dramatically improve the quality of care provided to these children and caregivers and also dramatically reduce tracheostomy-related adverse events.[46,47]

TRACHEOSTOMY TUBE TYPE

Tracheostomy tubes come in various dimensions and materials, and selecting an appropriately sized tracheostomy tube is important before placement. The age, size, and medical condition of the patient, as well as the indications for the tracheostomy, determine the type of tube selected. Most pediatric tracheostomy tubes currently in use are made of PVC (e.g., Shiley) or silicone (e.g., Bivona), both of which cause minimal tissue reaction. Some studies suggest there may be slow leakage of phthalates from these substances, which may be toxic to a patient over time.[48,49] Metal tubes, now rarely used in children, can still be manufactured if necessary on an individual basis and can be helpful in patients with stomal issues.

Adult Versus Pediatric Tubes

Regardless of manufacturer or tube type, pediatric tracheostomy tubes are single lumen—there is no removable inner cannula. Fenestrated pediatric tracheostomy tubes are also not available. Furthermore, pediatric tubes are manufactured in neonatal and pediatric sizes.

Infants up to approximately 5 kg typically use the neonatal size.

Tracheostomy Tube Size

Tracheostomy tube size in children is primarily based on both the size of the child's airway and the clinical indications for the tracheostomy. The general rule is that the smallest tube capable of providing adequate ventilation is chosen. A larger tube may be required for ventilator-dependent patients to prevent air leak. However, a tube that is too large may cause tracheal mucosa injury with ulceration and bleeding, with the formation of granulation tissue and even subsequent fistulization or tracheal stenosis. If the tube is too long, it may migrate into the right bronchus.

Tracheostomy tubes have three dimensions: inner diameter, outer diameter, and length. The size of the tube reflects the inner diameter, similar to ETTs. The depth of the tube from the flange to its tip is the measurement of the length. The difference between neonatal and pediatric tubes is length. Neonatal tracheostomy tubes are shorter, ranging from 30 to 34 mm. Pediatric tubes intended for older children are longer, starting at 38 mm in length. The adequate length of a tracheostomy tube for a child can be determined by performing a flexible tracheobronchoscopy through the tube lumen to assess the tube position in relation to the carina. The same formula used to estimate ETT size in children older than 1 year of age can be used to estimate the appropriate size tracheostomy tube: (age in years/4) + 4 mm = internal diameter. The dimensions of three common brands of tracheostomy tube are compared in Table 13-4.

Table 13-4 Dimensions of Three Commonly Used Brands of Tracheostomy Tube

Cannula	INNER DIAMETER (mm)	OUTER DIAMETER (mm)	LENGTH OF CANNULA (mm)
Shiley			
3.0 neonatal	3.0	4.5	30
3.5 neonatal	3.5	5.2	32
4.0 neonatal	4.0	5.9	34
3.0 pediatric	3.0	4.5	39
3.5 pediatric	3.5	5.2	40
4.0 pediatric	4.0	5.9	41
4.5 pediatric	4.5	6.0	42
5.0 pediatric	5.0	7.1	44
5.5 pediatric	5.5	7.7	46
Portex			
3.0	3.0	5.0	36
3.5	3.5	5.8	40
4.0	4.0	6.5	44
4.5	4.5	7.1	48
5.0	5.0	7.7	50
5.5	5.5	8.3	52
Bivona Neonatal Cuffless*			
2.5	2.5	4.0	30
3.0	3.0	4.7	32
3.5	3.5	5.3	34
4.0	4.0	6.0	36
Bivona Pediatric*			
2.5	2.5	4.0	38
3.0	3.0	4.7	39
3.5	3.5	5.3	40
4.0	4.0	6.0	41
4.5	4.5	6.7	42
5.0	5.0	7.3	44
5.5	5.5	8.0	46

*From Smiths Medical (St. Paul, MN).

Cuffed and Uncuffed Tubes

Ideally, uncuffed tracheostomy tubes are preferred in children; however, if there is a ventilatory requirement, a cuffed tube may be necessary. Previously, only cuffless pediatric tracheostomy tubes were available, with cuffed pediatric tubes introduced over the last decade. Bivona cuffed tubes, both neonatal and pediatric, are available in all sizes, down to a 2.5-mm neonatal cuffed tube. Shiley cuffed neonatal and pediatric tubes are available from a 3.0-mm size.

There are three basic types of cuffs: high-volume, low-pressure; foam; and tight to shaft (TTS). The first two are inflated with air, whereas the last one requires sterile water. Shiley pediatric tracheostomy tube cuffs are inflated with air. One of the most commonly used cuffed tubes currently is the Bivona TTS tube. Bivona TTS tracheostomy tubes have a low-volume, high-pressure TTS cuff that is inflated with sterile water using a minimal leak technique. The TTS cuff is inflated with sterile water because the cuff is made of silicone, which is gas-permeable and would allow diffusion of air through the cuff over time. Water does not diffuse, and thus a constant cuff volume is maintained. The TTS cuff, when inflated, seals the trachea for a ventilated patient, and when deflated, rests tight to the shaft of the tube with the appearance and profile of an uncuffed tube. This allows the tube to be used for weaning patients from a ventilator, without having to change to an uncuffed tube, and also aids in speaking.

It is important to avoid overinflation of the cuff. Overinflation may lead to several complications. Initially, it may misalign the tube in the airway or eventually cause the cuff to leak. Over time, an overinflated cuff may create contact points in the distal airway, leading to ulcerations, granulation tissue, or ultimately stenosis or scarring. It may be helpful to visualize the tracheostomy endoscopically with the cuff inflated with

the usual amount of water or air to avoid such positioning problems. If the cuff appears tight, then less air or saline should be used. Some cuffs may not inflate in a symmetrical way, particularly when partly inflated, which may lead to asymmetrical positioning in the airway. Foam cuffs are usually reserved for special ventilation situations such as jet or oscillating ventilation, which requires much higher pressures to reduce the leak during inspiration. The cuff inflation can be varied with the ventilator to allow for air exit during expiration. This greatly reduces the amount of time the trachea is exposed to pressure.[50] Prolonged exposure to increased pressure can lead to tracheal dilation or "tracheomegaly."[51] Careful management of the tube size and cuff may prevent this complication. Cuff pressure should be checked regularly and adjusted as needed. Near consensus was reached regarding this concept in a recent tracheostomy clinical consensus statement by an expert panel.[42] Use of a minimal leak technique to minimize cuff pressures, as outlined earlier regarding the use of ETTs, is a way to determine adequate cuff inflation.

Custom Tracheostomy Tubes

When a specifically longer or shorter length of tracheostomy tube is needed, a specialized or custom tube can be ordered. The demand for custom pediatric tubes has increased because of the increased survival of infants and children with complex upper-airway and tracheoesophageal anomalies. Custom-length tubes are commonly needed in children with severe tracheomalacia, to stent open the trachea and reduce the ventilatory requirement. Other modifications available for custom tubes include flange shape (V and straight), shaft angle, cuff position and design, shaft style (standard silicone, Hyperflex wire–reinforced silicone), and connector type (swivel, fixed).[50] FlexTend tubes by Bivona have a flexible tube extension on the proximal side of the neck flange that can be very helpful in keeping ventilator connections away from the neck in infants with short chubby necks.

Tracheostomy Ties

Several types of tracheostomy ties may be used by caregivers. These include tracheostomy string or cotton twill tape, synthetic fleece-like material with a hook-and-eye fastener (Figure 13-8), and metal chain. Hook-and-eye ties are most common, because they are single use and can be removed quickly in an emergency.

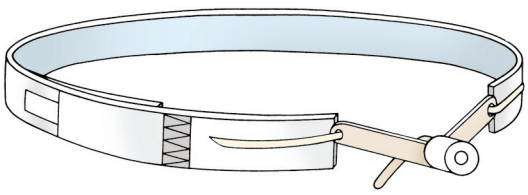


FIGURE 13-8 A tracheostomy-securing system with hook-and-eye ties.

PROCEDURE AND TECHNIQUE

Tracheostomy is primarily surgical in children. The percutaneous tracheostomy technique is rarely used in children because of technical anatomic limitations and concerns about the safety of the procedure, especially in infants and young children.[54,55] Although percutaneous tracheostomy has been performed in a few small series in pediatric patients, it has not been widely accepted because of the potential increase in complications.[55] First, the anatomic characteristics of this population make it more difficult to localize the trachea than in adults. The major landmarks, including the cricoid and thyroid cartilage, are not prominent, and in very young infants the thyroid cartilage is commonly completely covered by the hyoid bone. The trachea is smaller, is not as superficial, and is more mobile. Rapid placement of a tracheostomy tube through the cricothyroid membrane, or cricothyroidotomy, is not advisable in an infant or small child because of the risk of vocal cord or laryngeal injury, but may be performed in an emergency in an older child or adolescent.

Elective tracheostomy in infants and small children should be performed under controlled circumstances with general anesthesia and an endotracheal tube in place. If the airway is not already established, or if the child has had prolonged intubation or has failed a trial of extubation, then the child should undergo direct laryngobronchoscopy before tracheostomy, to ensure that there are no structural anatomic findings in the upper airway. These findings in themselves may be preventing the child from being extubated and in some cases may be treated, with the result that a tracheostomy is no longer required. There may be rare instances, such as impending airway compromise, when a tracheostomy is performed in an older child or adolescent with the use of local anesthesia. A child may be maintaining his or her airway but may decompensate with the induction of anesthesia or attempt at intubation. Cautious use of sedation or anxiolytics may be a useful adjunct in this situation. This should be avoided in small children. The airway can be managed by mask ventilation or by using an LMA in place of an endotracheal tube when intubation is not possible. This option may be particularly useful when performing a tracheostomy on a patient with a critical upper airway, such as patients with Pierre Robin sequence or craniofacial anomalies. Flexible fiberoptic intubation can sometimes be successfully accomplished through an LMA.[56] Challenging intubations such as these often require advanced airway management skills, and the most experienced people available should be notified. They should not be attempted by junior staff.

Once the airway is established, the child is positioned for tracheotomy. A shoulder roll is used for

hyperextension. The anesthesiologist is at the patient's head and has access to the airway at all times. An incision is made through the skin and subcutaneous tissue either in a transverse or vertical fashion. The strap muscles are separated to identify the midline, and careful midline dissection is performed to expose the trachea. The cricoid and then the upper tracheal cartilages are identified. Often the isthmus of the thyroid gland must be divided to expose the upper tracheal rings. The tracheostomy tube is usually placed between the second and fourth tracheal rings, depending on ease of exposure and size of the trachea and the tube to be placed. Two stay sutures are vertically placed on either side of the midline. These stay sutures are used to access the airway and readily locate the tracheostomy incision in the case of accidental decannulation. They are usually removed at the time of the first tracheostomy tube change. A vertical midline incision is made through the middle of the tracheal rings between the sutures, and the endotracheal tube is identified. Under direct visualization of the endotracheal tube, the surgeon instructs the anesthesiologist at the head of the bed to very slowly withdraw it cranially to just below the vocal cords. It is very important not to remove the endotracheal tube completely from the airway at this time, because if the tracheostomy tube cannot be placed in the airway, the ETT can easily be advanced back into the trachea, keeping the airway secure.

The tracheostomy tube is then placed in the airway with the use of the obturator. The obturator is removed, the tube is connected to the ventilatory circuit, and its correct position is confirmed. The monitor should display a normal CO_2 tracing and bilateral chest wall movement should occur with ventilation. The anesthesia team may auscultate for bilateral breath sounds. The position of the distal tip of the tracheostomy tube in relation to the carina should be checked by the surgeon using a flexible fiberoptic bronchoscope.[57] It should typically be at least two tracheal rings above the carina. It is important to remove the shoulder roll for this scope and release the child's neck extension, because this may reposition the tracheostomy tube lower in the airway. If the ventilatory status through the tracheostomy is satisfactory, the ETT can now be completely withdrawn from the patient's airway. The tracheostomy is then secured with hook-and-eye tracheostomy ties. The tube is no longer routinely sutured to the skin in children as it is in adults because of the risk of accidental decannulation occurring in a sutured tube and going unnoticed. The shaft of the tube could also slip out of the stoma without the sutures being removed, which would be difficult to identify. Less commonly, some surgeons prefer to suture a new tracheostomy tube in place until the first tracheostomy change. The first tracheostomy tube change is usually done 5 to 7 days after the procedure.[42]

Postoperative Care

It is customary to obtain a chest radiograph immediately after surgery to ensure adequate bilateral lung ventilation and no pneumothorax.[57] Immediate postoperative problems may include bleeding, pneumothorax, subcutaneous emphysema with expansion of soft tissues, and, rarely, pulmonary edema. Any of these can lead to respiratory distress and ventilation problems. Chest radiographs should certainly be considered in the face of any respiratory problems or other serious immediate postoperative complications. If the patient required mechanical ventilation before the procedure, the ventilator settings may need to be adjusted to accommodate changes in the patient's airway physiology after tracheostomy tube placement.

It is during the immediate postoperative period, before healing of the surgical site and formation of the fistula tract from the skin to the trachea, that the child is at the highest risk for inadvertent decannulation. This is best avoided by admission to an intensive care unit, with sedation as needed to avoided agitation and thrashing. Adequate analgesia should also be provided. Postoperative care should include regular suctioning as needed. There are often more secretions and blood in the tracheostomy tube in the initial postoperative period. It is essential to ensure adequate humidification to prevent dryness and crusting of blood and secretions, which could result in mucous plugs and tube obstruction. Most bedside ventilators now have built-in humidifiers. If the patient can be weaned from the ventilator, humidified air should be provided via a tracheostomy mist collar or a heat and moisture exchanger (HME). Excellent pulmonary hygiene and secretion management are important to avoid mucous plugging that might necessitate an early urgent tracheostomy tube change.

Ulceration or skin breakdown can occur around the circumference of the tube or under the chin or circumferentially around the neck where the ties are. It is important to remember that a tracheostomy wound is an "open" wound; sutures are not placed around the stoma to close the skin. It thus does take some time for the edges of the wound to heal by secondary intention. The stoma site should be cleaned at least daily, or as needed, with normal saline. Policies regarding tracheostomy wound care are often institution-specific. However, adequate wound care is essential in the postoperative period, including suctioning of the tracheostomy tube. Dressings may be placed carefully under the flanges of the tube to promote wound healing and absorb excessive secretions.[58] It is important to ensure that the attached ventilator circuit is not torqueing on the tracheostomy tube, because this may cause excessive pressure on the stomal skin and contribute to wound breakdown. At the discretion of the surgical service that placed the tracheostomy tube, the hook-and-eye ties can be changed if they become

excessively soiled or crusted before the first tracheostomy change.

The surgical team who performed the procedure routinely performs the first tracheostomy tube change. Should respiratory distress, ventilation problems, inadvertent decannulation, or any respiratory emergency arise before this planned tube change, notifying the surgical team who placed the tracheostomy tube is mandatory. It is important that appropriate equipment is readily available at the child's bedside in such an instance.[59] These include but are not limited to the obturator of the tracheostomy tube that is in place, spare tracheostomy tubes of the same size and smaller if available, appropriately sized suction catheters useful for all tubes at the bedside, saline, appropriate ETTs, scissors, and lubricant. Other items may be requested or common practice at a given institution, including a complete operative tracheostomy tray. The presence of the bedside equipment should be mandatory policy in any institution caring for patients with a tracheostomy. The equipment should be routinely checked twice daily by respiratory and nursing staff to ensure it is correct.

Once the first tracheostomy change has occurred and it has been determined that there is adequate healing and tract formation, routine bedside tracheostomy tube changes and care can occur and parental teaching usually can begin. Every institution should have a standardized tracheostomy education protocol for caregivers and family members. This may include the use of tracheostomy mannequins, checklists, pamphlets, videos, and online applications. It is important that caregivers demonstrate competency before the patient is discharged home and also understand under what conditions they should urgently seek help or return to the hospital.[60] Ventilated patients with new tracheostomies are highly likely to be readmitted to the hospital within the first 6 months, mostly secondary to their comorbidities, and it is helpful to clearly outline emergency notification parameters for caregivers.[31]

COMPLICATIONS

Mortality in children undergoing tracheostomy is high, especially in infants. More than 8% of children do not survive the hospital stay when the tracheostomy is placed.[40] In fact, in patients requiring ventilation who have undergone tracheostomy, mortality increases precipitously after 30 days of continued hospital stay.[32] Mortality rates of 9% to 15% have been reported up to 10 years after tracheostomy.[38,62,63] However, most of these deaths are attributed to the underlying complex conditions of these children, with 3% of this mortality being directly attributed to a tracheostomy-related adverse event. It has been reported that between 15% and 19% of children experience a tracheostomy-related adverse event, and in the first 2 years after tracheostomy this may be as high as 38.8%.[40]

Most of these deaths are avoidable. Tracheostomy-related adverse events include, among others, tracheostomy-related hemorrhage, tracheoesophageal fistula, tracheal stenosis, and tracheostomy tube obstruction. It has been demonstrated that care of a child with a tracheostomy can be dramatically improved and tracheostomy-related adverse events can be radically reduced by implementing tracheostomy care teams.[46,47,64,65] This allows for consistency of patient care and promotion of standardized tracheostomy protocols. All persons caring for a child in the hospital and the home should undergo a thorough education program.[30]

The ability to replace the tube in case of accidental decannulation, proper airway assessment, good hygiene, and adequate systemic hydration and nutrition are important factors for a successful long-term outcome for an infant or child with a tracheostomy tube. Caregivers should demonstrate competency at both emergency and routine tracheostomy tube care before discharge.[60] Teaching the parents or caregivers to teach others caring for the child how to care for the tracheotomy site is a critical component of this training.

The two most common reasons for the death of a tracheostomy tube–dependent child are plugging of the tube with mucus and accidental decannulation. Plugging with mucus occurs when thick, viscous mucus obstructs the lumen of the tracheostomy tube. Factors that lead to this problem include dehydration, infection, and lack of humidification. Many children with bronchopulmonary dysplasia develop frequent exacerbations of mucous plugging with increased bronchorrhea. Viral or bacterial tracheitis may also lead to an increase in thick secretions. These problems can be avoided with appropriate hydration and pulmonary hygiene. Antibiotic therapy may be necessary in the case of infection. The use of an HME or "trach" collar may help alleviate thick secretions. Acute mucous plugging requires emergency suctioning. The tube is changed immediately if suctioning does not relieve the obstruction. Once the obstruction is relieved and the patient is out of danger, appropriate treatments are initiated to help prevent a recurrence of the problem.

If the obstruction is not relieved by tracheostomy tube change, steps should be taken to ensure that the tube is in the trachea and additional resources are mobilized. If available, the lumen and position of the tube should be checked by passing a flexible scope through the tube. One can attempt to pass a suction catheter and bag ventilate the patient while assessing the chest wall mobility to assess the tube placement. One should take steps to ensure adequate delivery of oxygen in the case of hypoxia. If ventilation is not successful through the tracheostomy tube and the patient continues to deteriorate, the tube should be removed and replaced. Oral mask ventilation or oral intubation can also be performed if there is difficulty replacing the tube. All

caregivers and staff should be aware of the status of the child's airway before tracheostomy and the original indications for it.

Another serious complication is accidental dislodgment of the tracheostomy tube. This accounts for a considerable number tracheostomy-related deaths.[27,66,67] Accidental dislodgment may occur during play activities, routine tracheostomy care, or when the child is sleeping or unsupervised. Immediate reinsertion of the tube is required. This may be difficult during an emergency situation. If the same size tracheostomy tube cannot be inserted, then a tube one size smaller should be placed. If this is unsuccessful, the patient should be ventilated with a bag and mask if in distress until additional medical help arrives. Parents are usually sent home with a mask and bag for use in case of such an emergency. It is important to remember to cover the stoma during any attempt at oral ventilation to prevent air escaping through the stoma. When there is a critical airway and there is no available tracheostomy tube, then an ETT can be placed in the stoma to secure the airway. If this is not possible and the patient experiences full arrest, rescue breaths can be delivered into the stoma directly if mouth-to-mouth breaths do not achieve adequate ventilation.

Other complications associated with tracheostomy use include bleeding, granulation tissue, tracheal erosion, tracheomalacia, and distal airway stenosis. External granulations may be managed conservatively if they do not interfere with tracheostomy tube changes or care. If granulation causes bleeding or there is difficulty with tube changes, it can be cauterized or removed surgically. Suprastomal granulation is not routinely removed during endoscopy unless it is obstructive, it is causing bleeding, it is interfering with tube changes, or there are plans for decannulation in the near future.[68] Granulation tissue causing obstruction beyond the distal end of the tracheostomy tube often requires treatment, because it can cause bleeding on suctioning and tube change and can obstruct the distal airway. It can either be surgically removed or treated with topical steroids and antibiotic drops.

Bleeding from the tracheostomy tube is usually related to suction trauma or inflammation as a result of infection or tracheitis, but on occasion it may be caused by granulation or even erosion of the tracheal wall. Bleeding from suction trauma is usually self-limited and often occurs after a period of increased secretions or respiratory illness. Suctioning beyond the end of the tracheostomy tube should be avoided to prevent direct tracheal trauma and bleeding.

Sudden massive hemorrhage from the tracheostomy may be secondary to a tracheoinnominate artery fistula.[69] This occurs when the tip of the tracheostomy tube erodes through the anterior tracheal wall into the innominate artery. Often this bleeding will be heralded by smaller sentinel bleeds. It is also more likely to occur in children with chronic tracheostomy dependence.

Innominate arterial bleeding can be life-threatening and should initially be tamponaded with digital pressure, followed by placement of a cuffed endotracheal tube. The fistula can be repaired with cardiothoracic surgery if the patient survives the bleeding. Although tracheoinnominate artery fistula is extremely rare, its mortality rate approaches 100%. Any child with frequent tracheostomy bleeding with no identifiable source should have a thorough evaluation of the tracheotomy by the ORL service. If pulsations are seen in the region of the innominate artery, a computed tomography arteriogram should be performed to assess the position of the innominate artery in relation to the tracheostomy tube.

Surveillance of the airway may help prevent such serious complications. If there are problems, a direct laryngobronchoscopy (DLB) should be performed under general anesthesia. There is, however, no consensus on the frequency with which DLB should be performed in a child with a long-term tracheostomy, and practice varies widely.[62,70] Surveillance DLBs are typically no longer routinely performed unless the child is having problems with the tracheostomy, is undergoing anesthesia for another reason, or is being worked up for decannulation.

Distal tracheal stenosis in children with a long-term tracheostomy is uncommon but may occur if there is granulation tissue or an inappropriate size tube. It may be possible to bypass a tracheal tube with a longer custom tube. However, it is prudent to address the cause of scar tissue formation, because it can recur in the more distal trachea.[62] Consultation with a tracheostomy specialist, pediatric otolaryngologist, or pediatric pulmonologist is recommended before increasing the length or size of a tracheostomy tube in a complex child with a long-term tracheostomy.

Other problems encountered with a chronic tracheostomy include speech delay and difficulty with phonation. The tracheostomy is designed to bypass the larynx and therefore often interferes with speech production. Some children can phonate around the tube, especially if it is uncuffed, by occluding the opening, allowing air up through the vocal cords. This does require that the airway is patent above the tracheostomy tube. Use of a cuff usually precludes this option, except if the child has a TTS cuff, which can be deflated to allow for phonation. Children who require their tracheostomy only during sleep may be able to tolerate a speaking valve, use a Passy-Muir valve, or cap the tracheostomy tube completely during the day.[71,72] A Passy-Muir valve is a one-way speaking valve that permits inspiration through the stoma but occludes it during expiration, redirecting air up around the tracheostomy tube and through the vocal cords to allow phonation. Consultation with a

speech therapist is appropriate in these situations.[72] Capping requires the child to breathe around the tracheostomy on both inspiration and expiration.

Swallowing Problems

The presence of a tracheostomy alone is not a contraindication to oral feeding. However, children with tracheostomies all have significant reduction in laryngeal elevation during swallowing. The tracheostomy anchors the trachea to the strap muscle and tethers the suprahyoid muscles. This can contribute to swallowing difficulties. An inflated tracheostomy cuff may also increase pressure in the hypopharynx. The underlying medical condition necessitating the tracheostomy tube may also contribute to the swallowing dysfunction. Neuromuscular problems or degenerative diseases can lead to motor weakness, reduced reflexes, and diminished coordination of the complex functions involved in swallowing. Children who have prolonged intubations at a young age often experience oral aversion, which may require intensive oromotor therapy to overcome. Finally, the sense of smell and therefore taste may be altered in a child when the nasal airway is bypassed. Close work with a speech and swallowing therapist can be very important for a young child or infant with a tracheostomy, particularly children who fed orally before tracheostomy placement.[72]

ROUTINE TRACHEOSTOMY TUBE CHANGES

The first tracheostomy tube change is customarily done by the surgical team that performed the tracheostomy. Generally, after the first change, the stoma has healed adequately to allow for routine tracheostomy care and changes and teaching family members to perform them as well. Safe tube changes are an important part of routine tracheostomy care. It is essential that the child's parents or caregivers learn proper tracheostomy tube care before the child is discharged. Tracheostomy tube changes are at a minimum once a month but may be up to once a week, depending on the child and the clinical condition. A tube change will be made urgently when there is suspected obstruction or respiratory distress. Preparation is the key to safety. It is always imperative that the child travels everywhere with equipment for a tracheostomy tube change. (Recommended equipment is listed in Box 13-2.) It is also important to perform routine tracheostomy tube changes during daytime hours when everyone is alert and another caregiver is available. Proper lighting and position are essential. One must always communicate with the other caregiver, be prepared for the worst, and remain calm, especially during an emergency.[73,74] The person performing the tube change must use proper hand hygiene before any manipulation of the tracheostomy tube when possible (i.e., unless the situation is an emergency).

Box 13-2 Equipment Needed for Tracheostomy Tube Changes

- Correct-size tracheostomy tube and obturator
- Smaller-size tracheostomy tube
- Blanket roll
- Lubricant
- Tracheotomy ties
- Scissors
- Clean wet and dry gauze
- Resuscitation bag with mask
- Oxygen source

Ideally, at least 2 hours should have passed after the last feeding before the tracheostomy tube is changed to minimize the risk of vomiting or aspiration during the change. All supplies and emergency equipment are prepared. The role of the other caregiver is determined, and then the child is placed in the supine position on a shoulder roll with the neck hyperextended to make tube insertion easier. It is important to be prepared for any emergency, such as a difficult insertion, inability to access the airway, significant respiratory distress, bradycardia, or desaturation.

If possible, the caregiver should try to calm the child if he or she is agitated. Tracheostomy tube changes can be much more difficult if the child is agitated or fighting. Supplemental oxygen or bag ventilation is provided if needed, and the tracheostomy tube is suctioned if needed before the change. It is important to test the cuff, if appropriate, on the new tracheostomy tube that is going to be placed. One caregiver releases the tracheostomy ties and deflates the cuff fully on the tube *in situ*. One person holds the tracheostomy tube in place. When both caregivers are ready, the lead caregiver counts to three. One caregiver removes the old tracheostomy tube and the other immediately replaces the new tube with the obturator in place. The obturator is removed, and if the patient is on a ventilator, the circuit is immediately connected to the new tube. The patient is then assessed for breathing by watching for respiratory efforts and chest wall motion. Auscultation with a stethoscope may also be performed. Once the tube is confirmed to be in the correct position, the ties are secured. The ties should be tight enough to hold the tube in place without movement yet not bind or pinch the neck—usually one fingerbreadth under the ties is appropriate.[74] Suctioning can be performed if necessary.

TRACHEOSTOMY HOME CARE

Many of the complications of tracheostomy take place in the home. Therefore an optimal home-care environment is essential. Parents and caregivers should be able to smoothly and quickly perform tracheostomy tube changes even in an urgent situation, both with another caregiver and alone, if necessary. These skills

should be demonstrated to appropriate staff before discharge home from the hospital or extended-care facility.[75] It is advisable that caregivers be trained in cardiopulmonary resuscitation.[27] They must be able to perform routine tracheostomy care, including suctioning and cleaning. Adequate tracheostomy equipment should always be available. This includes such items as the obturator of the tube in place, a spare tracheostomy tube, a smaller-size tracheostomy tube, tracheostomy ties, dressing, suction catheters, suction machine, humidity devices, and monitors, if indicated.[73,74] Home nursing care may also be required based on the patient's needs. This should be determined and set up before discharge from the hospital. Each patient and family has unique needs, resources, and capabilities, and these should be assessed before the child's discharge from the hospital.

DECANNULATION

A patient may be considered for decannulation or removal of the tracheostomy when the following indicators are met:

- The original indication for the tracheostomy tube has resolved or been corrected.
- The patient is tolerating either a cap or a Passy-Muir speaking valve during most or all waking hours. The patient should not require removal of either for suctioning or respiratory complaints.

An ideal decannulation protocol should involve the following:

- Tracheostomy size reduction and clinical observation
- Complete upper airway evaluation, including a flexible laryngoscopy and direct laryngobronchoscopy
- Daytime tracheostomy capping trials at home
- A capped polysomnogram, if available
- Admission for decannulation with observation for a minimum of 24 hours after

The child should have an effective cough to clear secretions and an adequate level of consciousness and pharyngeal function to protect the airway from frank aspiration. An upper airway evaluation (DLB) under general anesthesia should be performed before tracheostomy removal. Any obstructing supraglottic granulation tissue should be removed at this time. If the child has a difficult airway or is difficult to intubate, consideration should be made for the need for future surgeries. A flexible laryngoscopy should also be performed by an otolaryngologist to assess for upper airway obstruction in the form of adenotonsillar hypertrophy and to ensure vocal cord mobility is normal. Any abnormality of these may prevent decannulation. If sleep studies are available, a capped sleep study is very helpful to assess for readiness for decannulation and to ensure resolution of upper airway obstruction manifesting as obstructive sleep apnea or central apnea that may have been present.[76] A supplemental oxygen requirement should not preclude a decannulation trial as long as the child can tolerate oxygen administration via nasal cannula. If the child is being transitioned to noninvasive ventilation after decannulation, it is important to ensure that he or she tolerates this with the tracheostomy capped before removal of the tube.

Downsizing, use of a speaking valve, and ultimately capping can allow for a gradual transition to breathing through the nose and upper airway after a long period of breathing through a tracheostomy. An abrupt change in the airway such as tracheostomy removal can lead to anxiety and even respiratory distress, resulting in failed decannulation.[77] Once the tube is removed, an occlusive dressing should be applied until the stoma has closed spontaneously. The child is then observed as an inpatient for a minimum of 24 hours after decannulation. A persistent tracheocutaneous fistula that requires surgical closure may occur in up to 40% of children who have had a long-term tracheostomy.[78,79]

SUCTIONING

Suctioning secretions from an ETT or tracheostomy tube maintains patency, prevents aspiration, assists an ineffective cough, and can be used to obtain specimens for diagnostic purposes. Because suctioning is not a benign procedure, recognizing when it is indicated is important. Indications may include diminished breath sounds, a possible mucous plug, difficulty with ventilation, decreasing oxygen saturation, and increased airway secretions occluding the ETT or airway.[80] Although there are no absolute contraindications to suctioning, relative contraindications include patients with bleeding disorders (e.g., thrombocytopenia) and patients with labile cardiovascular or respiratory conditions. It is best to suction only when required and to prevent the potential complications of repeated suctioning without indication.

PROCEDURE

The necessary equipment for suctioning is gathered before initiating the procedure. This includes oxygen, a resuscitation bag and mask, suction catheters, sterile gloves, lavage fluid, a stethoscope, and a suction regulator to set the appropriate vacuum pressure. The vacuum pressure is set at 60 to 80 mm Hg for a neonate and at 80 to 100 mm Hg for a pediatric patient. The appropriate catheter length is determined by measuring the length of the ETT or tracheostomy tube against the suction catheter. The proper length should pass just beyond the end of the tube.[81] Optimally, the catheter should be less than one-half the size of the internal diameter of the ETT to avoid total obstruction of the tube, but this is often impossible in smaller inner diameter tubes.

The patient's breath sounds, heart rate, respiratory rate, arterial oxygen saturation, and ventilator pressure are monitored continuously. As with all procedures, the

suctioning process should be explained to the child and caregivers. The patient is ventilated with an Fio_2 of at least 0.1 to 0.2 greater than the oxygen being delivered at the time of the intervention, or an Fio_2 of 1.0 when necessary. The same peak inspiratory pressures and PEEP as set on the ventilator are used.

To suction, the catheter is moistened with saline (often the humidity alone is enough to lubricate) and, without applying suction, inserted into the airway to the predetermined length, or until resistance is met. It is pulled back 0.5 to 1.5 cm, and intermittent suction is applied using the thumb port, while withdrawing and rotating the catheter. Hypoxemia and atelectasis are avoided by keeping the duration of suctioning to less than 10 seconds per pass, and less than 5 seconds when applying the vacuum. The patient is oxygenated and ventilated between passes while observing the patient's vital signs on the monitors. Breath sounds are checked to evaluate the need for repeating the procedure. The need for further suctioning is reevaluated on the basis of the patient's clinical status. Potentially, rotating the head to the right facilitates entry into the left mainstem bronchus, whereas turning the head to the left facilitates entering the right mainstem bronchus if required for aggressive suctioning.

Although not always required and somewhat controversial,[80,81] and clinical practices vary among institutions, it is a practice in many institutions to instill a lavage solution, such as normal saline, to facilitate removal of mucous plugs or thick, tenacious secretions. The volume of solution instilled varies with the weight of the patient. Once the solution is instilled into the airway, hand ventilation with a breathing bag is done for several breaths to disperse the solution throughout the lung fields to help liquefy and loosen secretions.

The suctioning algorithm in Figure 13-9 is recommended.

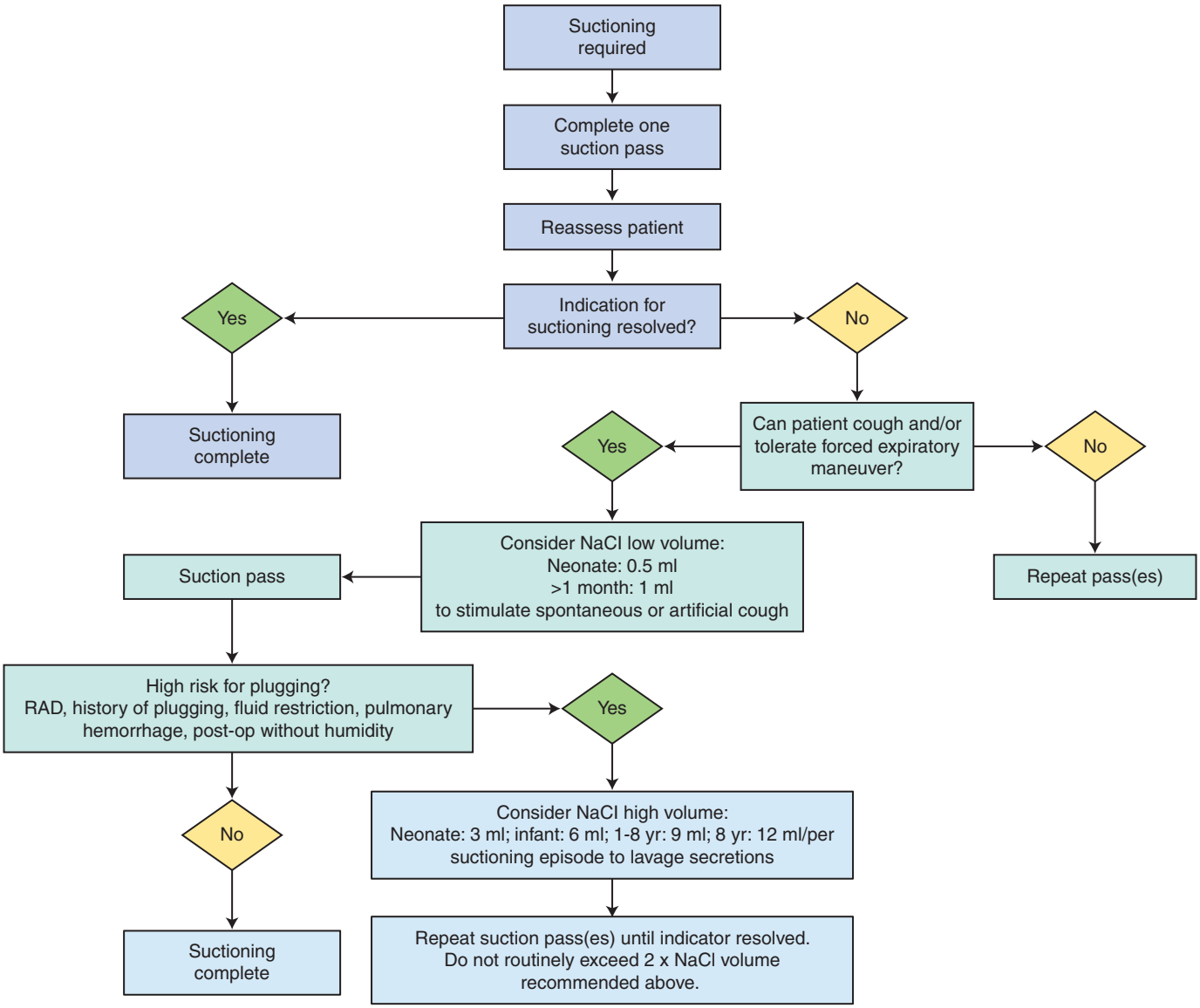


FIGURE 13-9 Suggested suctioning and saline use algorithm.

CLOSED TRACHEAL SUCTION SYSTEMS

As the frequency of suctioning increases, the need for a closed tracheal suction system or special suctioning adapter becomes imperative. These systems are necessary to prevent alveolar collapse associated with the loss of distention from PEEP during suctioning and to reduce suction-related pulmonary complications. Closed tracheal suction systems are designed to allow minimal disruption with mechanical ventilation, to prevent the loss of PEEP, and to prevent hypoxia. This system is added to an adapter, as well as an irrigation port, protective sleeve, closed lock, and control valve, and markings on the suction catheter help determine the approximate depth of suctioning. Additional advantages include less contamination of the sheathed catheter, a decrease in airborne particles being introduced into the ETT, and a faster return to the preoxygenation baseline.

There are some disadvantages with these systems. Bacterial growth can occur if the catheter is not changed in a timely manner, but this is no different than with the ETT itself. Failure to pull the catheter back fully into the correct position can cause damage to or occlude the airway. Other disadvantages include the possibility of leaving the continuous suction in the "on" position, causing hypoxemia and increased dead space if an inappropriate adapter size is used.

Key Points

- Intubation is not a benign procedure; however, with proper care and preparation, it can be safely performed.
- When complications of intubation occur, simple adjunct devices or techniques can provide life-sustaining results.
- Tracheostomies provide a stable and, if required, long-term airway. Formal standardized education of staff and caregivers can dramatically reduce adverse events.
- All staff and caregivers caring for a child with a tracheostomy must be aware of the indication for the tracheostomy. This ensures proper care in case of an emergency.
- Standardization of decannulation protocols will allow more successful decannulation in children.
- Suctioning is routinely required in children with artificial airways to maintain patency. Indications and timing of suctioning must be individually assessed, and it must be performed only when necessary.
- Adequate airway humidification is essential to prevent crusting of secretions and the development of mucus plugs.

Assessment Questions

See Evolve Resources for answers.

1. Which is not a reason for intubation?
   - **A.** Pulmonary function
   - **B.** Central apnea
   - **C.** Upper airway obstruction
   - **D.** Pulmonary hygiene
2. What is the age-appropriate ETT for a 1-year-old? A 2-year-old? A 4-year-old? A 6-year-old?
   - **A.** 4.0, 4.5, 5.0, 5.5
   - **B.** 3.5, 5.0, 5.5, 6.0
   - **C.** 4.0, 5.0, 6.0, 7.0
   - **D.** 4.5, 5.5, 6.5, 7.0
3. When would one consider an LMA instead of intubation?
   - **A.** Awake, short-term ventilation
   - **B.** To protect against aspiration
   - **C.** To protect the vocal cords
   - **D.** Unconscious, backup for intubation
4. What are the disadvantages of nasotracheal intubation?
   - **A.** Sinusitis
   - **B.** Pressure necrosis and bleeding
   - **C.** Postextubation atelectasis
   - **D.** All of the above
5. What intubation approach should one consider using in a larynx that is difficult or impossible to expose with a standard rigid laryngoscope?
   - **A.** LMA
   - **B.** Cricothyroidotomy
   - **C.** Flexible fiberoptic intubation
   - **D.** Tracheostomy
6. Which of the following may be used or performed to treat extubation failure?
   - **A.** Reintubation
   - **B.** Steroids
   - **C.** Heliox
   - **D.** Tracheostomy
   - **E.** All of the above
7. Which of the following is not an indication for tracheotomy?
   - **A.** Severe subglottic stenosis
   - **B.** Mild laryngomalacia
   - **C.** Chronic ventilation
   - **D.** Poor pulmonary hygiene
8. What is the difference between the outside diameter of a tracheostomy tube and an ETT?
   - **A.** The tracheostomy tube has a larger outside diameter.
   - **B.** They have the same outside diameter.
   - **C.** The endotracheal tube has a much larger outside diameter.
   - **D.** It depends on the manufacturer.
9. Which tracheostomy complication can be life-threatening?
   - **A.** Mucous plugging or accidental dislodgement
   - **B.** Distal granulation
   - **C.** Tracheal–esophageal fistula
   - **D.** All of the above
10. When should you not consider a trial of decannulation?
    - **A.** Resolution of the original indication for tracheostomy
    - **B.** When the child is tolerating capping during the day
    - **C.** If the child is successfully using noninvasive ventilation via a face mask
    - **D.** If the child has an oxygen requirement
    - **E.** None of the above

REFERENCES

1. Difficult Airway society. https://www.das.uk.com.
2. Apfelbaum JL, Hagberg CA, Caplan RA, et al. Practice Guidelines for Management of the Difficult Airway: An Updated Report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. *Anesthesiology*. 2013;118(2):251-270.
3. Black AE, Flynn PE, Smith HL, Thomas ML, Wilkinson KA. Development of a guideline for the management of the unanticipated difficult airway in pediatric practice. *Paediatr Anaesth*. 2015;25(4):346-362.
4. Thompson AE, Salonia R. *Airway Management Pediatric Critical Care Medicine*. 5th ed. Philadelphia: Elsevier; 2017: Ch 129;1756.
5. Keep PJ, Manford ML. Endotracheal tube sizes for children. *Anaesthesia*. 1974;29:181.
6. Luten RC, Wears RL, Broselow J, et al. Length-based endotracheal tube and emergency equipment selection in pediatrics. *Ann Emerg Med*. 1992;21:900.
7. Berry FA, Yemen TA. Pediatric airway in health and disease. *Pediatr Clin North Am*. 1994;41:153.
8. Litman RS, Maxwell LG. Cuffed versus uncuffed endotracheal tubes in pediatric anesthesia: the debate should finally end. *Anesthesiology*. 2013;118(3):500-501.
9. Vlatten A, Aucoin S, Litz S, Macmanus B, Soder C. A comparison of the STORZ video laryngoscope and standard direct laryngoscopy for intubation in the pediatric airway—a randomized clinical trial. *Paediatr Anaesth*. 2009;19:1102-1107.
10. Brain AIJ. The laryngeal mask: a new concept in airway management. *Br J Anaesth*. 1983;55:801.
11. Ovassapian A, Salem MR. Sellick's maneuver. To do or not do. *Anesth Analg*. 2009;109:1360.
12. Boet S, Duttchen K, Chan J, et al. Cricoid pressure provides incomplete esophageal occlusion associated with lateral deviation: a magnetic resonance imaging study. *J Emerg Med*. 2012;42:606.
13. Brown MS. Prevention of accidental extubation in newborns. *Am J Dis Child*. 1988;142:1240.
14. Volsko TA, Chatburn RL. Comparison of two methods for securing the endotracheal tube in neonates. *Respir Care*. 1997;42:288.
15. Holm-Knudsen R. The difficult pediatric airway—a review of new devices for indirect laryngoscopy in children younger than two years of age. *Paediatr Anaesth*. 2011;21:98.
16. Markovitz BP, Randolph AG. Corticosteriods for the prevention of reintubation and postextubation stridor in pediatric patients: a meta analysis. *Pediatr Crit Care*. 2002;3:223.
17. Duncan PG. Efficacy of helium–oxygen mixtures in the management of severe viral and postintubation croup. *Can Anaesth Soc J*. 1979;26:206.
18. Chavez A, dela Cruz R, Zaritsky A. Spontaneous breathing trial predicts successful extubation in infants and children. *Pediatr Crit Care Med*. 2006;7(4):324.
19. Kurachek SC, Newth CJ, Quasney MW, et al. Extubation failure in pediatric intensive care: a multiple-center study of risk factors and outcomes. *Crit Care Med*. 2003;31(11): 2657.
20. Suominen PK, Tuominen NA, Salminen JT, et al. The air-leak test is not a good predictor of postextubation adverse events in children undergoing cardiac surgery. *J Cardiothorac Vasc Anesth*. 2007;21(2):197-202.
21. Malhotra D, Gurcoo S, Qazi S, Gupta S. Randomized comparative efficacy of dexamethasone to prevent postextubation upper airway complications in children and adults in ICU. *Indian J Anaesth*. 2009;53(4):442.
22. Khemani RG, Randolph A, Markovitz B. Steroids for post extubation stridor: pediatric evidence is still inconclusive. *Intensive Care Med*. 2010;36(7):1276.
23. Whigham AS, Howell R, Choi S, Peña M, Zalzal G, Preciado D. Outcomes of balloon dilation in pediatric subglottic stenosis. *Ann Otol Rhinol Laryngol*. 2012;121(7):442.
24. Myer CM, O'Conner DM, Cotton RT. A proposed laryngotracheal stenosis grading system based on endotracheal tube size. *Ann Otol Rhinol Laryngol*. 2012;103;319.
25. Eze NN, Wyatt ME, Hartley BE. The role of the anterior cricoids split in facilitation extubation in infants. *Int J Pediatr Otorhinolaryngol*. 2005;69(6):843.
26. Rudnick EF, Mitchell RB. Tracheostomy in children. In: Pereira KD, Mitchell RB, eds. *Pediatric Otolaryngology for the Clinician*. Totowa, NJ: Humana Press; 2009: 159-163.
27. Wetmore RF, Marsh RR, Thompson ME, Tom LW. Pediatric tracheostomy: a changing procedure? *Ann Otol Rhinol Laryngol*. 1999;108(7 Pt 1):695.
28. Palmer PM, Dutton JM, McCulloch TM, Smith RJ. Trends in the use of tracheotomy in the pediatric patient: the Iowa experience. *Head Neck*. 1995;17:328-333.
29. Potsic WP, Cotton RT, Handler SD. *Surgical Pediatric Otolaryngology: Head and Neck Surgery*. New York: Thieme Medical Publishers; 1997.
30. Corbett HJ, Mann KS, Mitra I, Jesudason EC, Losty PD, Clarke RW. Tracheostomy—a 10-year experience from a UK pediatric surgical center. *J Pediatr Surg*. 2007;42(7): 1251.
31. Graf JM, Montagnino BA, Hueckel R, McPherson ML. Pediatric tracheostomies: a recent experience from one academic center. *Pediatr Crit Care Med*. 2008;9(1):96-100.
32. Schroeder Jr JW, Holinger LD. Congenital laryngeal stenosis. *Otolaryngol Clin North Am*. 2008;41(5):865.
33. Santos D, Mitchell R. The history of pediatric airway reconstruction. *Laryngoscope*. 2010;120(4):815.
34. Daya H, Hosni A, Bejar-Solar I, Evans JN, Bailey CM. Pediatric vocal fold paralysis: a long-term retrospective study. *Arch Otolaryngol Head Neck Surg*. 2000;126(1):21.
35. Miyamoto RC, Parikh SR, Gellad W, Licameli GR. Bilateral congenital vocal cord paralysis: a 16-year institutional review. *Otolaryngol Head Neck Surg*. 2005;133(2):241.
36. Berkowitz RG. Natural history of tracheostomy-dependent idiopathic congenital bilateral vocal fold paralysis. *Otolaryngol Head Neck Surg*. 2007;136(4):649.
37. Lapeña Jr JF, Berkowitz RG. Neuromuscular disorders presenting as congenital bilateral vocal cord paralysis. *Ann Otol Rhinol Laryngol*. 2001;110(10):952.
38. Pereira KD, MacGregor AR, Mitchell RB. Complications of neonatal tracheostomy: a 5-year review. *Otolaryngol Head Neck Surg*. 2004;131:810.
39. Hasan RA, Nikolis A, Dutta S, Jackson IT. Clinical outcome of perioperative airway and ventilatory management in children undergoing craniofacial surgery. *J Craniofac Surg*. 2004;15(4):655.
40. Watters K, O'Neill M, Zhu H, Graham RJ, Hall M, Berry J. Two year mortality, complications, and healthcare use in children with medicaid following tracheostomy. *Laryngoscope*. 2016;126(11):2611-2617.
41. Berry JG, Goldmann DA, Mandl KD, et al. Health information management and perceptions of the quality of care for children with tracheotomy: a qualitative study. *BMC Health Serv Res*. 2011;11:117.
42. Mitchell RB, Hussey HM, Setzen G, et al. Clinical consensus statement: tracheostomy care. *Otolaryngol Head Neck Surg*. 2013;148(1):6-20.
43. Srivastava R, Stone BL, Murphy NA. Hospitalist care of the medically complex child. *Pediatr Clin North Am*. 2005;52(4): 1165.
44. Shields L, Zhou H, Pratt J, Taylor M, Hunter J, Pascoe E. Family-centred care for hospitalized children aged 0-12 years. *Cochrane Database Syst Rev*. 2012;10:CD004811.

45. Corbett HJ, Mann KS, Mitra I, Jesudason EC, Losty PD, Clarke RW. Tracheostomy: A 10-year experience from a UK pediatric surgical center. *J Pediatr Surg*. 2007;42(7):1251.
46. Garrubba M, Turner T, Grieveson C. Multidisciplinary care for tracheostomy patients: a systematic review. *Crit Care*. 2009;13:177.
47. Cetto R, Arora A, Hettige R, et al. Improving tracheostomy care: a prospective study of the multidisciplinary approach. *Clin Otolaryngol*. 2011;36:482-488.
48. Chiellini F, Ferri M, Latini G. Physical-chemical assessment of di-(2-ethylhexyl)-phthalate leakage from poly(vinyl chloride) endotracheal tubes after application in high risk newborns. *Int J Pharm*. 2011;409(1-2):57–61.
49. Mankidy R, Wiseman S, Ma H, Giesy JP. Biological impact of phthalates. *Toxicol Lett*. 2013;217(1)50-58.
50. Arjmand, EM, Brenski AC. Advances in tracheostomy in the pediatric age group. *Adv Otolaryngol Head Neck Surg*. 2001;15:41-69.
51. Keszler M, Nassabeh-Montazami S, Abubakar K. Evolution of tidal volume requirement during the first 3 weeks of life in infants 800 g ventilated with volume guarantee. *Arch Dis Child Fetal Neonatal Ed*. 2009;94(4):F279-F282.
52. Vigliaroli L, De Vivo P, Mione C, Pretto G. Clinical experience with Ciaglia's percutaneous tracheostomy. *Eur Arch Otorhinolaryngol*. 1999;256(8):426-428.
53. Scott CJ, Darowski M, Crabbe DC. Complications of percutaneous dilatational tracheostomy in children. *Anaesthesia*. 1998;53(5):477-480.
54. Hernandez MR, Klock Jr PA, Ovassapian A. Evolution of the extraglottic airway: a review of its history, applications, and practical tips for success. *Anesth Analg*. 2012;114(2):349.
55. Genther DJ, Thorne MC. Utility of routine postoperative chest radiography in pediatric tracheostomy. *Int J Pediatr Otorhinolaryngol*. 2010;74(12):1397.
56. Boesch RP, Myers C, Garrett T, et al. Prevention of tracheostomy-related pressure ulcers in children. *Pediatrics*. 2012;129(3): e792.
57. Gluth MB, Maska S, Nelson J, Otto RA. Postoperative management of pediatric tracheostomy: results of a nationwide survey. *Otolaryngol Head Neck Surg*. 2000;122:701-705.
58. Kun SS, Davidson-Ward SL, Hulse LM, Keens TG. How much do primary care givers know about tracheostomy and home ventilator emergency care? *Pediatr Pulmonol*. 2010; 45(3):270.
59. Spentzas T, Auth M, Hess P, Minarik M, Storgion S, Stidham G. Natural course following pediatric tracheostomy. *J Intensive Care Med*. 2010;25(1):39-45.
60. Zhu H, Das P, Brereton J, Roberson D, Shah RK. Surveillance and management practices in tracheostomy patients. *Laryngoscope*. 2012;122(1):46-50.
61. Cotts T, Hirsch J, Thorne M, Gajarski R. Tracheostomy after pediatric cardiac surgery: frequency, indications, and outcomes. *J Thorac Cardiovasc Surg*. 2011;141(2):413.
62. Abode KA, Drake AF, Zdanski CJ, Retsch-Bogart GZ, Gee AB, Noah TL. A multidisciplinary children's airway center: impact of the care of patients with tracheostomy. *Pediatrics*. 2016;137(2):e20150455.
63. Hettige R, Arora A, Ifeacho S, Narula A. Improving tracheostomy management through design, implementation and prospective audit of a care bundle: how we do it. *Clin Otolaryngol*. 2008;33(5):488-491.
64. Tantinikorn W, Alper CM, Bluestone CD, Casselbrant ML. Outcome in pediatric tracheotomy. *Am J Otolaryngol*. 2003;24(3):131.
65. Wood D, McShane P, Davis P. Tracheostomy in children admitted to paediatric intensive care. *Arch Dis Child*. 2012; 97(10):866.
66. Chen C, Bent JP, Parikh SR. Powered debridement of suprastomal granulation tissue to facilitate pediatric tracheotomy decannulation. *Int J Pediatr Otorhinolaryngol*. 2011;75(12):1558.
67. Das P, Zhu H, Shah RK, Roberson DW, Berry J, Skinner ML. Tracheotomy-related catastrophic events: results of a national survey. *Laryngoscope*. 2012;122:30-37.
68. Kharasch VS, Dumas HM, Haley SM, et al. Bronchoscopy findings in children and young adults with tracheostomy due to congenital anomalies and neurological impairment. *J Pediatr Rehabil Med*. 2008;1(2):137.
69. Gereau SA, Navarro GC, Cluteria B, Mullan E, Bassila M, Ruben RJ. Selection of pediatric patients for use of the Passy-Muir valve for speech production. *Int J Pediatric Otolaryngol*. 1996;35:11-17.
70. Baumgartner CA, Bewyer E, Bruner D. Management of communication and swallowing in intensive care: the role of the speech pathologist. *AACN Adv Crit Care*. 2008;19(4):433.
71. Cincinnati Children's Hospital Medical Center. *Tracheotomy Care Handbook*. Cincinnati: Cincinnati Children's Hospital Medical Center, KN-00209; 2010.
72. Dallas Children's Medical Center. *Home Instructions for the Caregivers of a Child with a Tracheostomy: A Guide for Caring for Your Child*. Dallas: Dallas Children's Medical Center; 2011.
73. Joseph RA. Tracheostomy in infants: parent education for home care. *Neonatal Netw*. 2011;30(4):231.
74. Roland PS, Rosenfeld RM, Brooks LJ, et al. Clinical practice guideline: polysomnography for sleep-disordered breathing prior to tonsillectomy in children. *Otolaryngol Head Neck Surg*. 2011;145(suppl 1):S1-S15.
75. Black RJ, Baldwin DL, Johns AN. Tracheostomy "decannulation panic" in children: fact or fiction? *J Laryngol Otol*. 1984;98(3):297-304.
76. Tunkel DE, et al. Polysomnography in the evaluation of readiness for decannulation in children. *Arch Otolaryngol Head Neck Surg*. 1996;122:721.
77. Gallagher TQ, Hartnick CJ. Tracheocutaneous fistula closure. *Adv Otorhinolaryngol*. 2012;73:76.
78. Hagler DA, Traver GA. Endotracheal saline and suction catheters: sources of lower airway contamination. *Am J Crit Care*. 1994;3:444.
79. Raymond SJ. Normal saline instillation before suctioning: helpful or harmful? A review of the literature. *Am J Crit Care*. 1995;4:267.

14 Surfactant Replacement Therapy

Santina A. Zanelli, David Kaufman

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. Explain how surfactant affects surface tension and improves lung function
2. Identify disease processes associated with surfactant deficiency, dysfunction, or inactivation
3. Discuss the delivery, benefits, and adverse effects of surfactant replacement
4. Identify patients and disease processes that may benefit from surfactant replacement therapy

Key Terms

compliance
pulmonary surfactant
respiratory distress syndrome
surfactant proteins
surfactant replacement therapy
surface tension

The successful introduction of surfactant therapy into clinical care is one of the best examples of how discoveries in the laboratory can be directly translated into improved patient care. Basic scientific research linked relative or total lack of surfactant secondary to decreased production or inactivation to **respiratory distress syndrome** (RDS) in preterm infants. The phenomenal success of **surfactant replacement therapy** in RDS has prompted investigation into the possible role of surfactant therapy in other types of acute lung injuries, including acute RDS (ARDS).[1,2] It is clear that qualitative and quantitative surfactant abnormalities are present in many non-RDS types of acute lung injuries and that the expanding role of surfactant replacement must be explored.

THE DISCOVERY OF SURFACTANT

The seeds were sown in the early nineteenth century with the observations of Pierre Simon Laplace and Thomas Young.[3] In their theory of capillary action, they described the relationship of distending pressure and **surface tension** at a gas–fluid interface in a sphere as $P = 2 \times ST/R$ (where P is the trans surface or distending pressure, ST is surface tension, and R is the radius of the sphere). More than a century later, in 1929, the Swedish physiologist Kurt von Neergaard,[4] while studying respiratory mechanics, discovered that the retractile force of the lung was dependent on the surface tension in the alveoli (Figure 14-1). Twenty years later, Macklin[5] postulated the existence of a "mucoprotein" lining in the lung that had the surface tension–lowering properties observed by von Neergaard. In the 1950s, Mead and co-workers[6,7] at the Harvard School of Public Health discovered that surface forces at the lung's air–liquid interface contributed to elastic recoil, especially at large lung volumes. Simultaneously, Clements[8] discovered the role of the alveolar lining layer in mediating surface tension changes with area, thereby stabilizing air-filled spaces at low lung

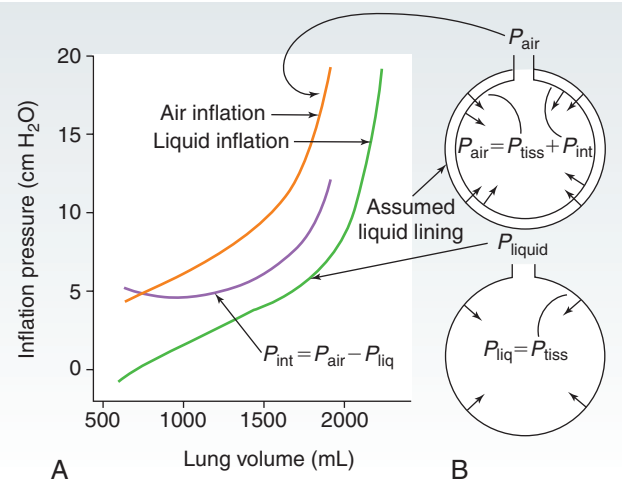


FIGURE 14-1 **A,** Pressure–volume relationship of air-filled versus liquid-filled lung from von Neergaard's original data (1929). **B,** The difference in recoil attributed to a liquid–air interface (i.e., "bubble lining") that is eliminated by a liquid-only interface. *int,* Air–liquid interface; *liq,* liquid; *P,* pressure; *tiss,* tissue. (From Hills BA: *Biology of surfactant,* Cambridge, 1988, Cambridge University Press.

volumes and augmenting elastic recoil at large lung volumes. He named the material "pulmonary surfactant" and established its role as an antiatelectasis factor. In 1955, Pattle[9] discovered that bubbles expressed from the lungs of fetal guinea pigs did not have the stability of those found in term mammalian lungs, stating that the immature lung of the premature baby may have increased surface forces. In 1959, Avery and Mead[10] noted from autopsies that the lungs of infants who died of hyaline membrane disease never had foam in their airways. They lacked foam because they lacked surfactant and therefore the capacity to reduce surface tension when surface area is reduced during exhalation. These findings identified surfactant deficiency as the cause of RDS. Finally, in 1980, Fujiwara and colleagues reported success in producing and using surfactant replacement for preterm infants with RDS.[11] The release of surfactant for clinical use in the United States by the US Food and Drug Administration in 1990 resulted in a measurable reduction in perinatal mortality and morbidity. The use of exogenous surfactants for treatment of lung injury beyond the neonatal period is only now being studied and may offer similar promise.[12-14]

SURFACTANT PHYSIOLOGY

FUNCTION

A surfactant is any molecule that localizes on aqueous surfaces. In the lung, alveolar surfaces are lined by a layer of fluid, called *surfactant.* **Pulmonary surfactant** creates an air–liquid interface that reduces surface tension proportionally to alveolar size. Surface tension is created by the attraction of water molecules to one another. This is best illustrated by observing that water placed on a flat surface coalesces to form a droplet. During respiration, carbon dioxide and water are exhaled at the surface of the alveoli, creating a liquid interface with inhaled air. As indicated by the Laplace law, this attraction would lead to the collapse of alveoli as each alveolus becomes smaller. However, in the presence of surfactant, water molecules are pushed apart in the alveolus, preventing alveolar collapse during exhalation. Surface tension is reduced in proportion to the number of surfactant molecules per surface area. Surfactant displaces water from the air–liquid surface and lowers the surface tension from 75 to 25 dyn/cm (during inflation).[15]

The lung can be thought of as a large number of interconnected bubbles that form the interface between the gaseous environment and the wet alveolar surface. If this interface were without surfactant, two consequences would ensue: (1) Every breath would take a considerable amount of pressure to expand the lung, comparable to the 80 to 90 cm H_2O of pressure required for a newborn's first breath, and (2) the lung would rapidly collapse during exhalation.

Pulmonary surfactant lowers surface tension at all lung volumes, a critical function as alveolar surface decreases during expiration (Figure 14-2). If surface tension did not decrease with decreasing lung volume, alveoli of different sizes would require different distending pressures. Small alveoli would empty into large ones and there would be an overall tendency for the lung to coalesce into a smaller number of large alveoli as lung volume diminished. This would significantly decrease the surface area for gas exchange as well. Surfactant not only decreases surface tension but also reduces it to a greater degree at low lung volume, counteracting the effects of decreasing alveolar size.

Functionally, surfactant increases lung **compliance,** promotes homogeneous gas distribution during inhalation, and allows a residual volume of gas to be evenly distributed throughout the lung during exhalation; that is, it maintains functional residual capacity. In the absence of surfactant, distribution of ventilation becomes uneven, the lungs become stiff, and atelectasis ensues during exhalation. The result is increased work of breathing, hypoxia, and respiratory failure, the clinical picture exemplified by preterm infants with RDS. Surfactant functions are summarized in Box 14-1.

SURFACTANT METABOLISM AND COMPOSITION

Surfactant is produced by type II alveolar epithelial cells (pneumocytes) in the lung (Figure 14-3). After synthesis, the surfactant components are packaged in the form of lamellar bodies and secreted into the fluid layer lining the alveoli in response to a variety of

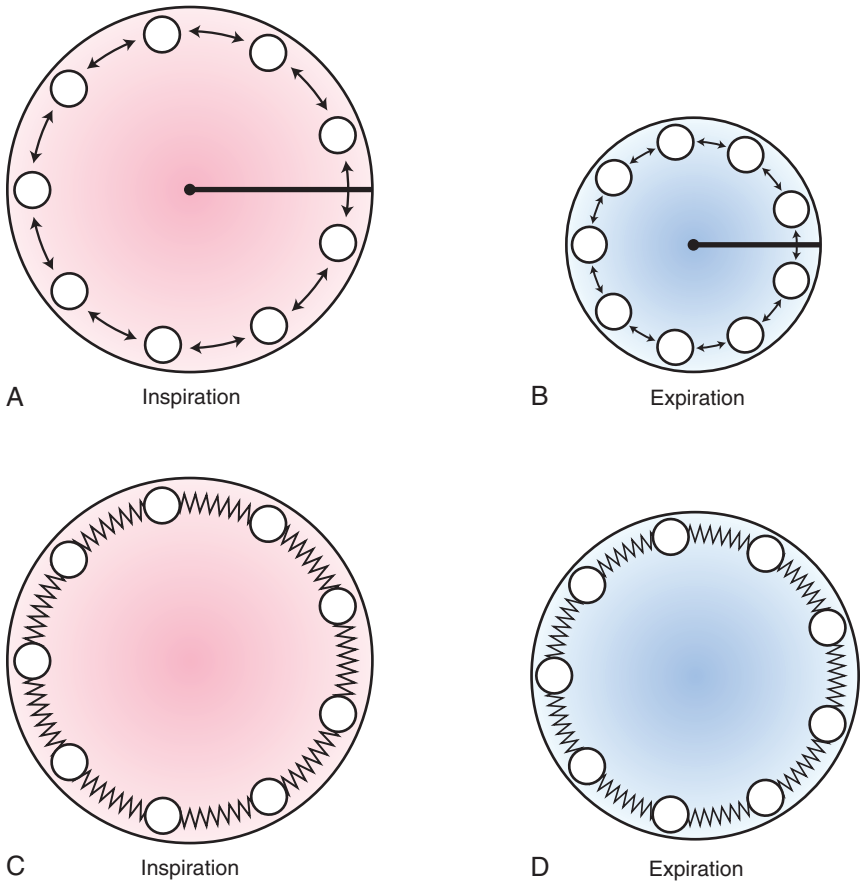


FIGURE 14-2 **A,** Alveolar surface tension is a manifestation of the strong attraction between molecules that are aligned on the surface of the alveoli. **B,** During expiration, when the alveolar radius is smaller, attraction between the molecules is stronger and there is a greater tendency to collapse. **C,** When surfactant is present, it spreads over the alveolus and dilutes the molecules. **D,** During expiration, the surfactant is compressed and the alveolar surface tension is lowered. This stabilizes the alveoli and prevents collapse of those alveoli with smaller radii.

Box 14-1 Surfactant Function

- Prevents collapse of lung during deflation (expiration)
- Lessens work of breathing (oxygen consumption)
- Optimizes surface area for gas exchange and ventilation–perfusion matching
- Optimizes lung compliance (high at low lung volumes and low at high lung volumes)
- Protects the lung epithelium and facilitates clearance of foreign material
- Prevents capillary leakage of fluid into alveoli
- Defends against microorganisms (infection)

stimuli, including mechanical stretch (Figure 14-4). After secretion into the alveolar space, surfactant is transformed into tubular myelin, a highly organized, lipid-rich monolayer responsible for reducing surface tension. The half-time for turnover of human surfactant is not known, but in animals such as rats and rabbits it is 5 to 10 hours.[16] Secretion and clearance are balanced, with 90% of the surfactant being recycled by the type II pneumocytes. Studies using labeled surfactant introduced into the airways have shown the majority being taken up directly by the pneumocytes and being repackaged in lamellar bodies and eventually resecreted.[17] The remaining 10% are cleared by alveolar macrophages.

Surfactant composition is fairly constant among mammalian species. Surfactant is composed of approximately 90% lipids (of which 80% to 85% are phospholipids) and approximately 10% proteins (Table 14-1).[18] Phosphatidylcholine (PC) is the most abundant phospholipid (75% to 80%) and is mostly saturated (40% to 55%) in the form of dipalmitoylphosphatidylcholine (DPPC). DPPC is the most important surfactant component in reducing surface tension and consists of two molecules of palmitic acid and one molecule of phosphatidylcholine attached to a glycerol backbone. DPPC has a hydrophobic end (fatty acids) and a hydrophilic end (nitrogenous base) and aligns itself in the air–liquid interface with the hydrophobic end toward the gas phase and the hydrophilic end toward the liquid phase (Figure 14-5). This configuration aligns negative charges in the gas phase and positive charges in the liquid phase, allowing like charges to repel each other, displacing water and creating the pressure required to keep alveoli expanded during expiration. This alignment of DPPC is critical to the

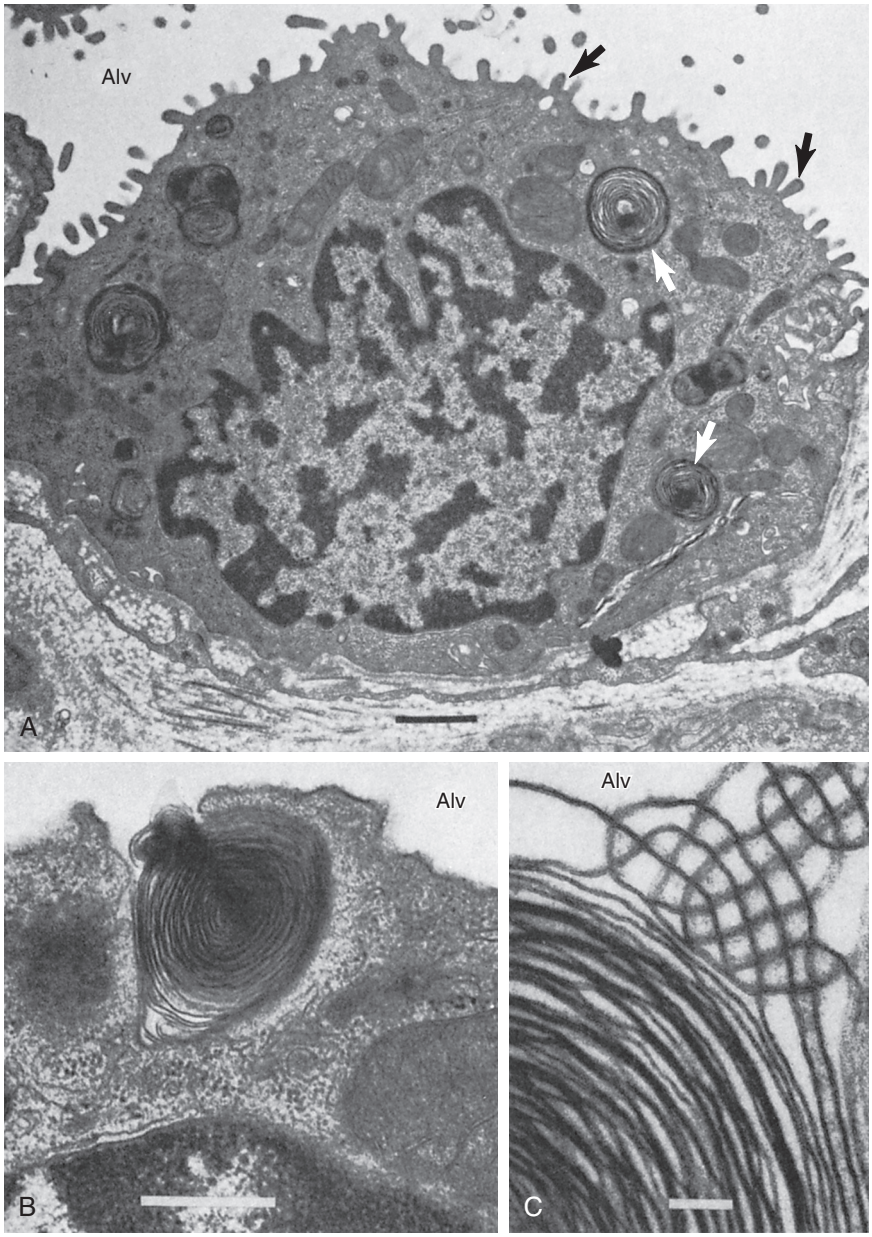


FIGURE 14-3 **A,** Type II cell from a human lung, showing characteristic lamellar inclusion bodies *(open arrows)* within the cell, which are the storage sites of intracellular surfactant. Microvilli *(solid arrows)* are projecting into the alveolus *(Alv).* **B,** Beginning exocytosis of a lamellar body into the alveolar space of a human lung. **C,** Secreted lamellar body and newly formed tubular myelin (appearing as a lattice) in the alveolar liquid in a fetal rat lung. Membrane continuities between outer lamellar bodies and adjacent tubular myelin provide evidence of intraalveolar tubular myelin formation. (From Murray JF: *The normal lung,* ed 2, Philadelphia, 1986, WB Saunders. Courtesy Dr. Mary C. Williams.)

ability of surfactant to lower surface tension, and **surfactant proteins** B and C appear vital for this process. If proper alignment does not occur, positive and negative ends of DPPC attract and cause surfactant to clump together, rendering it ineffective and actually resulting in atelectasis.

Surfactant protein (SP)-A, SP-B, SP-C, and SP-D are the known proteins associated with surfactant.[13-22] SP-A and SP-D are hydrophilic (water soluble) and SP-B and SP-C are hydrophobic (lipid soluble and positively charged).

SP-A is a calcium-dependent collectin (collagen-like lectin). Collectins bind to the surface of microorganisms via polysaccharides, phospholipids, and glycolipid-dependent interactions and lead to aggregation, opsonization, and clearance of the organisms by alveolar macrophages in the lung. SP-A is the most abundant of the surfactant-associated proteins. It is thought to be important in the regulation of surfactant metabolism, as well as in tubular myelin formation.[23] The most important role of SP-A, however, is in innate host defense of the lung.[24] SP-A functions as an

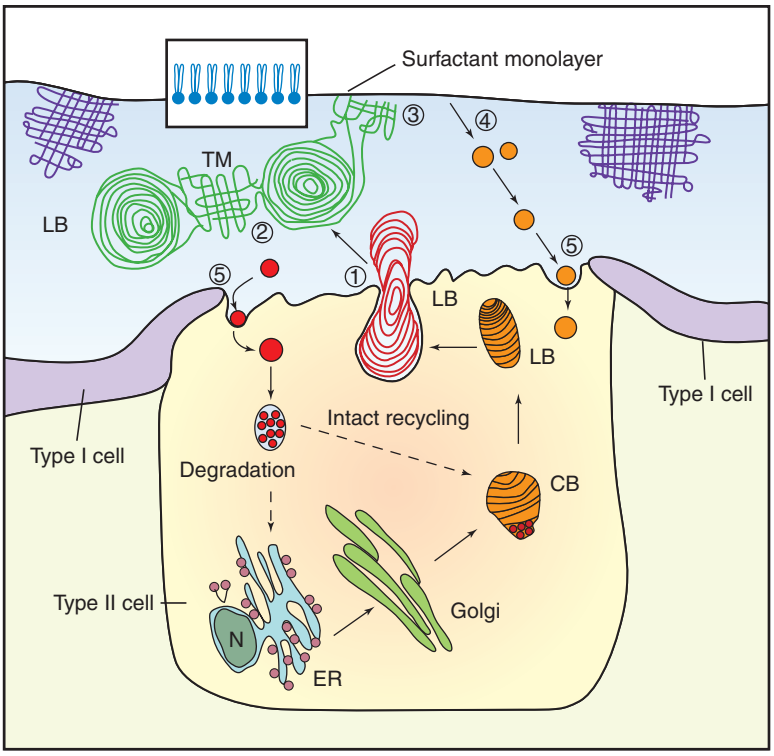


FIGURE 14-4 Surfactant metabolism. 1, Secretion of LB; 2, conversion of LB into TM; 3, generation of monolayer from TM material; 4, formation of small aggregate material from monolayer; 5, reuptake of surfactant material. In general, *solid arrows* indicate accepted pathways. Probable pathways are indicated by *dashed arrows. CB,* Composite body; *ER,* endoplasmic reticulum; *LB,* lamellar body; *N,* nucleus; *TM,* tubular myelin. (Redrawn from Batenburg JJ: Biosynthesis, secretion, and recycling of surfactant components. In Robertson B, Taesch HW, editors: *Surfactant therapy for lung disease,* New York, 1985, Courtesy Marcel Dekker, Inc.)

Table 14-1 Components of Pulmonary Surfactant

COMPONENT	AMOUNT	FUNCTION
Lipids	90%-95%	
1- Phospholipids	80%-85%	
1-1 Phosphatidylcholine (PC) - Dipalmitoylphosphatidylcholine (DPCC, saturated) - 1-palmitoyl-2-oleoyl-phosphatidylcholine (POPC, unsaturated)	70%-75% of phospholipids 50% of PC 50% of PC	 Major surface-active species Contributes to fluidity and improves dynamic behavior of surfactant
1-2 Anionic phospholipids: - Phosphatidylglycerol - Phosphatidylinositol - Phosphatidylserine	8%-15% of phospholipids	
1-3 Other phospholipids: - Phosphatidylethanolamine - Sphingomyelin	5% of phospholipids	
2- Neutral lipids (mostly cholesterol [90%], diglycerides, triglycerides)	5%-10%	Antioxidant Membrane structure
3- Other lipids	2%	
Proteins	5%-10%	
1- Loosely associated (mainly serum)	0%-5%	
2- Surfactant apoproteins		
Hydrophilic proteins, SP-A, SP-D*	2%-4%	Participate in the innate host defense immune system
Hydrophobic proteins, SP-B, SP-C*	1%-2%	Enhance stability and spreading of lipids Critical for lamellar bodies formation (SP-B)

SP-A, Surfactant protein A; *SP-B,* surfactant protein B; *SP-C,* surfactant protein C; *SP-D,* surfactant protein D.
*Data from Rooney SA: The surfactant system and lung phospholipid biochemistry, *Am Rev Respir Dis*131:439, 1985; Young SL, et al: Pulmonary surfactant lipid production in oxygen-exposed rat lungs, *Lab Invest*46:570, 1982; Veldhuizen R, et al: The role of lipids in pulmonary surfactant, *Biochim Biophys Acta* 1408(2-3): 90-108, 1998; and Glasser JR et al: Surfactant and its role in the pathobiology of pulmonary infection, *Microbes Infect* 14(1):17-25, 2012.

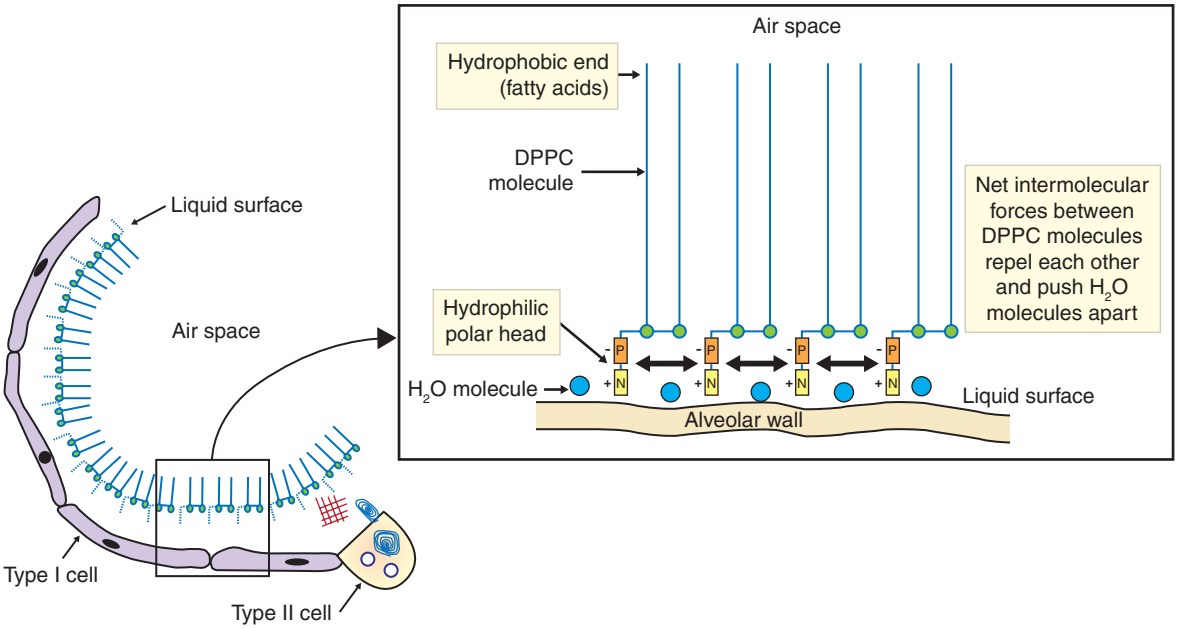


FIGURE 14-5 A cross-section of an alveolus wall. In the presence of surfactant protein B (not shown), dipalmitoylphosphatidylcholine (DPPC) aligns in the air–liquid interface with the hydrophobic end toward the gas phase (air space) and hydrophilic end toward the liquid phase (liquid surface). Strong molecular interactions occur between the polar heads of the hydrophobic end. Note that the polar head has a positive charge associated with its nitrogenous base (N) and a negative charge associated with its phosphate group (P). This alignment creates electrostatic forces of repulsion, pushing water molecules apart, preventing atelectasis, and holding the airway open during exhalation.

opsonin for bacteria, fungi, and viruses. In SP-A–deficient mice, tubular myelin is absent, but surfactant processing and function are intact. Despite relatively normal lung function, SP-A–deficient mice are highly susceptible to infections. In humans, gene polymorphisms have been described in lung cancer, interstitial lung disease, idiopathic pulmonary fibrosis, asthma, and chronic obstructive pulmonary disease.[24A]

SP-D is also a collectin and enhances the binding, phagocytosis, and killing of microbes by alveolar macrophages.[24] In addition, SP-D has a role in the suppression of proinflammatory responses. Lack of SP-D in transgenic mice leads to emphysema, macrophage activation, accumulation of oxygen-reactive species, and increased surfactant alveolar pools. So SP-D also plays a key role in surfactant homeostasis. Polymorphisms of the human genes for SP-A and SP-D have been documented and result in increased susceptibility to infections with respiratory syncytial virus and *Mycobacterium tuberculosis.*

SP-B is a membrane-associated protein that binds to the surface of lipid bilayers. SP-B, as discussed previously, is critical for alignment of surfactant at the air–liquid interface and for the formation of surfactant storage lamellar bodies in type II cells. SP-B is the only surfactant protein that humans cannot live without. SP-B protein deficiency is fatal in infancy without lung transplantation.

SP-C is necessary for the stability of the surfactant phospholipid film and for stability during dynamic compression in the respiratory cycle.[25] SP-C–deficient mice develop interstitial lung disease with emphysema, epithelial cell dysplasia, and inflammation. Infants with SP-C deficiency have RDS and pulmonary fibrosis. SP-C is not required for the formation of lamellar bodies or tubular myelin.

Other nonpulmonary surfactant-associated alveolar proteins are important in host defense: fibronectin, lysozyme, antiproteases, immunoglobulins (IgA), defensins, mucins, and Clara cell proteins. Excluding nonsurfactant proteins from the alveolus is critical to surfactant function and processing, because surfactant homeostasis may be disrupted by blood proteins, albumin, fibrin, and edema, as well as other substances.

HORMONAL EFFECTS ON SURFACTANT PRODUCTION

Antenatal steroids have been extensively studied and have been shown to decrease RDS in infants between 24 and 34 weeks of gestation. There is no increased infection risk with rupture of membranes, including prolonged rupture of membranes or chorioamnionitis. A single course of corticosteroids is currently recommended by the American College of Obstetricians and Gynecologists (ACOG) for pregnant women between 24 weeks and 34 weeks of gestation who are at risk of preterm delivery within 7 days.[26] This course may consist of betamethasone (2 doses, 24 hours apart) or dexamethasone (4 doses, 12 hours apart). A single rescue course may be considered if the first course was given more than 2 weeks prior in

women less than 32⁶⁄₇ weeks of gestation who are likely to deliver within the next week. Additional repeat courses have not demonstrated any benefit, may be associated with poorer outcomes, and are not recommended.[27,28] There is an increase in RNA within 2 hours of the first dose and an increase in protein secretion within 12 hours.[29] The full effect on surfactant production is present by 48 hours after the first dose. Antenatal steroid use in infants with less than 24 weeks of gestation has not been studied prospectively, but its use may be beneficial if resuscitation is planned.

Thyroid hormones, in addition to other hormones, are also important for lung development. Because thyroid hormones do not cross the placenta, several investigators examined antenatal thyrotropin-releasing hormone for the prevention of RDS in preterm infants. Unfortunately, no benefit was demonstrated in multicenter clinical trials.[30,31]

FETAL LUNG MATURITY TESTING

Measurement of phospholipids in the amniotic fluid can be used to determine fetal lung maturity, because phosphatidylglycerol (PG) and phosphatidylcholine (lecithin) increase while sphingomyelin decreases during gestation. Available tests include quantification of phospholipids present in the amniotic fluid and measurement of surfactant characteristics as well as function and number of lamellar bodies (Table 14-2).[32] The first test used for this purpose was based on the lecithin/sphingomyelin ratio. PG measurement in the amniotic fluid is a more accurate test than lecithin/sphingomyelin ratios. PG is produced by type II pneumocytes and is nearly undetectable until 35 weeks of gestation. Interestingly, PG is not required for surfactant function but correlates with pulmonary maturity. PG is now the basis of a rapid and inexpensive slide agglutination test (Amniostat-FLM-PG; Irvine Scientific, Santa Ana, CA) with 90% sensitivity. PG can be used for both amniotic fluid and vaginal pool samples in infants with premature rupture of membranes. False positives can occur if the samples are contaminated by bacteria containing PG in their cell wall. The TDx-FLMII (Abbott Diagnostics, Abbott Park, IL), a widely used method to assess fetal lung maturity, is no longer available. The lamellar body count has now increased in popularity, because it requires less than 1 mL of amniotic fluid, can be performed in 15 minutes, and retains a good specificity, with a count greater than 32,000 predicting a mature lecithin/sphingomyelin ratio in 99% of cases. Specific clinical settings need to be considered, because gestational diabetes delays maturation and PG is the preferred test. Fetal lung maturity may be accelerated in some but not all pregnancies with pregnancy-induced hypertension, intrauterine growth restriction, and *in utero* exposure to maternal smoking and cocaine.

Table 14-2 Fetal Lung Maturity Testing*

QUANTIFICATION OF SURFACTANT COMPONENTS	MATURE	TRANSITIONAL	IMMATURE
Phospholipid measurement			
Lecithin/sphingomyelin ratio	>2.0	1.5-2.0	<1.5
Phosphatidylglycerol	Present	Trace	Absent
Desaturated phosphatidylcholine	>70	50-70	<50
Fluorescence detection	>50,000	15,000-70,000	<15,000
Microviscometer assay			
Lamellar bodies			
Lamellar body count	>32,000		
Surfactant characteristics			
Surfactant function			
Foam stability index	>48%	47%	<47%
Shake test			
Tap test			
Amniotic fluid turbidity			
Optical density			
Visual inspection			

*Includes testing values for the five most common tests.
From Geary CA, Whitsett JA: Amniotic fluid markers of fetal lung maturity. In Spitzer AR, editor: *Intensive care of the fetus and neonate,* ed 2, St. Louis, 2005, Elsevier Mosby.

SURFACTANT DYSFUNCTION IN ACUTE LUNG INJURY

Abnormalities in surfactant (quantity or pool size, function, composition, and metabolism), destruction or inactivation of surfactant, and direct type II cell damage have been described in ARDS and other types of acute lung injuries (Table 14-3).[34]

ALTERED SURFACTANT QUANTITY

The evidence related to altered surfactant pool size in acute lung injury is variable. Decreases, increases, and no changes in pool size have all been reported.[35-38] This confusion reflects the difficulty in quantifying surfactant material obtained from bronchoalveolar lavage. Different clinical factors or types of lung injuries may affect the lung and surfactant function differently. For

Table 14-3 Diseases that Affect Surfactant

SURFACTANT DEFICIENCY	SURFACTANT INACTIVATION/ INHIBITION	SURFACTANT DYSFUNCTION
Respiratory distress syndrome	Aspiration syndromes Meconium	SP-C deficiency
SP-B deficiency	Blood Amniotic fluid Pulmonary hemorrhage Infections Pneumonia Respiratory syncytial virus Sepsis ARDS caused by: Near drowning Smoke inhalation Transfusions Trauma Sepsis Pulmonary diseases Asthma Cystic fibrosis	ABCA3 deficiency Congenital diaphragmatic hernia Smoking and COPD Lung transplantation

ABCA3, Member A3 of the ATP binding cassette family of proteins; *ARDS*, Adult respiratory distress syndrome; *COPD*, chronic obstructive pulmonary disease; *SP-B*, surfactant protein B; *SP-C*, surfactant protein C.

example, prolonged exposure to 85% oxygen results in type II alveolar cell hyperplasia and increased surfactant secretion, whereas 100% exposure decreases alveolar cell numbers and surfactant secretion.[20,39] Direct type II cell injury or necrosis will result in a decreased surfactant pool. At present, no firm conclusions can be drawn regarding the effects of acute lung injury on the quantity of surfactant.

ALTERED SURFACTANT COMPOSITION

A consistent finding in studies of acute lung injury is that alterations in the composition of surfactant occur. These findings include a decrease in surfactant-associated proteins in patients with ARDS and decreases in the quantities of phosphatidylcholine and phosphatidylglycerol along with an increase in sphingomyelin and other phospholipids.[37,40] Furthermore, these abnormalities appear to reverse with recovery from acute lung injury.[41,42] The relationship of these abnormalities in surfactant composition to lung dysfunction is unknown, but surfactant isolated from animal models of lung injury has abnormal surface activity *in vitro*.[42,43]

ALTERED SURFACTANT METABOLISM

Studies indicate that surfactant metabolism may be altered in acute lung injury. Animals injured by hyperoxia have decreased incorporation of surfactant precursors into lung tissue that reverses with recovery.[44] Other animal models show more rapid conversion of large to small surfactant forms that have poor surface tension–lowering properties. Bronchoalveolar lavage specimens from patients with ARDS also support evidence of altered surfactant metabolism, showing increased levels of proteases and alterations in the density profiles of surfactant.[45]

SURFACTANT INACTIVATION

Inactivation by proteins is the most common surfactant abnormality seen in acute lung injury. These proteins competitively displace surfactant phospholipid from the alveolar monolayer and are less surface-active molecules than surfactant; this results in a decreased capacity to reduce surface tension.

Many etiologies are associated with increased capillary permeability leading to pulmonary edema and resulting in surfactant inactivation. Albumin, hemoglobin, fibrin, complement, blood, meconium, and other proteins may gain access to the alveolar space secondary to alveolar–capillary membrane damage and have been shown *in vitro* to diminish the surface tension–reducing properties of surfactant.[45-47] Proteins compete with surfactant for the air–fluid interface and interfere with monolayer formation.[48] Several blood components are strong inactivators of surfactant, including hemoglobin, fibrin, fibrinogen, red blood cell membrane lipids, immunoglobulins, and plasma proteins. Similarly, several substances in meconium inactivate or alter surfactant function, including proteolytic enzymes, free fatty acids, phospholipases, bile salts, lanugo, squamous cells, bilirubin, steroid compounds, cholesterol, and triglycerides.[12] Regardless of the etiology, surfactant inactivation leads to diminished lung compliance, increased intrapulmonary shunting, and atelectasis characteristic of ARDS (Figure 14-6).[49]

CLINICAL APPLICATIONS AND REPLACEMENT

The typical clinical presentation of surfactant deficiency is summarized in Table 14-4. At present, exogenous surfactant administration is most commonly used for prophylaxis or treatment of preterm infants with RDS. It is also increasingly used in neonates and pediatric and adult patients for diseases associated with or leading to surfactant inactivation.

RESPIRATORY DISTRESS SYNDROME

Incidence

Typically, RDS affects premature infants born before 35 weeks of gestation. Its incidence increases with lower gestational ages. RDS affects 86% of infants weighing 501 to 750 g at birth, 79% of infants weighing 751 to 1000 g, 48% of infants at 1000 to 1250 g, and 27% between 1251 and 1500 g.[50] Representative chest radiographs of a premature infant with RDS before

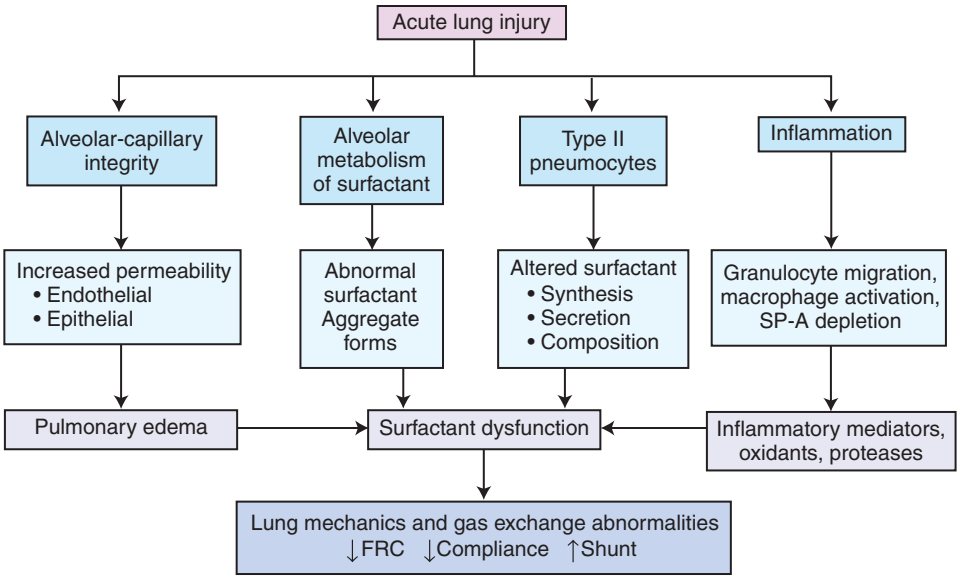


FIGURE 14-6 Four pathways that contribute to surfactant dysfunction during acute lung injury. *FRC,* Functional residual capacity; *SP-A,* surfactant protein A. (From Jobe AH, Ikegami M: Surfactant and acute lung injury, *Proc Assoc Am Phys* 110:489-495, 1998.)

Table 14-4 Clinical Presentation of Surfactant Deficiency Respiratory Distress Syndrome and Acute Respiratory Distress Syndrome

PATHOPHYSIOLOGY	LABORATORY CHANGES	PHYSICAL EXAMINATION	RADIOGRAPHIC CHANGES
Atelectasis	↓ Po2	Lung	Diffuse reticular granular pattern
↓ FRC	↑ Carbon dioxide	Tachypnea	Air bronchograms
Ventilation–perfusion mismatch	Metabolic acidosis	Apnea Increased work of breathing (nasal flaring, retractions, grunting) ↓ Breath sounds Poor air entry Cardiovascular Cyanosis (oxygen requirement) Pallor Poor perfusion	Atelectasis

FRC, Functional residual capacity; P_{O_2}, oxygen pressure.

and after surfactant administration as well as typical pathology findings in RDS are presented in Figure 14-7.

Treatment

Early experimental animal studies with administration of phospholipid mixtures showed some effect, but more dramatic and sustained improvements in oxygenation could be demonstrated only with natural surfactant complexes, harvested from the lavage of adult rabbit lungs, and later obtained from cows, pigs, and human amniotic fluid. Bioactivity of the synthetic preparations was improved with the addition of alcohols such as hexadecanol as well as tyloxapol (a formaldehyde polymer) to enhance dispersion and spread in the aqueous phase.

The first human trial in 1980 by Fujiwara and colleagues showed that natural animal-derived surfactant was effective in treating 10 premature infants with RDS.[11] The investigators instilled 3 to 5 mL of surfactant (from minced bovine extract and containing DPPC) directly to the trachea and enhanced distribution by changing the position of the infant. They demonstrated a prompt increase in oxygenation after one dose that was sustained for 2 to 3 days in some infants. This represented a marked improvement compared with results obtained with synthetic DPPC.

Large controlled trials have since established that surfactant preparations greatly reduce mortality in preterm infants. Surfactant replacement for prophylaxis or treatment of RDS has reduced the risk of

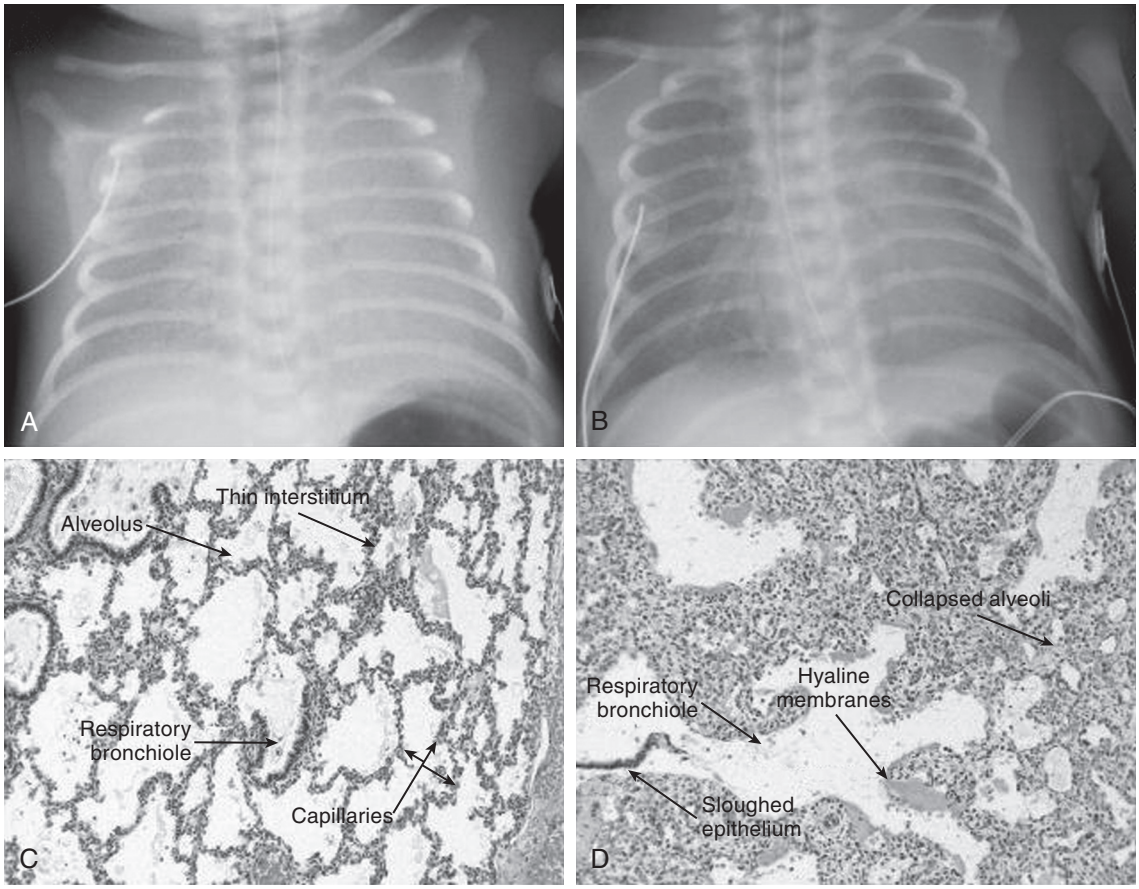


FIGURE 14-7 **A,** Chest radiograph of a premature infant with respiratory distress syndrome (RDS) demonstrating diffuse reticulogranular pattern (ground-glass appearance), air bronchograms, and low lung volume. **B,** Chest radiograph of the same premature infant after surfactant administration, demonstrating improved lung volumes. **C,** Photomicrograph of normal alveoli, demonstrating normal microscopic structure of the lung of a newborn infant. Clear areas are the air-containing expanded alveoli. The colored structures that form a honeycomb lattice are the walls that line the alveolar space. **D,** Microscopic structure of the lung from a premature infant who died of RDS. The normal honeycomb lattice is collapsed (atelectasis), the alveolar walls are adherent to each other, and the lung is almost airless. Those air-containing spaces (clear areas) that do remain are lined by a pink-staining layer of inflammatory protein termed the *hyaline membrane*. (Photos courtesy Drs. Kaufman and Robin LeGallo [Departments of Neonatology and Pathology, respectively, University of Virginia]).

pneumothorax by 30% to 65% and death by about 40%.[51] Early analysis showed a possible decrease in bronchopulmonary dysplasia, but it is now accepted by experts in the field that surfactants do not reduce the overall incidence of chronic lung disease or bronchopulmonary dysplasia.[2] Surfactant administration is also not associated with significant changes in intraventricular hemorrhage (IVH), patent ductus arteriosus (PDA), or retinopathy of prematurity. However, in one study, infants weighing more than 1250 g had a lower incidence of IVH and PDA.[52]

Two clinical strategies are currently used: (1) prophylaxis within 15 to 30 minutes of birth in small premature infants and (2) rescue treatment in infants with clinical evidence of RDS.

Prophylactic Surfactant

Prophylactic surfactant administration grew out of animal data demonstrating decreased epithelial damage and pulmonary edema when surfactant is given in the first 15 minutes of life.[53]

Prophylactic surfactant is administered after initial stabilization in the first 15 minutes after birth, compared with 1.5 to 7.4 hours in rescue strategies. Initial studies comparing prophylactic to rescue surfactant favored the former with noted decrease in mortality, pneumothorax, and pulmonary interstitial emphysema.[2] Most studies included larger premature infants (up to 30 weeks of gestation) and were conducted before the era of systematic antenatal steroid administration and routine postdelivery stabilization on continuous positive airway pressure (CPAP). All these factors are likely to have affected the rates of RDS, air leak, IVH, and mortality. Therefore, there is some debate as to whether a lower threshold for prophylaxis (e.g., less than 750 g, less than 1000 g, or less than 27 to 28 weeks of gestation) would define a higher risk group and prevent unnecessary prophylaxis of more mature infants.

Two large randomized controlled trials (the COIN and SUPPORT trials)[54,55] have examined the use of early stabilization with nasal CPAP (NCPAP) versus early intubation and surfactant administration in extremely low birth weight infants. In the COIN trial,[55] 610 extremely preterm infants (25 to 28 weeks of gestation), who were not intubated at 5 minutes of life, were randomized to either NCPAP or intubation with ventilation.[56] A distending pressure of 8 cm H_2O was used in the NCPAP group, notably higher than CPAP levels used in other centers. The authors' rationale to start with 8 cm was that distending pressure is important for maintaining functional residual capacity and for improving lung compliance and oxygenation, and 8 cm H_2O had been shown to be more effective than a lower pressure.[57] Forty-six percent of infants in the NCPAP group eventually required intubation (55% for infants born at 25 or 26 weeks of gestation and 40% for those born at 27 or 28 weeks of gestation). The total days requiring intubation and ventilation were less in the NCPAP group ($P < .001$). The need for surfactant use was 50% less in the NCPAP group (38% vs. 77%; $P < .001$). Pneumothorax was more common in the NCPAP group (9.1% vs. 3%; $P < .001$), with 98% of those infants needing intubation, but there was no increase in intracranial hemorrhage. There was no difference in oxygen requirement at 36 weeks postmenstrual age, mortality, or length of hospitalization. In the SUPPORT trial,[54] 1316 extremely preterm infants (24 to 27 weeks of gestation) were randomly assigned to nasal CPAP in the delivery room or intubation and surfactant treatment (less than 1 hour after birth). Infants in the CPAP group less frequently required intubation or postnatal corticosteroids for bronchopulmonary dysplasia ($P < .001$), required fewer days of mechanical ventilation ($P = .03$), and were more likely to be alive and free from the need for mechanical ventilation by day 7 ($P = .01$). There was no difference in the rate of bronchopulmonary disease (BPD; 47.8 vs. 51%).

These studies suggest that for infants older than 24 weeks and demonstrating adequate respiratory effort, the use of early CPAP is a reasonable alternative to early intubation for prophylactic surfactant. However, clear guidelines for surfactant administration need to be in place if such strategies are to be applied successfully. It is also important to remember that in ventilated preterm infants, early surfactant administration results in decreased mortality (relative risk [RR], 0.84; 95% confidence interval [CI], 0.74 to 0.95) and chronic lung disease (RR, 0.69; 95% CI, 0.55 to 0.86).[58]

Strategies for surfactant administration are summarized in Table 14-5.

Table 14-5 Surfactant Delivery

	COMMENTS	STUDIES
Timing		
Prophylaxis	Surfactant given <15 minutes after birth, before symptoms appear	↓ PTX and mortality in infants <31 wk.[72]
Rescue	At time of clinical signs and symptoms	↓ PTX and mortality.[2]
Subsequent dosing	Required if inactivation or insufficient delivery of surfactant	Surfactant may be redosed in the first 48-96 h after presentation. Usually one or two doses are sufficient. Third and fourth doses did not improve outcomes.[73]
Administration		
Adapter	ETT with side adapter or Y-adapter attached to ETT	Minimizes desaturation caused by disconnection from positive pressure ventilation or the ventilator for administration.
Delivery	Bolus intratracheal administration	Bolus administration ↓ homogeneous distribution. Slow infusion ↓ nonhomogeneous distribution pattern in animals. Aerosolization ↓ only small amounts of aerosolized surfactant are delivered to the lung.[74] Efficacy currently being reevaluated as noninvasive ventilation becomes more common.[64,75]
Dose	75-100 mg/kg	75-100 mg/kg to overcome destruction by macrophages and inhibition by plasma proteins. 100 and 120 mg/kg produced better results than 50 and 60 mg/kg.[76,77] Equal efficacy of 100 and 200 mg/kg of porcine surfactant.[78,79]

Table 14-5 Surfactant Delivery—cont'd

	COMMENTS	STUDIES
Surfactant products and dose (phospholipid/dose)	Intratracheal administration	Calfactant: 3 mL/kg (105 mg) every 6 h up to four doses. Poractant: 2.5 mL/kg (200 mg), then 1.25 mL/kg (100 mg) every 12 h Beractant 4 mL/kg (100) every 6 h up to four doses.
Aliquots	To enhance delivery distribution in the lung	No difference if dose is divided into two or four aliquots.[80]
Positioning	Position infant with either the right or left side dependent for administration in two aliquots. Deliver as fast as possible for improved distribution Maintain the position for about 10 seconds. Note: A four-position, four-aliquot technique is equivalent.[80]	Although recommended, it is not necessary to move the infant into different positions during instillation, because exogenous surfactant has remarkable spreading properties
Monitoring		
	Oxygenation	Side effects include cyanosis, bradycardia, reflux of surfactant into the ETT, and airway obstruction. Surfactant delivery should be paused until vital signs recover and ETT clears of visible surfactant. Infant may need to be repositioned prone and positive pressure ventilation increased for lung inflation.
	Heart rate	
	Presence of surfactant in the ETT	

ETT, Endotracheal tube; *PTX*, pneumothorax.

Rescue Surfactant and Repeat Doses

In patients to whom prophylactic surfactant is not given, clinical signs and symptoms of RDS can be used to determine the need for surfactant administration (see Table 14-4). However, specific criteria for surfactant administration for infants on CPAP are still an area of debate. A reasonable approach would be to provide early rescue surfactant for those infants with evidence of moderate to severe RDS on chest radiograph and fraction of inspired oxygen (Fio_2) above 30% to 50% (depending on gestational age and whether antenatal steroids were used).[59] There is evidence that early rescue surfactant results in decreased need for mechanical ventilation, decreased BPD, and decreased pneumothoraces, particularly when given at a lower threshold ($Fio_2 < 0.45$).[60,61] Surfactant can be provided using the intubation-surfactant-extubation (INSURE) procedure. Risk factors for INSURE failure include weight less than 750 g, Po_2/Fio_2 less than 218, and arterial/alveolar oxygen tension ratio (a/APo_2) less than 0.44.[62] The use of a laryngeal mask airway, obviating the need for intubation and possibly mechanical ventilation, has been shown to be effective in larger infants.[63] Additionally, other minimally invasive methods of surfactant administration, including aerosolized surfactant[64] or via insertion of a thin catheter into the trachea,[65] are currently being investigated to facilitate the administration of surfactant in spontaneously breathing infants with RDS.

Redosing of surfactant in infants with RDS has been shown to result in improved oxygenation, decreased ventilatory requirements, and fewer pneumothoraces.[66] The criteria for surfactant redosing remains an area of controversy. A few studies have demonstrated some short-term but no long-term benefits with retreatment at a low threshold (still intubated, mean airway pressure greater than 6 cm H_2O, with Fio_2 more than 0.030), versus high threshold (still intubated, mean airway pressure greater than 7 cm H_2O and Fio_2 more than 0.040) or an increase in Fio_2 up to 0.10.[51] Early rescue compared with late rescue strategies have demonstrated decreased mortality and decreased incidence of pneumothorax.[67]

Surfactant Administration Methods

Surfactant is most commonly administered via bolus dosing using an endotracheal tube. Less invasive surfactant administration (LISA) or minimally invasive surfactant therapies (MIST) have been developed for

infants breathing spontaneously on CPAP but for whom surfactant administration is required for moderate-to-severe RDS. These techniques have several advantages in that they do not require intubation, limit the need for premedication, and (very importantly) significantly reduce the need for mechanical ventilation. Although techniques such as INSURE (intubation, surfactant administration, early extubation) are meant to include rapid extubation, prolonged mechanical intubation after intubation for surfactant administration is not uncommon. Various minimally invasive techniques of surfactant administration using a wide variety of equipment have been described.

LISA techniques are increasingly used with good results, particularly in Europe. In a recent survey, the use of LISA/MIST within 37 European countries was shown to be widespread, with 52% of respondents using LISA/MIST.[67A] In a randomized controlled trial of 211 preterm infants (23.0 to 26.8 weeks of gestational age), LISA was associated with increased survival without major complications, but not with increased survival without bronchopulmonary dysplasia.[67B] In randomized controlled trials comparing LISA/MIST with conventional surfactant administration, the administration of surfactant through a thin catheter decreases the incidence of mechanical ventilation and BPD without an increase in complications.[67C] Finally, results from another metaanalysis comparing ventilation strategies for preterm infants indicate that the use of LISA is associated with the lowest likelihood of death or bronchopulmonary dysplasia.[67D] Surfactant aerosolization is another noninvasive technique under investigation. Preclinical studies indicate that aerosolized KL4 surfactant has similar efficacy to surfactant delivered by standard methods in models of acute lung injury.[67E,67F] It is clear that these noninvasive methods of surfactant administration will become more standard practice as evidence of their efficacy continues to mount.

Natural Versus Synthetic Preparations

At present there are several different types of exogenous commercial surfactants[51,68] (Table 14-6): minced bovine lung lipid extracts enriched with synthetic lipids (beractant [Survanta, Abbott Nutrition, Columbus, OH] and surfactant TA [Surfacten, Mitsubishi Tokyo Tanabe Pharma, Tokyo, Japan]), bovine lung lavage lipid extracts (calfactant [Infasurf, ONY Inc., Amherst, NY] and bovactant SF-RI [Alveofact, Boehringer Ingelheim, Ingelheim, Germany]), minced porcine lung enriched by chromatography (poractant alpha [Curosurf; Chiesi Farmaceutici, Parma, Italy], and a mixture of synthetic lipids. The bovine surfactants contain SP-B and SP-C, but not SP-A. Calfactant contains much more SP-B and SP-C than does beractant. The synthetic surfactants contain no proteins. Compared with older synthetic surfactants, natural surfactants have a more rapid onset of action, allow the fraction of inspired oxygen to be reduced faster, and decrease the incidence of pneumothorax as well as mortality. Clinical trials comparing different natural surfactants have not clearly demonstrated one product to be better than another.[2] A new generation of synthetic surfactants incorporating genetically engineered SP-B or SP-C protein equivalent (pumactant [Zofac, airPharma, Overland Park, KS, and ALEC, Britannia Pharmaceuticals, Crawley, UK] and lucinactant [Surfaxin, Discovery Laboratories, Warrington, PA], respectively) are currently being studied. In trials, lucinactant appears to offer a level of efficacy similar to that of natural surfactants.[1,69-71] There are currently five surfactants approved by the Food and Drug Administration for use in the United States: the recently approved lucinactant, beractant, poractant alpha, calfactant, and colfosceril palmitate (which is no longer marketed).

Nonresponders

Although most infants respond favorably to treatment, about 20% of infants believed to have RDS have little or no response. These infants may have other disease processes such as pneumonia, pulmonary hypoplasia, or congenital heart disease. Full-term infants with RDS, surfactant nonresponders, and infants who cannot be extubated in the first weeks of life because of their respiratory condition should be evaluated for SP-B deficiency, alveolar capillary dysplasia, and α1-antitrypsin deficiency.

PULMONARY HEMORRHAGE

Blood is a strong inactivator of surfactant, with several of its components (such as hemoglobin, fibrin, fibrinogen, red blood cell membrane lipids, immunoglobulins, and plasma proteins) contributing to this process. Inactivation can occur as a result of pulmonary hemorrhage, hemorrhagic edema, or blood aspiration during birth or trauma.

Pulmonary hemorrhage or hemorrhagic edema occurs in 3% to 5% of infants with RDS.[81] The presence of a PDA is a risk factor because of the potential large systemic-to-pulmonary vascular pressure difference between the descending aorta and pulmonary vasculature. Pulmonary hemorrhage can occur after subsequent surfactant administration because it decreases pulmonary vascular resistance further and increases the potential for a large pressure gradient if a PDA is present. The efficacy of surfactant therapy was reported in 15 neonates with respiratory deterioration caused by pulmonary hemorrhage.[82] Mean oxygen index improved from 24.6 at 0 to 3 hours presurfactant to 8.6 at 3 to 6 hours postsurfactant ($P < .001$). No patient deteriorated after surfactant therapy. Randomized controlled trials evaluating surfactant replacement therapy

Table 14-6 Exogenous Commercial Surfactants

SURFACTANT TYPE	COMPOSITION					
Generic (Trade Name)	**% DPPC**	**Protein**	**Phospholipid Concentration**	**Suggested Dose (Phospholipids/Dose)**	**Advantages**	**Disadvantages**
Native Surfactant						
	40%-50%	SP-A, B, C, D				
Synthetic Surfactants						
Colfosceril palmitate (Exosurf)* Glaxo Wellcome, USA	84.5%	None	13.5 mg/mL	5 mL/kg (67.5 mg/kg)	No risk of disease transmission Less immunological rejection Completely defined formulation	Lower resistance to inactivation Lack surface active apoprotein Less rapid improvement in gas exchange (Exosurf, ALEC)
Pumactant (ALEC) Britannia Pharmaceutical, UK	70%	None	40 mg/mL	1.2 mL/kg (100 mg/kg)		
Lucinactant (Surfaxin)* Discovery Laboratories, US	75%	Sinalpultide (KL-4) = SP-B equivalent	30 mg/mL	5.8 mL/kg (175 mg/kg)		
rSP-C (Ventricute) Byk Gulden, Germany	67%	rSP-C	50 mg/mL	1 mL/kg (50 mg/ml)		
Modified Natural Surfactants						
Bovine					Contains surfactant apoproteins SP-B and SP-C Higher resistance to inactivation	Transmission risk Unwanted constituents May contain proinflammatory mediators May be immunogenic
Surfactant TA (Surfacten) Tokyo Tanabe Co, Japan	50%	<0.5% SP-B; SP-C	30 mg/mL	4 mL/kg (120 mg/kg)		
Beractant (Survanta)* Abbott Laboratories, US	50%	<0.5% SP-B; SP-C	25 mg/mL	4 mL/kg (100 mg/kg)		
Bovactant SF-RI (Alveofact)† Boehringer Ingelheim, Germany	40%	~1% SP-B; SP-C	41.7 mg/mL	1.2 mL/kg (50 mg/kg)		
Calfactant (Infasurf)*† ONY Inc., US	50%	SP-B; SP-C	35 mg/mL	3 mL/kg (105 mg/kg)		
Bovine lipid extract surfactant (bLES) BLES Pharmaceuticals, Canada	40%	~1% SP-B; SP-C	27 mg/mL	5 mL/kg (135 mg/kg)		
Porcine						
Poractant alpha (Curosurf)* Chiesi Farmaceutici Pharma, Italy	35%	~1% SP-B; SP-C	76 mg/mL	2.5 mL/kg then 1.25 mL/kg (200 mg/kg then 100 mg/kg)		

ALEC, Artificial lung-expanding compound; *DPPC,* dipalmitoylphosphatidylcholine; *rSP-C,* recombinant surfactant protein C; *SP,* surfactant protein.
*FDA approved for use in the United States.
†Obtained from lung lavage as opposed to minced lung extracts.

for neonates with pulmonary hemorrhage are still lacking.[83]

MECONIUM ASPIRATION SYNDROME

Meconium aspiration syndrome (MAS) affects 5% to 10% of all infants born through meconium-stained fluid. The pathophysiology of MAS includes mechanical airway obstruction, chemical pneumonitis, and secondary infection. Mounting evidence also points to the role of surfactant inactivation in the development of MAS.[84,85] Mechanisms of surfactant inactivation in MAS include the following[12]:

- Disruption of the surfactant monolayer by fatty acids present in the meconium
- Production of holes in type II cells by phospholipids, causing asymmetry of the surfactant monolayer
- Bile acid–induced calcium influx in type II cells
- Influx of neutrophils producing proteases that degrade surfactant 1 to 2 hours after aspiration
- Decreased levels of SP-A and SP-B

These alterations interfere with the ability of surfactant to lower surface tension in children with MAS.

The efficacy of surfactant replacement therapy in MAS was first reported in a retrospective study and has been confirmed in several uncontrolled, retrospective studies, four randomized controlled trials, and a metaanalysis.[86-88] Findlay and co-workers studied 40 term infants receiving mechanical ventilation for MAS and randomized them to either beractant or placebo.[88] They reported that surfactant replacement, started within 6 hours of birth, improves oxygenation, reduces the incidence of air leaks, and reduces the severity of pulmonary morbidity. It also decreased the need for extracorporeal membrane oxygenation (ECMO) from 30% to 5%. Dosing was 6 mL/kg (150 mg) of surfactant, which is slightly higher than is used for RDS alone, and surfactant was administered every 6 hours for up to four doses.

Lotze and co-workers, in a multicenter, randomized, double-blind, placebo-controlled trial of beractant versus placebo, demonstrated that surfactant significantly decreased the need for ECMO in the treatment of term newborns with respiratory failure.[89] There may also have been benefit for infants in this study with persistent pulmonary hypertension and sepsis. This was not associated with increase in the risk of complications, including no change in the incidence of air leak. Findlay and co-workers demonstrated improved outcomes with earlier administration compared with Lotze and co-workers (6 hours vs. 31 hours).

Finally, the Chinese Collaborative Study Group for Neonatal Respiratory Diseases published the results of a multicenter, controlled trial of 61 term infants with severe MAS randomized to receive poractant alpha (200 mg/kg) versus placebo. There was a significant improvement in oxygenation in the poractant alpha–treated group, with no change in the incidence of major complications or difference in survival (no patients received ECMO).[90]

A metaanalysis confirmed that surfactant replacement for MAS decreases the need for ECMO (RR, 0.64; 95% CI, 0.46, 0.91), with a number needed to treat of 6 (95% CI, 3, 25). While the use of surfactant decreased the severity of illness and progression to ECMO, it did not have a significant effect on mortality (RR, 0.98; 95% CI, 0.41, 2.39). Further there was no significant reduction in duration of assisted ventilation or supplemental oxygen, respiratory complications (e.g. pneumothorax, pulmonary interstitial emphysema), or chronic lung disease.[91]

The use of dilute surfactant lavage has also been studied in severe MAS. The principle is that both surfactant delivery and meconium removal can be achieved by lavage, because surfactant facilitates the removal of foreign debris. A pilot trial using large volumes (48 mL/kg) of lucinactant reported not statistically significant trends toward more rapid extubation and decreased Fio_2 requirements for lucinactant-lavaged infants.[92] However, one-third of the patients had bloody effluents, and more infants in the lavage group (one-third) met failure criteria. In addition, surfactant–saline lavage was associated with significant oxygen desaturation during administration, resulting in interruption of the procedure in 20% of the subjects because of hypoxemia or hypotension. The effects of surfactant lavage with lower volume (15 mL/kg) of lucinactant were evaluated in a small randomized controlled trial (66 infants with MAS).[93] There was no change in duration of respiratory support, but the combined outcome of mortality or need for ECMO was reduced in the lung lavage group (10% vs. 31%; odds ratio [OR], 0.24; 95% CI, 0.060 to 0.97). Tolerance was improved with this lower volume of lung lavage, with only transient desaturations and no associated changes in heart rate or blood pressure noted during administration.

Randomized trials are needed to compare surfactant lavage strategies versus standard surfactant administration, because they may have the same efficacy. In addition, saline may not be an ideal fluid for lung lavage, and perfluorocarbons (used in liquid ventilation trials) may offer an attractive alternative because they have gas exchange properties.

In summary, for MAS, surfactant given early in patients meeting similar respiratory criteria as those with surfactant deficiency (intubated on more than 30% to 40% oxygen) and redosing using similar criteria is important for translating this evidence into clinical practice.

PNEUMONIA AND SEPSIS

Infection and inflammation are associated with inflammatory mediators (transforming growth factor β,

tumor necrosis factor α, interleukin [IL]-1, IL-5, IL-6, and IL-8) that lead to surfactant alteration, some degree of capillary leak, and pulmonary edema.[94] The combination of edema and leak of plasma proteins into the alveolus leads to surfactant dysfunction. Microorganisms may also directly injure type II cells. Specific microbes may produce substances that downregulate SP-B and SP-C production, catalyze phospholipid hydrolysis (breakdown), and alter fatty acid composition. In animal studies of group B *Streptococcus* pneumonia, surfactant decreased bacterial proliferation and improved compliance compared with controls.[95,96]

A retrospective study of 118 infants with group B *Streptococcus* infection demonstrated improvement in oxygenation and mean airway pressure.[97] The authors compared the infected surfactant-treated group with infants with RDS and noted that the infected patients had a slower response and were more likely to need repeated doses. In the multicenter placebo-controlled trial in neonates by Lotze and co-workers discussed earlier, 30% of the enrolled infants in both groups had sepsis.[89] Surfactant decreased the need for ECMO, and the effect was greatest in the infants with an oxygen index between 15 and 22, suggesting that earlier treatment may improve outcomes. Randomized controlled trials are required to evaluate this issue further.[98]

CONGENITAL DIAPHRAGMATIC HERNIA

Infants with congenital diaphragmatic hernia (CDH) have immature lung development. In addition, relative surfactant deficiency has been demonstrated in animal models as well as in infants with CDH.[99,100] Exogenous surfactant replacement first demonstrated some efficacy in infants with CDH in a series of small case reports.[101-103] Several large series have reported improved outcomes (survival and no need for ECMO) in infants with CDH. In these studies patients received surfactant as part of a gentle ventilation strategy aimed at limiting barotraumas and volutrauma (with either conventional or high-frequency ventilation), with some patients also receiving nitric oxide.[104-108] The use of surfactant in infants with CDH has been incorporated into the treatment protocols of patients with CDH at many centers. Analysis of data from the CDH registry regarding surfactant use in infants with CDH did not demonstrate any benefit.[109-112] However, the subjects were not randomized, only a subset of the registry was analyzed, and there were no specific guidelines for surfactant use or criteria for ECMO. Therefore, it is possible that the more severely affected infants with CDH received surfactant, skewing the results. Randomized controlled trials in this area are still needed to clarify the potential benefits of surfactant replacement therapy in infants with CDH.

EXTRACORPOREAL MEMBRANE OXYGENATION

ECMO and cardiopulmonary bypass are associated with the development of an inflammatory-mediated capillary leak syndrome. This leads to fluid and neutrophil accumulation in the lungs and interstitial tissues, resulting in pulmonary edema and in turn prolonging time receiving ECMO. Inflammatory mediators attract and activate white blood cells, possibly contributing to lung injury and edema. Some infants receiving ECMO are unable to wean and may benefit from surfactant administration if surfactant inhibition is contributory to their respiratory failure. A blinded, randomized, controlled study of multiple-dose surfactant therapy demonstrated decreased ECMO duration as well as reduced disease complications.[113] Four doses of modified bovine lung surfactant extract (beractant) were administered to the surfactant group (n = 28); and an equal volume of air was administered to the control group (n = 28). The ECMO treatment period was significantly shorter in the surfactant group (P = 0.023). The overall incidence of complications after ECMO was also decreased in the surfactant group (18% vs. 46%; $P = 0.025$).

Infants with CDH requiring ECMO are a challenging patient group to manage. After surgery, failure to wean off of ECMO may be related to the following:

- Severe pulmonary hypoplasia (as indicated by ECMO requirement for their management)
- Severe pulmonary hypertension
- Pulmonary edema
- Surfactant inactivation
- Complications of surgery

One study examined whether surfactant administration could improve outcomes and decrease the duration of ECMO for infants with CDH.[114] These infants received either four doses of surfactant (beractant, n = 9) or an equal volume of air (control group, n = 8). Tracheal aspirate SP-A concentrations were initially low, and then increased over time in both CDH groups. Lung compliance, time to extubation, time on oxygen, and total number of hospital days were not different between the two groups.

ACUTE RESPIRATORY DISTRESS SYNDROME

Significant impairments of surfactant production and composition have been demonstrated in the lungs of patients with ARDS. Surfactant alterations include reduced phospholipid content and, in particular, reduced DPPC levels, as well as decreased levels of surfactant-associated proteins.[37,115,116] These changes lead to decreased surface activity, resulting in the

atelectasis and decreased lung compliance characteristic of ARDS.

Three large trials failed to demonstrate a benefit of surfactant therapy in adult patients with ARDS.[117-119] In children with ARDS, the efficacy of surfactant therapy has been assessed in several pilot studies. Calfactant administration to children with hypoxemic respiratory failure resulted in immediate improvement in oxygenation, as well as a 32% reduction in time requiring mechanical ventilation and a 30% reduction in stay in the pediatric intensive care unit.[120]

In a separate study, 20 children with an acute pulmonary disease and severe hypoxemia (13 with systemic or pulmonary disease and 7 with cardiac disease) received poractant alpha. There was a moderate improvement in oxygenation among patients with systemic or pulmonary disease but not in children with hypoxemic pulmonary pathology in the postoperative period of cardiovascular surgery. The improvement in oxygenation of the patients who survived was greater than that of those who died.[121]

A multicenter, randomized control trial was published comparing 153 children with respiratory failure from acute lung injury and assigned to two doses of calfactant 12 hours apart versus placebo.[122] Calfactant acutely improved oxygenation, with a decrease in the oxygen index from 20 to 13.9. In addition, there was a significant decrease in mortality in the calfactant group, with an OR of 2.32 (95% CI, 1.15 to 4.85). In this study, no difference in duration of mechanical ventilation, intensive care unit stay, or hospital stay was noted. Adverse effects of the therapy were minimal, and in those patients who did not benefit it did not cause harm. The authors of this study have discussed that although this treatment is still under investigation, patients with direct lung injury such as near drowning, pneumonia, or trauma with severe pulmonary compromise may benefit, whereas patients with diseases involving ongoing capillary leak (e.g., sepsis) do not respond.

Although promising, the results of these studies are confounded by variability in dosing, time of administration, and type of surfactant. In addition, attention to patient population, immune status, and mechanism of lung injury should be integrated into the design of future surfactant trials for ARDS.

VIRAL BRONCHIOLITIS

Impairment in surfactant function has been reported in patients with viral bronchiolitis,[123] including reduced levels of SP-A, SP-B, and SP-D as well as decreased DPPC.[124,125] In a small randomized controlled trial of poractant alpha in 20 infants with severe respiratory syncytial virus (RSV) bronchiolitis, surfactant therapy appeared to improve gas exchange, reduce peak inspiratory pressure, and shorten time on conventional ventilation and duration of intensive care unit stay.[126] In a second randomized trial, 19 ventilated infants with RSV bronchiolitis received beractant or placebo. Again, patients in the surfactant group had improved oxygenation, improved lung compliance, and shortened time on ventilation.[127] A recent Cochrane review concluded that larger trials are required to evaluate the efficacy of surfactant replacement in bronchiolitis.[128]

ASTHMA

Decreased SP-A levels have been reported in sputum from patients with acute asthma.[129] In addition, antigen challenge of patients with asthma results in altered phospholipid properties and increased surface tension.[130] A pilot placebo-controlled trial of surfactant replacement therapy (Surfactant TA) was conducted in 11 adult patients with acute asthma. Respiratory functions were significantly improved in all patients in the surfactant group, including forced vital capacity, forced expiratory volume in 1 second, and arterial partial pressure of oxygen. No difference was detected in arterial partial pressure of carbon dioxide.[131] However, in 12 children with asthma, there was no significant improvement in airflow obstruction and bronchial responsiveness to histamine after surfactant nebulization (Bovactant SF-RI).[132] Additional studies, particularly those focusing on synthetic surfactant to prevent a potential immune response to natural surfactant, are necessary to clarify the benefits of surfactant replacement in asthma.[133]

CYSTIC FIBROSIS

Multiple studies have looked at surfactant in patients with cystic fibrosis (CF), with contrasting results that may be explained in part by the age of the patients. In young patients, no difference in SP-A levels are noted; however, with the development of inflammation, increased levels are observed.[134] In patients with more chronic CF, SP-A levels decrease.[135,136] Griese and co-workers also demonstrated deficient surface tension ability of phospholipids in patients with CF compared with healthy control subjects.[137] In contrast, Postle and co-workers found no difference in phospholipids.[136] In 2005 the surfactant function of 20 patients with CF was studied longitudinally. The study demonstrated a progressive loss of surfactant function, which correlated with increased inflammation and decreased lung function. In this study, the concentrations of SP-A, SP-C, and SP-D did not change, whereas that of SP-B increased.[138]

No therapeutic trials in children have been published. A pilot study of Bovactant SF-RI versus placebo in adults with severe CF showed no improvement in lung function or oxygenation.[137]

FUTURE DIRECTIONS

Today, thanks to surfactant replacement therapy, RDS is an uncommon cause of death in preterm infants. Annual deaths from RDS in the United States have decreased from 10,000 to 15,000 per year in the 1950s to less than 1000 in 2002. If surfactant replacement is unequivocally effective in treating surfactant-deficient preterm infants, current evidence suggests that it may prove useful as an adjunctive therapy when surfactant dysfunction is a contributing factor in acute respiratory failure. Thus surfactant replacement offers promise to improve disturbed lung physiology and allow moderation of ventilator support in children with acute respiratory failure.

However, challenges remain in the area of surfactant uses and delivery. Technical aspects, including timing of delivery, number of doses, and mode of delivery, need to be studied in relation to specific disease type. The development of less-invasive modes of surfactant delivery is currently being evaluated and will likely change clinical practice in the near future. Other future developments are likely to focus on increased use of synthetic surfactants containing genetically engineered surfactant-associated proteins. These synthetic surfactants are potentially more effective because of their constant and known composition, but they also offer less risk to the patient.

Finally, increased understanding of individual genetic polymorphisms regarding surfactant-associated proteins[130,140] may lead to the identification of patients who will or will not benefit from surfactant administration.

Key Points

- Pulmonary surfactant is a complex mixture of lipids and protein that lowers surface tension proportionally to alveolar size and prevents alveolar collapse during expiration.
- Surfactant proteins A and D are important components of innate immunity for inhaled pathogens.
- Surfactant deficiency, dysfunction, or inactivation underlies the pathophysiology of many respiratory disorders, including RDS, ARDS, and MAS.
- Exogenous surfactant replacement therapy was first used successfully to treat neonatal RDS.
- Surfactant replacement therapy is an active area of research, with studies investigating its efficacy in other patient populations, including those with ARDS, asthma, and CF.

Case Study 1

An 800-g baby boy is born by spontaneous vaginal delivery at 26 weeks of gestation as a result of cervical incompetence. The infant is active, with Apgar scores of 5 and 6, and needs positive pressure ventilation to establish regular respirations. Grunting occurs immediately, and a nasal continuous positive airway pressure (NCPAP) of 5 cm H_2O is applied after positive pressure ventilation at 5 minutes. The chest radiograph demonstrates a homogeneous ground-glass pattern. The infant's first arterial blood gas determination at 30 minutes of life on 70% oxygen produces the following results: pH 7.10; P_{CO_2}, 78 mm Hg; P_{O_2}, 52 mm Hg.

What would you do at this point? (Note: More than one answer may be acceptable.)

A. Continue NCPAP.
B. Perform endotracheal intubation.
C. Perform endotracheal intubation and administer surfactant.
D. Increase the F_{IO_2}.

See Evolve Resources for answers.

Case Study 2

A full-term infant is delivered by emergency cesarian section for fetal heart rate decelerations. Thick meconium is noted when membranes are ruptured during the cesarian section. The obstetrician suctions the infant and then the pediatrician performs endotracheal intubation and suctions the airway. On physical examination, the infant has significant grunting and intercostal retractions. The trachea is reintubated and the infant is placed on high-frequency oscillatory ventilation. He requires an F_{IO_2} of 1.0 and has preductal saturations of 90% and postductal saturations of 85%. The chest radiograph demonstrates bilateral streaky densities throughout the lung fields.

What is this infant at risk for? (Note: More than one answer may be acceptable.)

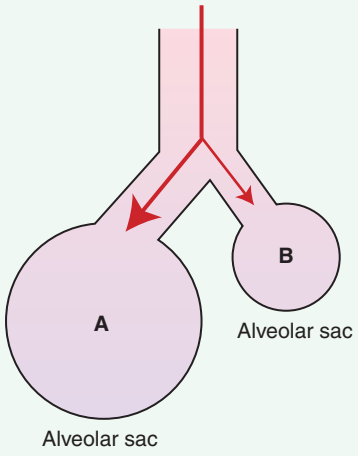
A. Pneumothorax
B. Persistent pulmonary hypertension of the newborn
C. Respiratory distress syndrome
D. Aspiration pneumonia

See Evolve Resources for answers.

Assessment Questions

See Evolve Resources for answers.

1. What is/are the most abundant components of surfactant?
   - **A.** Dipalmitoylphosphatidylcholine (DPPC)
   - **B.** Surfactant protein B
   - **C.** SP-C
   - **D.** Phosphatidylglycerol
2. Surfactant inactivation and dysfunction have not been described in which of the following diseases?
   - **A.** Meconium aspiration syndrome
   - **B.** Asthma
   - **C.** Cystic fibrosis
   - **D.** Congenital heart disease
   - **E.** Sepsis
3. Natural surfactant preparations come from which of the following mammals (select all that apply)?
   - **A.** Pigs
   - **B.** Cows
   - **C.** Calves
   - **D.** Horses
   - **E.** Whales
4. Which air sac in the following diagram requires higher pressure to inflate (assuming similar surface tension)?



   - **A.** Air sac A
   - **B.** Air sac B
5. Which surfactant-associated protein deficiency is fatal in infancy without lung transplantation?
   - **A.** SP-A deficiency
   - **B.** SP-B deficiency
   - **C.** SP-C deficiency
   - **D.** SP-D deficiency
6. Which surfactant protein(s) is/are important in defense against infection (pick all that apply)?
   - **A.** SP-A
   - **B.** SP-B
   - **C.** SP-C
   - **D.** SP-D
7. What is the most common complication of surfactant administration in a preterm neonate?
   - **A.** Hypoxemia
   - **B.** Airway obstruction
   - **C.** Pulmonary hemorrhage
   - **D.** Infection
   - **E.** Hypotension
8. What are the benefits of surfactant replacement therapy in infants with RDS (pick all that apply)?
   - **A.** Reduction in the severity of RDS
   - **B.** Reduction in the incidence of air leaks (pneumothorax and pulmonary interstitial emphysema)
   - **C.** Reduction in mortality from RDS by 40% to 60%
   - **D.** Reduction in the incidence of bronchopulmonary dysplasia
   - **E.** Reduction in the incidence of intraventricular hemorrhage
9. What component(s) of natural surfactant increase(s) efficacy compared with synthetic surfactants (pick all that apply)?
   - **A.** SP-B
   - **B.** Percentage of DPPC
   - **C.** SP-C
   - **D.** Cholesterol
10. What radiographic findings are typical of a child with RDS (pick all that apply)?
    - **A.** Large lung volume
    - **B.** Atelectasis
    - **C.** Air bronchograms
    - **D.** Pulmonary interstitial emphysema
    - **E.** Ground-glass pattern

REFERENCES

1. Pfister RH, Soll RF. New synthetic surfactants: the next generation? *Biol Neonate*. 2005;87:338-344.
2. Suresh GK, Soll RF. Overview of surfactant replacement trials. *J Perinatol*. 2005;25(suppl 2):S40-S44.
3. Obladen M. History of surfactant up to 1980. *Biol Neonate*. 2005;87:308-316.
4. Von Neergaard K. Neue Auffassugen uber einen Grundbegriff der Atemmechanik: Die Retraktionskraft der Lunge, abhangig von der Oberflachenspannung in den Alveolen. *Z Gesamte Exp Med*. 1929;66:373.
5. Macklin CC. The pulmonary alveolar mucoid film and the pneumonocytes. *Lancet*. 1954;266:1099-1104.
6. Mead J, Lindgren I, Gaensler EA. The mechanical properties of the lungs in emphysema. *J Clin Invest*. 1955;34:1005-1016.
7. Avery ME. Surfactant deficiency in hyaline membrane disease: the story of discovery. *Am J Respir Crit Care Med*. 2000;161:1074-1075.
8. Clements JA. Surface tension of lung extracts. *Proc Soc Exp Biol Med*. 1957;95:170-172.
9. Pattle RE. Properties, function and origin of the alveolar lining layer. *Nature*. 1955;175:1125-1126.
10. Avery ME, Mead J. Surface properties in relation to atelectasis and hyaline membrane disease. *AMA J Dis Child*. 1959;97:517-523.

11. Fujiwara T, Maeta H, Chida S, Morita T, Watabe Y, Abe T. Artificial surfactant therapy in hyaline-membrane disease. *Lancet*. 1980;1:55-59.
12. Wiswell TE. Expanded uses of surfactant therapy. *Clin Perinatol*. 2001;28:695-711.
13. Poynter SE, LeVine AM. Surfactant biology and clinical application. *Crit Care Clin*. 2003;19:459-472.
14. Finer NN. Surfactant use for neonatal lung injury: beyond respiratory distress syndrome. *Paediatr Respir Rev*. 2004; 5(suppl A):S289-S297.
15. Jobe AH, Ikegami M. Biology of surfactant. *Clin Perinatol*. 2001;28:655-669, vii-viii.
16. Fujiwara T, Konishi M, Chida S, et al. Surfactant replacement therapy with a single postventilatory dose of a reconstituted bovine surfactant in preterm neonates with respiratory distress syndrome: final analysis of a multicenter, double-blind, randomized trial and comparison with similar trials. The Surfactant-TA Study Group. *Pediatrics*. 1990;86: 753-764.
17. Williams MC. Uptake of lectins by pulmonary alveolar type II cells: subsequent deposition into lamellar bodies. *Proc Natl Acad Sci U S A*. 1984;81:6383-6387.
18. Glasser JR, Mallampalli RK. Surfactant and its role in the pathobiology of pulmonary infection. *Microbes Infect*. 2012; 14:17-25.
19. Rooney SA. The surfactant system and lung phospholipid biochemistry. *Am Rev Respir Dis*. 1985;131:439-460.
20. Young SL, Crapo JD, Kremers SA, Brumley GW. Pulmonary surfactant lipid production in oxygen-exposed rat lungs. *Lab Invest*. 1982;46:570-576.
21. Veldhuizen R, Nag K, Orgeig S, Possmayer F. The role of lipids in pulmonary surfactant. *Biochim Biophys Acta*. 1998; 1408:90-108.
22. Creuwels LA, van Golde LM, Haagsman HP. The pulmonary surfactant system: biochemical and clinical aspects. *Lung*. 1997;175:1-39.
23. Chung J, Yu SH, Whitsett JA, Harding PG, Possmayer F. Effect of surfactant-associated protein-A (SP-A) on the activity of lipid extract surfactant. *Biochim Biophys Acta*. 1989; 1002:348-358.
24. Bersani I, Speer CP, Kunzmann S. Surfactant proteins A and D in pulmonary diseases of preterm infants. *Expert Rev Anti Infect Ther*. 2012;10:573-584.

24A. Nathan N, Taytard J, Duquesnoy P, et al. Surfactant protein A: a key player in lung homeostasis. *Int J Biochem Cell Biol*. 2016;81:151-155.

25. Curstedt T. Surfactant protein C: basics to bedside. *J Perinatol*. 2005;25(suppl 2):S36-S38.
26. ACOG Committee on Obstetric Practice. ACOG Committee Opinion No. 475: Antenatal corticosteroid therapy for fetal maturation. *Obstet Gynecol*. 2011;117:422-424.
27. Lee MJ, Davies J, Guinn D, et al. Single versus weekly courses of antenatal corticosteroids in preterm premature rupture of membranes. *Obstet Gynecol*. 2004;103:274-281.
28. Banks BA, Macones G, Cnaan A, et al. Multiple courses of antenatal corticosteroids are associated with early severe lung disease in preterm neonates. *J Perinatol*. 2002;22:101-107.
29. Zimmermann LJ, Janssen DJ, Tibboel D, Hamvas A, Carnielli VP. Surfactant metabolism in the neonate. *Biol Neonate*. 2005; 87:296-307.
30. Ballard RA, Ballard PL, Cnaan A, et al. Antenatal thyrotropin-releasing hormone to prevent lung disease in preterm infants. North American Thyrotropin-Releasing Hormone Study Group. *N Engl J Med*. 1998;338:493-498.
31. Australian collaborative trial of antenatal thyrotropin-releasing hormone (ACTOBAT) for prevention of neonatal respiratory disease. *Lancet*. 1995;345:877-882.
32. Geary CA, Whitsett JA. Amniotic fluid markers of fetal lung maturity. In: Spitzer AR, ed. Intensive Care of the Fetus and Neonate. 2nd ed. Philadelphia, PA: Elsevier Mosby; 2005: 122-132.
33. O'Neill E, Thorp J. Antepartum evaluation of the fetus and fetal well being. *Clin Obstet Gynecol*. 2012;55:722-730.
34. Jobe AH, Ikegami M. Surfactant and acute lung injury. *Proc Assoc Am Physicians*.1998;110:489-495.
35. Pison U, Seeger W, Buchhorn R, et al. Surfactant abnormalities in patients with respiratory failure after multiple trauma. *Am Rev Respir Dis*. 1989;140:1033-1039.
36. Pison U, Obertacke U, Brand M, et al. Altered pulmonary surfactant in uncomplicated and septicemia-complicated courses of acute respiratory failure. *J Trauma*. 1990;30: 19-26.
37. Gregory TJ, Longmore WJ, Moxley MA, et al. Surfactant chemical composition and biophysical activity in acute respiratory distress syndrome. *J Clin Invest*. 1991;88: 1976-1981.
38. Low RB, Adler KB, Woodcock-Mitchell J, Giancola MS, Vacek PM. Bronchoalveolar lavage lipids during development of bleomycin-induced fibrosis in rats. Relationship to altered epithelial cell morphology. *Am Rev Respir Dis*. 1988; 138:709-713.
39. Holm BA, Notter RH, Siegle J, Matalon S. Pulmonary physiological and surfactant changes during injury and recovery from hyperoxia. *J Appl Physiol*. 1985;59:1402-1409.
40. Pison U, Gono E, Joka T, Obertacke U. Phospholipid lung profile in adult respiratory distress syndrome—evidence for surfactant abnormality. *Prog Clin Biol Res*. 1987;236A: 517-523.
41. Lewis JF, Jobe AH. Surfactant and the adult respiratory distress syndrome. *Am Rev Respir Dis*. 1993;147:218-233.
42. Veldhuizen RA, McCaig LA, Akino T, Lewis JF. Pulmonary surfactant subfractions in patients with the acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 1995;152: 1867-1871.
43. Ueda T, Ikegami M, Jobe A. Surfactant subtypes. In vitro conversion, in vivo function, and effects of serum proteins. *Am J Respir Crit Care Med*. 1994;149:1254-1259.
44. Holm BA, Matalon S, Finkelstein JN, Notter RH. Type II pneumocyte changes during hyperoxic lung injury and recovery. *J Appl Physiol*. 1988;65:2672-2678.
45. Seeger W, Günther A, Walmrath HD, Grimminger F, Lasch HG. Alveolar surfactant and adult respiratory distress syndrome. Pathogenetic role and therapeutic prospects. *Clin Investig*. 1993;71:177-190.
46. Kobayashi T, Nitta K, Ganzuka M, Inui S, Grossmann G, Robertson B. Inactivation of exogenous surfactant by pulmonary edema fluid. *Pediatr Res*. 1991;29:353-356.
47. Bruni R, Fan BR, David-Cu R, Taeusch HW, Walther FJ. Inactivation of surfactant in rat lungs. *Pediatr Res*. 1996;39: 236-240.
48. Holm BA, Enhorning G, Notter RH. A biophysical mechanism by which plasma proteins inhibit lung surfactant activity. *Chem Phys Lipids*. 1988;49:49-55.
49. Holm BA, Matalon S. Role of pulmonary surfactant in the development and treatment of adult respiratory distress syndrome. *Anesth Analg*. 1989;69:805-818.
50. Hack M, Wright LL, Shankaran S, et al. Very-low-birthweight outcomes of the National Institute of Child Health and Human Development Neonatal Network, November 1989 to October 1990. *Am J Obstet Gynecol*. 1995;172: 457-464.
51. Suresh GK, Soll RF. Current surfactant use in premature infants. *Clin Perinatol*. 2001;28:671-694.
52. Long W, Corbet A, Cotton R, et al. A controlled trial of synthetic surfactant in infants weighing 1250 g or more with respiratory distress syndrome. The American Exosurf Neonatal Study Group I, and the Canadian Exosurf Neonatal Study Group. *N Engl J Med*. 1991;325:1696-1703.

53. Jobe AH, Mitchell BR, Gunkel JH. Beneficial effects of the combined use of prenatal corticosteroids and postnatal surfactant on preterm infants. *Am J Obstet Gynecol*. 1993;168: 508-513.
54. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med*. 2010;362:1970-1979.
55. Morley CJ, Davis PG, Doyle LW, et al. Nasal CPAP or intubation at birth for very preterm infants. *N Engl J Med*. 2008;358:700-708.
56. Morley CJ, Davis PG. Continuous positive airway pressure: scientific and clinical rationale. *Curr Opin Pediatr*. 2008;20: 119-124.
57. Elgellab A, Riou Y, Abbazine A, et al. Effects of nasal continuous positive airway pressure (NCPAP) on breathing pattern in spontaneously breathing premature newborn infants. *Intensive Care Med*. 2001;27:1782-1787.
58. Bahadue FL, Soll R. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. *Cochrane Database Syst Rev*. 2012;11:CD001456.
59. Halliday HL. Surfactants: past, present and future. *J Perinatol*. 2008;28(suppl 1):S47-S56.
60. Stevens TP, Harrington EW, Blennow M, Soll RF. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. *Cochrane Database Syst Rev*. 2007;4:CD003063.
61. Dani C, Bertini G, Pezzati M, Cecchi A, Caviglioli C, Rubaltelli FF. Early extubation and nasal continuous positive airway pressure after surfactant treatment for respiratory distress syndrome among preterm infants <30 weeks' gestation. *Pediatrics*. 2004;113:e560-e563.
62. Dani C, Corsini I, Poggi C. Risk factors for intubation-surfactant-extubation (INSURE) failure and multiple INSURE strategy in preterm infants. *Early Hum Dev*. 2012;88(suppl 1):S3-S4.
63. Trevisanuto D, Grazzina N, Ferrarese P, Micaglio M, Verghese C, Zanardo V. Laryngeal mask airway used as a delivery conduit for the administration of surfactant to preterm infants with respiratory distress syndrome. *Biol Neonate*. 2005;87: 217-220.
64. Mazela J, Merritt TA, Finer NN. Aerosolized surfactants. *Curr Opin Pediatr*. 2007;19:155-162.
65. Göpel W, Kribs A, Ziegler A, et al. Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial. *Lancet*. 2011;378:1627-1634.
66. Soll R, Ozek E. Multiple versus single doses of exogenous surfactant for the prevention or treatment of neonatal respiratory distress syndrome. *Cochrane Database Syst Rev*. 2009;1: CD000141.
67. Yost CC, Soll RF. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. *Cochrane Database Syst Rev*. 2000;2:CD001456.
67A. Klotz D, Porcaro U, Fleck T, Fuchs H. European perspective on less invasive surfactant administration-a survey. *Eur J Pediatr*. 2017;176:147-154.
67B. Kribs A, Roll C, Göpel W, et al. Nonintubated Surfactant Application vs Conventional Therapy in Extremely Preterm Infants: A Randomized Clinical Trial. *JAMA Pediatr*. 2015; 169:723-730.
67C. Wu W, Shi Y, Li F, Wen Z, Liu H. Surfactant administration via a thin endotracheal catheter during spontaneous breathing in preterm infants. *Pediatr Pulmonol*. 2017;52:844-854.
67D. Isayama T, Iwami H, McDonald S, Beyene J. Association of noninvasive ventilation strategies with mortality and bronchopulmonary dysplasia among preterm infants: a systematic review and meta-analysis. *JAMA*. 2016;316:611-624.
67E. Lampland AL, Plumm B, Worwa C, Meyers P, Mammel MC. Bi-level CPAP does not improve gas exchange when compared with conventional CPAP for the treatment of neonates recovering from respiratory distress syndrome. *Arch Dis Child Fetal Neonatal Ed*. 2015;100:F31-F34.
67F. Ricci F, Catozzi C, Murgia X, et al. Physiological, Biochemical, and Biophysical Characterization of the Lung-Lavaged Spontaneously-Breathing Rabbit as a Model for Respiratory Distress Syndrome. *PLoS One*. 2017;12:e0169190.
68. Lacaze-Masmonteil T. Exogenous surfactant therapy: newer developments. *Semin Neonatol*. 2003;8:433-440.
69. Curstedt T, Johansson J. New synthetic surfactants—basic science. *Biol Neonate*. 2005;87: 332-337.
70. Moya FR, Gadzinowski J, Bancalari E, et al. A multicenter, randomized, masked, comparison trial of lucinactant, colfosceril palmitate, and beractant for the prevention of respiratory distress syndrome among very preterm infants. *Pediatrics*. 2005;115:1018-1029.
71. Sinha SK, Lacaze-Masmonteil T, Soler A, et al. A multicenter, randomized, controlled trial of lucinactant versus poractant alfa among very premature infants at high risk for respiratory distress syndrome. *Pediatrics*. 2005;115:1030-1038.
72. Soll RF, Morley CJ. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. *Cochrane Database Syst Rev*. 2001;2:CD000510.
73. Early versus delayed neonatal administration of a synthetic surfactant—the judgment of OSIRIS. The OSIRIS Collaborative Group (open study of infants at high risk of or with respiratory insufficiency—the role of surfactant). *Lancet*. 1992; 340:1363-1369.
74. Berggren E, Liljedahl M, Winbladh B, et al. Pilot study of nebulized surfactant therapy for neonatal respiratory distress syndrome. *Acta Paediatr*. 2000;89:460-464.
75. Donn SM, Sinha SK. Aerosolized lucinactant: a potential alternative to intratracheal surfactant replacement therapy. *Expert Opin Pharmacother*. 2008;9:475-478.
76. Gortner L, Pohlandt F, Bartmann P, et al. High-dose versus low-dose bovine surfactant treatment in very premature infants. *Acta Paediatr*. 1994;83:135-141.
77. Konishi M, Fujiwara T, Naito T, et al. Surfactant replacement therapy in neonatal respiratory distress syndrome. A multicentre, randomized clinical trial: comparison of high- versus low-dose of surfactant TA. *Eur J Pediatr*. 1988;147:20-25.
78. Halliday HL, Tarnow-Mordi WO, Corcoran JD, Patterson CC. Multicentre randomised trial comparing high and low dose surfactant regimens for the treatment of respiratory distress syndrome (the Curosurf 4 trial). *Arch Dis Child*. 1993;69:276-280.
79. Herting E, Tubman R, Halliday HL, et al. [Effect of 2 different dosages of a porcine surfactant on pulmonary gas exchange of premature infants with severe respiratory distress syndrome]. *Monatsschr Kinderheilkd*. 1993;141:721-727.
80. Zola EM, Gunkel JH, Chan RK, et al. Comparison of three dosing procedures for administration of bovine surfactant to neonates with respiratory distress syndrome. *J Pediatr*. 1993; 122:453-459.
81. Lin TW, Su BH, Lin HC, et al. Risk factors of pulmonary hemorrhage in very-low-birth-weight infants: a two-year retrospective study. *Acta Paediatr Taiwan*. 2000;41:255-258.
82. Pandit PB, Dunn MS, Colucci EA. Surfactant therapy in neonates with respiratory deterioration due to pulmonary hemorrhage. *Pediatrics*. 1995;95:32-36.
83. Aziz A, Ohlsson A. Surfactant for pulmonary haemorrhage in neonates. *Cochrane Database Syst Rev*. 2012;7: CD005254.
84. Moses D, Holm BA, Spitale P, Liu MY, Enhorning G. Inhibition of pulmonary surfactant function by meconium. *Am J Obstet Gynecol*. 1991;164:477-481.
85. Sun B, Curstedt T, Song GW, Robertson B. Surfactant improves lung function and morphology in newborn rabbits with meconium aspiration. *Biol Neonate*. 1993;63:96-104.

86. Halliday HL, Speer CP, Robertson B. Treatment of severe meconium aspiration syndrome with porcine surfactant. Collaborative Surfactant Study Group. *Eur J Pediatr*. 1996;155:1047-1051.
87. Khammash H, Perlman M, Wojtulewicz J, Dunn M. Surfactant therapy in full-term neonates with severe respiratory failure. *Pediatrics*. 1993;92:135-139.
88. Findlay RD, Taeusch HW, Walther FJ. Surfactant replacement therapy for meconium aspiration syndrome. *Pediatrics*. 1996;97:48-52.
89. Lotze A, Mitchell BR, Bulas DI, Zola EM, Shalwitz RA, Gunkel JH. Multicenter study of surfactant (beractant) use in the treatment of term infants with severe respiratory failure. Survanta in Term Infants Study Group. *J Pediatr*. 1998;132:40-47.
90. Chinese Collaborative Study Group for Neonatal Respiratory Diseases. Treatment of severe meconium aspiration syndrome with porcine surfactant: a multicentre, randomized, controlled trial. *Acta Paediatr*. 2005;94:896-902.
91. El Shahed AI, Dargaville PA, Ohlsson A, Soll R. Surfactant for meconium aspiration syndrome in term and late preterm infants. *Cochrane Database Syst Rev.* 2014 Dec 14;(12): CD002054.
92. Wiswell TE, Knight GR, Finer NN, et al. A multicenter, randomized, controlled trial comparing Surfaxin (Lucinactant) lavage with standard care for treatment of meconium aspiration syndrome. *Pediatrics*. 2002;109:1081-1087.
93. Dargaville PA, Copnell B, Mills JF, et al: Randomized controlled trial of lung lavage with dilute surfactant for meconium aspiration syndrome. *J Pediatr*. 2011;158:383-389.
94. Merrill JD, Ballard RA. Pulmonary surfactant for neonatal respiratory disorders. *Curr Opin Pediatr*. 2003;15:149-154.
95. Herting E, Sun B, Jarstrand C, Curstedt T, Robertson B. Surfactant improves lung function and mitigates bacterial growth in immature ventilated rabbits with experimentally induced neonatal group B streptococcal pneumonia. *Arch Dis Child Fetal Neonatal Ed*. 1997;76:F3-F8.
96. Herting E, Gan X, Rauprich P, Jarstrand C, Robertson B. Combined treatment with surfactant and specific immunoglobulin reduces bacterial proliferation in experimental neonatal group B streptococcal pneumonia. *Am J Respir Crit Care Med*. 1999;159:1862-1867.
97. Herting E, Gefeller O, Land M, van Sonderen L, Harms K, Robertson B. Surfactant treatment of neonates with respiratory failure and group B streptococcal infection. Members of the Collaborative European Multicenter Study Group. *Pediatrics*. 2000;106:957-964.
98. Tan K, Lai NM, Sharma A. Surfactant for bacterial pneumonia in late preterm and term infants. *Cochrane Database Syst Rev*. 2012;2:CD008155.
99. Wilcox DT, Glick PL, Karamanoukian HL, Holm BA. Contributions by individual lungs to the surfactant status in congenital diaphragmatic hernia. *Pediatr Res*. 1997;41: 686-691.
100. Moya FR, Thomas VL, Romaguera J, et al. Fetal lung maturation in congenital diaphragmatic hernia. *Am J Obstet Gynecol*. 1995;173:1401-1405.
101. Glick PL, Leach CL, Besner GE, et al. Pathophysiology of congenital diaphragmatic hernia. III: Exogenous surfactant therapy for the high-risk neonate with CDH. *J Pediatr Surg*. 1992;27:866-869.
102. Bos AP, Tibboel D, Hazebroek FW, Molenaar JC, Lachmann B, Gommers D. Surfactant replacement therapy in high-risk congenital diaphragmatic hernia. *Lancet*. 1991;338:1279.
103. Bae CW, Jang CK, Chung SJ, et al. Exogenous pulmonary surfactant replacement therapy in a neonate with pulmonary hypoplasia accompanying congenital diaphragmatic hernia—a case report. *J Korean Med Sci*. 1996;11:265-270.
104. Dubois A, Storme L, Jaillard S, et al. [Congenital hernia of the diaphragm. A retrospective study of 123 cases recorded in the Neonatal Medicine Department, URHC in Lille between 1985 and 1996]. *Arch Pediatr*. 2000;7:132-142.
105. Somaschini M, Locatelli G, Salvoni L, Bellan C, Colombo A. Impact of new treatments for respiratory failure on outcome of infants with congenital diaphragmatic hernia. *Eur J Pediatr*. 1999;158:780-784.
106. Kays DW, Langham Jr MR, Ledbetter DJ, Talbert JL. Detrimental effects of standard medical therapy in congenital diaphragmatic hernia. *Ann Surg*. 1999;230:340-348.
107. Langham Jr MR, Kays DW, Beierle EA, et al. Twenty years of progress in congenital diaphragmatic hernia at the University of Florida. *Am Surg*. 2003;69:45-52.
108. Boloker J, Bateman DA, Wung JT, Stolar CJ. Congenital diaphragmatic hernia in 120 infants treated consecutively with permissive hypercapnea/spontaneous respiration/elective repair. *J Pediatr Surg*. 2002;37:357-366.
109. Colby CE, Lally KP, Hintz SR, et al. Surfactant replacement therapy on ECMO does not improve outcome in neonates with congenital diaphragmatic hernia. *J Pediatr Surg*. 2004; 39:1632-1637.
110. Doyle NM, Lally KP. The CDH Study Group and advances in the clinical care of the patient with congenital diaphragmatic hernia. *Semin Perinatol*. 2004;28:174-184.
111. Lally KP, Lally PA, Langham MR, et al. Surfactant does not improve survival rate in preterm infants with congenital diaphragmatic hernia. *J Pediatr Surg*. 2004;39:829-833.
112. Van Meurs K, Congenital Diaphragmatic Hernia Study Group. Is surfactant therapy beneficial in the treatment of the term newborn infant with congenital diaphragmatic hernia? *J Pediatr*. 2004;145:312-316.
113. Lotze A, Knight GR, Martin GR, et al. Improved pulmonary outcome after exogenous surfactant therapy for respiratory failure in term infants requiring extracorporeal membrane oxygenation. *J Pediatr*. 1993;122:261-268.
114. Lotze A, Knight GR, Anderson KD, et al. Surfactant (beractant) therapy for infants with congenital diaphragmatic hernia on ECMO: evidence of persistent surfactant deficiency. *J Pediatr Surg*. 1994;29:407-412.
115. Greene KE, Wright JR, Steinberg KP, et al. Serial changes in surfactant-associated proteins in lung and serum before and after onset of ARDS. *Am J Respir Crit Care Med*. 1999; 160:1843-1850.
116. Baker CS, Evans TW, Randle BJ, Haslam PL. Damage to surfactant-specific protein in acute respiratory distress syndrome. *Lancet*. 1999;353:1232-1237.
117. Anzueto A, Baughman RP, Guntupalli KK, et al. Aerosolized surfactant in adults with sepsis-induced acute respiratory distress syndrome. Exosurf Acute Respiratory Distress Syndrome Sepsis Study Group. *N Engl J Med*. 1996;334:1417-1421.
118. Gregory TJ, Steinberg KP, Spragg R, et al. Bovine surfactant therapy for patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 1997;155:1309-1315.
119. Spragg RG, Lewis JF, Walmrath HD, et al. Effect of recombinant surfactant protein C-based surfactant on the acute respiratory distress syndrome. *N Engl J Med*. 2004;351:884-892.
120. Willson DF, Zaritsky A, Bauman LA, et al. Instillation of calf lung surfactant extract (calfactant) is beneficial in pediatric acute hypoxemic respiratory failure. Members of the Mid-Atlantic Pediatric Critical Care Network. *Crit Care Med*. 1999;27:188-195.
121. López-Herce J, de Lucas N, Carrillo A, Bustinza A, Moral R. Surfactant treatment for acute respiratory distress syndrome. *Arch Dis Child*. 1999;80:248-252.
122. Willson DF, Thomas NJ, Markovitz BP, et al. Effect of exogenous surfactant (calfactant) in pediatric acute lung injury: a randomized controlled trial. *JAMA*. 2005;293:470-476.
123. Dargaville PA, South M, McDougall PN. Surfactant abnormalities in infants with severe viral bronchiolitis. *Arch Dis Child*. 1996;75:133-136.

124. Skelton R, Holland P, Darowski M, Chetcuti PA, Morgan LW, Harwood JL. Abnormal surfactant composition and activity in severe bronchiolitis. *Acta Paediatr*. 1999;88: 942-946.
125. Kerr MH, Paton JY. Surfactant protein levels in severe respiratory syncytial virus infection. *Am J Respir Crit Care Med*. 1999;159:1115-1118.
126. Luchetti M, Casiraghi G, Valsecchi R, Galassini E, Marraro G. Porcine-derived surfactant treatment of severe bronchiolitis. *Acta Anaesthesiol Scand*. 1998;42:805-810.
127. Tibby SM, Hatherill M, Wright SM, Wilson P, Postle AD, Murdoch IA. Exogenous surfactant supplementation in infants with respiratory syncytial virus bronchiolitis. *Am J Respir Crit Care Med*. 2000;162:1251-1256.
128. Jat KR, Chawla D. Surfactant therapy for bronchiolitis in critically ill infants. *Cochrane Database Syst Rev*. 2012;9: CD009194.
129. Kurashima K, Fujimura M, Matsuda T, Kobayashi T. Surface activity of sputum from acute asthmatic patients. *Am J Respir Crit Care Med*. 1997;155:1254-1259.
130. Hite RD, Seeds MC, Bowton DL, et al. Surfactant phospholipid changes after antigen challenge: a role for phosphatidylglycerol in dysfunction. *Am J Physiol Lung Cell Mol Physiol*. 2005;288:L610-L617.
131. Kurashima K, Ogawa H, Ohka T, Fujimura M, Matsuda T, Kobayashi T. A pilot study of surfactant inhalation in the treatment of asthmatic attack. *Arerugi*. 1991;40:160-163.
132. Oetomo SB, Dorrepaal C, Bos H, et al. Surfactant nebulization does not alter airflow obstruction and bronchial responsiveness to histamine in asthmatic children. *Am J Respir Crit Care Med*. 1996;153:1148-1152.
133. Erpenbeck VJ, Krug N, Hohlfeld JM. Therapeutic use of surfactant components in allergic asthma. *Naunyn Schmiedebergs Arch Pharmacol*. 2009;379:217-224.
134. Hull J, South M, Phelan P, Grimwood K. Surfactant composition in infants and young children with cystic fibrosis. *Am J Respir Crit Care Med*. 1997;156:161-165.
135. Griese M, Birrer P, Demirsoy A. Pulmonary surfactant in cystic fibrosis. *Eur Respir J*. 1997;10:1983-1988.
136. Postle AD, Mander A, Reid KB, et al. Deficient hydrophilic lung surfactant proteins A and D with normal surfactant phospholipid molecular species in cystic fibrosis. *Am J Respir Cell Mol Biol*. 1999;20:90-98.
137. Griese M, Bufler P, Teller J, Reinhardt D. Nebulization of a bovine surfactant in cystic fibrosis: a pilot study. *Eur Respir J*. 1997;10:1989-1994.
138. Griese M, Essl R, Schmidt R, et al. Sequential analysis of surfactant, lung function and inflammation in cystic fibrosis patients. *Respir Res*. 2005;6:133.
139. Hallman M, Haataja R. Genetic basis of respiratory distress syndrome. *Front Biosci*. 2007;12:2670-2682.
140. Silveyra P, Floros J. Genetic variant associations of human SP-A and SP-D with acute and chronic lung injury. *Front Biosci (Landmark Ed)*. 2012;17:407-429.

Noninvasive Mechanical Ventilation and Continuous Positive Pressure of the Neonate

15

Brian K. Walsh

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. Provide a brief history of the various methods used to generate continuous positive airway pressure (CPAP) in infants.
2. Describe the various physiologic effects of CPAP.
3. Describe the indications and contraindications for CPAP.
4. Identify commonly used delivery systems and nasal interfaces for delivering CPAP.
5. Discuss potential differences in the operation and patient response between gas delivery systems and CPAP interfaces.
6. Determine various strategies used to manage patients receiving CPAP and how these may impact outcomes.
7. Describe monitoring strategies for determining positive and negative responses to CPAP.
8. Identify common complications and how they can be avoided when using CPAP.
9. Review bedside care procedures performed by clinicians that contribute to the successful use of CPAP in infants.
10. Describe various weaning strategies that have been used for withdrawing CPAP in infants.
11. Describe when noninvasive intermittent positive pressure ventilation may be beneficial.

Key Terms

chronic lung disease
continuous positive airway pressure (CPAP)
functional residual capacity (FRC)
high-flow nasal cannulas (HFNC)
mechanical ventilation
partial pressure of carbon dioxide in arterial blood ($Paco_2$)
partial pressure of oxygen in arterial blood (Pao_2)
work of breathing

Continuous positive airway pressure (CPAP), also called *continuous distending pressure (CDP)*, refers to the application of continuous (i.e., constant) pressure during both inspiration and expiration in a spontaneously breathing neonate. This pressure is intended to keep the alveoli open, which maintains or increases the **functional residual capacity (FRC)** of the lung, thus resulting in better gas exchange.[1] CPAP has been a standard of care for managing critically ill infants for nearly 4 decades and has had a significant impact on improving patient outcomes, particularly when considering the morbidity and mortality of low-birth-weight premature infants.

CPAP use in neonates was first described by Gregory and colleagues[2] in 1971 during an era when efforts to mechanically ventilate infants with respiratory distress often resulted in pulmonary air leaks and death. Their rationale for applying CPAP was to reproduce the physiological effects of expiratory grunting, exhibited by infants in respiratory distress, to maintain their FRC. They accomplished this by allowing intubated subjects to breathe spontaneously through a modified T-piece system using an oxygen-enriched, humidified gas source and a flow-inflating resuscitation bag with a screw-clamp at the tail of the bag. This system maintained a relatively constant pressure by restricting flow to the atmosphere (Figure 15-1). In

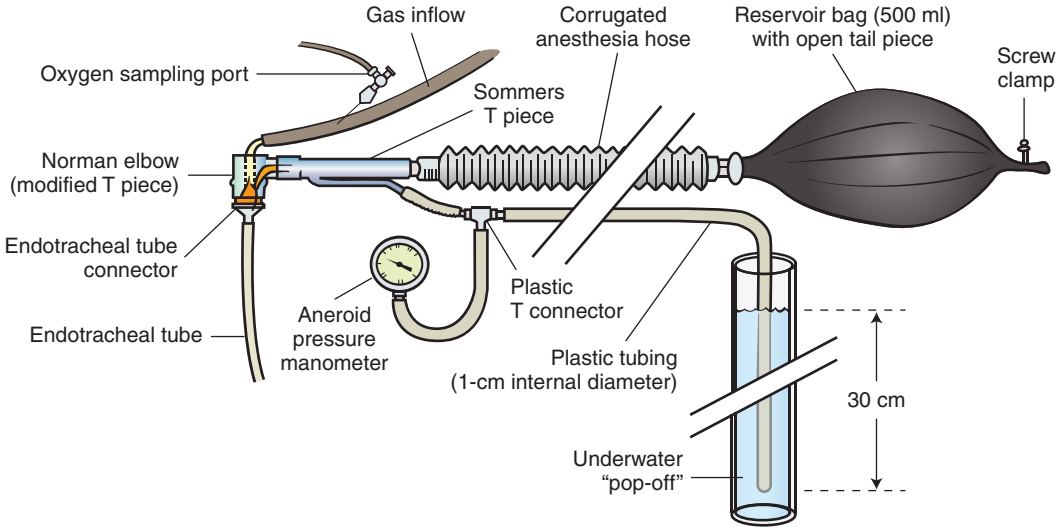


FIGURE 15-1 Early system for applying continuous positive airway pressure (CPAP) to infants through an endotracheal tube.

another method, nonintubated subjects were placed into a sealed head chamber that was pressurized with fresh gas to produce effects similar to endotracheal tube CPAP but without the potential risks associated with the use of an endotracheal tube.[2]

Early attempts were made to provide a noninvasive form of CPAP. For example, infants were placed in a box with the head out through a loose-fitting cuff around the neck, and pressure below atmospheric pressure was applied continuously to the infant's chest wall.[3-5] Further efforts to avoid intubation were accomplished with the application of nasal prong CPAP, which was first described by Kattwinkel and colleagues in 1973.[6] Today, nasal prong CPAP is the most common method by which CPAP is delivered to spontaneously breathing infants with respiratory disease.

This discussion focuses primarily on nasal CPAP delivery systems and interfaces that are most commonly used in clinical practice for newborn infants. These systems include ventilator-derived CPAP (V-CPAP), bubble CPAP (B-CPAP), and Infant Flow CPAP (IF-CPAP). Box 15-1 lists terms that are often used to describe the modes and methods described in this chapter.

Chapter 16 discusses noninvasive forms of support, including CPAP, that are commonly used in larger infants and pediatric patients. Chapter 17 discusses CPAP delivery through the mechanical ventilator when using an endotracheal or tracheostomy tube.

Box 15-1 Terms Used to Describe Noninvasive Pressure

CPAP: Continuous positive airway pressure
V-CPAP: Continuous positive airway pressure delivered by a ventilator
B-CPAP: Bubble continuous positive airway pressure
IF-CPAP: Infant Flow continuous positive airway pressure
NIPPV: Noninvasive intermittent positive pressure ventilation
IF-SiPAP: Infant Flow "sigh" positive airway pressure (a form of NIPPV)

PHYSIOLOGICAL EFFECTS

CPAP increases FRC in patients with respiratory distress syndrome. It improves **partial pressure of oxygen in arterial blood (Pao_2),**[7] improves lung mechanics,[8,9] reduces thoracoabdominal asynchrony,[10,11] stabilizes the chest wall,[12] improves the ventilation/perfusion ratio,[13] and improves the distribution of ventilation.[7] CPAP in spontaneously breathing infants with respiratory failure improves the breathing strategy, as reflected by improved **work of breathing,** increased tidal volume, and a reduction in "labor breathing index."[11] CPAP decreases the respiratory rate and increases the expiratory time and the time constant of the respiratory system.[14] The characteristic protective expiratory braking observed in premature newborn infants is abolished by CPAP.[14] A decreased respiratory rate is not a result of altered ventilatory response to carbon dioxide.[15] The decrease in minute volume is likely related to reductions in alveolar dead space.[2] Box 15-2 shows physiological effects that are commonly associated with CPAP.

An increasing body of evidence demonstrates that by using CPAP, mechanical ventilation can be avoided, resulting in a lower incidence of lung injury and hence chronic lung disease.[16,17] By applying CPAP, the airways can be protected from mechanical injury and colonization related to the endotracheal tube.[18] Infants

Box 15-2 Physiological Effects of Continuous Positive Airway Pressure

- Increases functional residual capacity and tidal volume
- Decreases intrapulmonary shunt
- Increases pulmonary compliance and reduces alveolar dead space
- Decreases airway resistance
- Decreases work of breathing
- Stabilizes the chest wall and the upper airways, thus preventing obstructive apnea
- Improves the distribution of ventilation, ventilation-to-perfusion ratio, and gas exchange
- Protects the developing lung
- Promotes better type 2 pneumocyte function and even recycling of surfactant, thus contributing to early recovery from respiratory distress syndrome (RDS)
- Decreases cellular indicators of lung injury
- Reduces the need for intubation and mechanical ventilation
- Stimulates J receptors in the pleura and provides positive feedback to the respiratory center by Hering-Breuer reflex

treated with CPAP have been found to have a lower incidence of complications related to mechanical ventilation, including respiratory-related nosocomial infections, apnea, intraventricular hemorrhage, retinopathy of prematurity, and chronic lung disease, compared with infants who were intubated and treated with mechanical ventilation. Although a thorough discussion describing the effects of ventilator-induced lung injury in infants is beyond the scope of this chapter, it is important to realize that a major goal of CPAP is to eliminate or reduce the need for prolonged ventilator support.

Postnatal lung development in low-birth-weight infants—specifically, primary and secondary septation-forming saccules and alveoli and angiogenesis[18-23]—may be arrested or altered by mechanical ventilation, placing the infant at risk for developing **chronic lung disease.**[19] CPAP decreases indicators of lung injury.[20] Early application of CPAP reduces the need for intubation and counters the arrest of postnatal lung development in infants, and hence may decrease the incidence of chronic lung disease.

INDICATIONS

CPAP is clinically indicated in infants with both obstructive and restrictive lung diseases. Box 15-3 lists the indications and contraindications regarding CPAP use. The use of CPAP can clinically affect lung disease predominantly to improve oxygenation, counter atelectasis,[7,21-25] and stabilize the chest wall.[12] CPAP is also used to stent open airways and hence lower airway resistance to gas flow in patients with obstructive lung disease and apnea.[26-31] CPAP is often used to maintain airway patency in infants with obstructive apnea[29,10,32-34] and obstructive airway diseases.[28,35-38] Figure 15-2 shows the effect of CPAP on the anatomic structures of the upper airways.

According to American Association for Respiratory Care (AARC) clinical practice guidelines,[39] neonates presenting with a respiratory rate greater than 30% of normal and paradoxical chest wall movement[40] with suprasternal and substernal retractions, grunting, nasal flaring, and cyanotic skin color[41] should be considered for CPAP administration as long as they are able to demonstrate adequate ventilation, as defined by a **partial pressure of carbon dioxide in arterial**

Box 15-3 Indications for and Contraindications to Continuous Positive Airway Pressure

INDICATIONS

1. Premature infants
   - Delivery room CPAP and prophylactic CPAP[21,44-51,53]
   - Respiratory distress syndrome[21,42]
   - Apnea of prematurity
   - After extubation from mechanical ventilation[43]
   - Early surfactant administration followed by NCPAP[52]
2. Obstructive airway diseases
   - Obstructive apnea
   - Laryngeal or tracheal malacia
   - Bronchopulmonary dysplasia
   - Viral bronchiolitis
3. Pneumonia
   - Viral or bacterial
   - Aspiration
4. Transient tachypnea of the newborn[55]
5. Meconium aspiration syndrome[67]
6. Other possible indications
   a. Used in conjunction with:
      - Surfactant administration
      - Nitric oxide administration
      - Extracorporeal membrane oxygenation
   b. Paralysis of a hemidiaphragm
   c. Congestive heart failure, pulmonary edema, pulmonary hemorrhage

CONTRAINDICATIONS

1. Criteria for CPAP failure requiring mechanical ventilation
   - $Paco_2 > 60$ mm Hg consistently
   - pH < 7.25
2. Upper airway abnormalities
   - Choanal atresia
   - Cleft palate
   - Tracheoesophageal fistula
3. Untreated congenital diaphragmatic hernia
4. Neuromuscular disorders
5. Central nervous system depressant medications
6. Central or frequent apnea

CPAP, Continuous positive airway pressure; *NCPAP,* nasal continuous positive airway pressure.

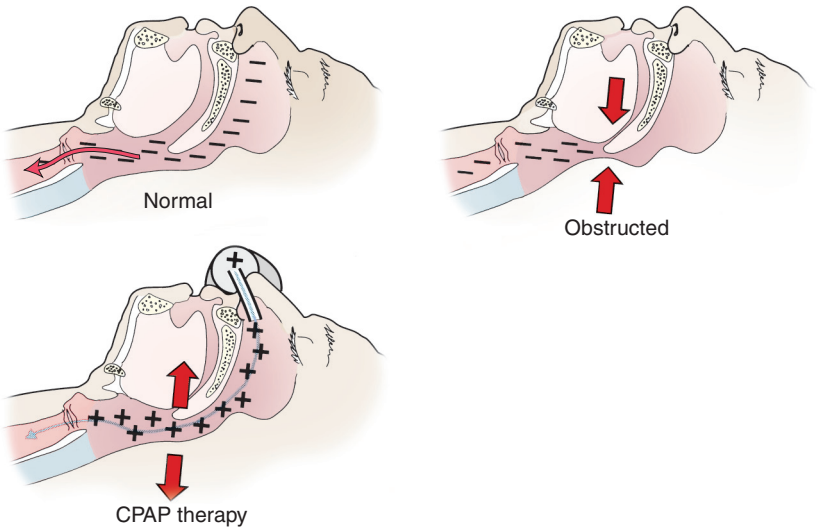


FIGURE 15-2 Top left, Normal patent upper airway. Top right, Tongue obstructing upper airway. Bottom, Continuous positive airway pressure (CPAP) distending structures of oropharynx, preventing obstruction by the tongue and soft palate.

blood ($Paco_2$) less than 60 mm Hg and a pH greater than 7.25.[39]

Nasal CPAP has been used as the primary modality in respiratory distress syndrome.[21,42] In addition, CPAP is an effective option for prevention of extubation failure.[43] It is also used as a primary modality in the delivery room[21,44-51] and after early surfactant delivery.[52] Recent trials on CPAP use in the delivery room have focused on smaller and more immature neonates. The Surfactant Positive Pressure and Pulse Oximetry Randomized Trial (SUPPORT) compared[48] delivery room CPAP with limited ventilation strategy against ventilation and surfactant administration within 60 minutes of birth and demonstrated CPAP as an effective initial ventilatory strategy. The COIN (CPAP or Intubation) trial reported a trend toward a lower rate of death or bronchopulmonary disease (BPD) at 36 weeks in infants who received CPAP.[51] Similar findings were also reported, in addition to a reduction in the need of mechanical ventilation after early CPAP, in the recent trial published by the South American Neocosur Network.[53] Overall, CPAP started soon after birth appears to reduce BPD and death and is an acceptable alternative to endotracheal intubation in the delivery room. CPAP has also been successful in the treatment of pneumonia,[54] transient tachypnea of the newborn,[55] meconium aspiration syndrome,[56-58] and paralysis of the hemidiaphragm. It has been used for infants with pulmonary edema and patent ductus arteriosus.[59]

CPAP has been shown to improve lung function in patients with postoperative congenital heart disease[60,61] and after surgical repair of abdominal wall defects; however, increased abdominal pressure may adversely affect pulmonary function.[62] CPAP use in infants with diaphragmatic hernia is indicated only after surgical repair. CPAP is used in conjunction with the administration of surfactant[16,52,63-65] and nitric oxide[66] and as a source of high airway pressure in infants receiving extracorporeal membrane oxygenation.[67]

CPAP is an effective option for preventing extubation failure.[43] In addition, it is used as a primary modality in respiratory distress syndrome,[21-42] as a modality in the delivery room[21,44-51] and immediately after early surfactant delivery.[52]

CONTRAINDICATIONS

Infants with persistent apneic episodes who are unable to maintain $Paco_2$ less than 60 mm Hg and pH greater than 7.25 should not be given CPAP; if they are already receiving CPAP, then mechanical ventilation is indicated.[39] Infants with congenital anomalies such as choanal atresia, cleft palate, tracheoesophageal fistula, or preoperative diaphragmatic hernia should not receive CPAP. CPAP is contraindicated in infants with neuromuscular disorders, infants receiving central nervous system (CNS) depressants, and infants with central apnea or frequent apneic episodes resulting in desaturation or bradycardia.[39] In addition, severe cardiorespiratory instability and poor respiratory drive are also contraindications to the initiation of CPAP.

HAZARDS AND COMPLICATIONS

Noninvasive application of CPAP is considered a "gentler" method of support compared with mechanical ventilation; however, CPAP is still associated with some of the same hazards and complications that are often associated with mechanical ventilation. Pneumothorax is a complication that is occasionally reported in infants receiving CPAP.[69] This is a result of inadvertent positive end-expiratory pressure related to gas

trapping when infants are tachypneic and do not have a sufficient expiratory time. This may also occur after surfactant replacement therapy, when pulmonary compliance improves and the infant has not been weaned appropriately and thus is exposed to excessive airway and hence alveolar pressure. Other forms of air leak caused by inappropriately high CPAP levels may include pulmonary interstitial emphysema, pneumomediastinum, and pneumatocele.[70-76] Although extremely rare, vascular air embolism has been described in infants receiving CPAP.[75] This occurs when a laceration in the lung parenchyma introduces air into the cardiovascular system. Increased intracranial pressures related to lung overdistention may also occur as a result of CPAP.[76] CPAP has been reported to have an adverse effect on renal function, including decreased urine output and glomerular filtration rate.[77] Decreased gastrointestinal blood flow has been cited as a potential complication of endotracheal CPAP and may well manifest similarly in nasal CPAP.[78] Bowel distention is often noted with CPAP.[79] Infants may swallow gas, which can result in bulging flanks, increased abdominal girth, and visibly dilated intestinal loops on radiographs.

A study comparing spontaneously breathing unassisted premature infants with infants receiving CPAP showed that there were no detectable differences in hemodynamic values, including stroke volume and cardiac output as measured by echocardiogram.[80] This implies that there is no need to withhold CPAP support to prevent circulatory complications; however, hemodynamic compromise should always be considered as a factor when using any positive pressure device. Complications that have been described regarding problems with equipment include desaturation as a result of loss of airway pressure caused by inappropriate fit of nasal prongs or leak around a face mask. Face masks may also result in leaks around the eyes and damage to facial tissue from improper fixation. An open mouth can lead to a loss in airway pressure as a result of leaks.[81] Obstruction of nasal prongs from mucous plugging or tips pressed against the nasal mucosa can lead to losses in airway pressure unmeasured by low-pressure alarm systems and can increase work of breathing.[81] Leaks or obstruction can also lead to a loss in the inspired fraction of oxygen (Fio_2). Fluctuations in baseline pressure and increase in work of breathing can be caused by insufficient gas flow.[82]

Local irritation and trauma[83] to the nasal septum may occur because of misalignment or improper fixation of nasal prongs.[84] Nasal snubbing and circumferential distortion (widening) of the nares can be caused by nasal prongs, especially if CPAP is used for more than just a few days.[85] Breakdown and erosion low on the septum at the base of the philtrum can occur when using nasal masks.[85,86] Columella necrosis has been reported after only a few days of CPAP use (Figure 15-3).

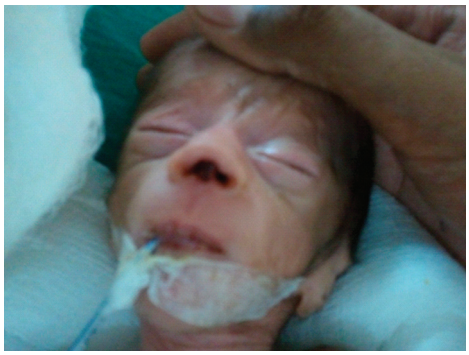


FIGURE 15-3 Columella necrosis resulting from short-term nasal continuous positive airway pressure (CPAP).

Inadequate humidification can lead to nasal mucosal damage.[87,88] Skin irritation of the head and neck from an improperly secured bonnets or CPAP head harnesses can also occur.[39] Equipment failure and dysfunction should always be considered as potential sources of complication for an infant's condition when providing CPAP.

DELIVERY SYSTEMS AND PATIENT INTERFACES

The term *delivery system* describes the mechanism by which fresh gas flow is generated and positive pressure is maintained at the patient's airway. A number of devices are commonly used to deliver CPAP to infants. They are characterized by their ability to provide either a constant or variable flow source. The system also includes a humidifier, circuit, and oxygen analyzer. Gas temperature and humidity are important aspects when maintaining the neutral thermal environment of a newborn infant and thus should be adjusted to provide a temperature between 37°C and 39°C and 100% humidity to the patient. The humidifier servoregulates temperature on the basis of measurements acquired at the humidifier probe and thus should not be placed within an incubator or directly beneath a radiant warmer. The circuit should be constructed of flexible and lightweight material to prevent traction and torque on the nasal interface. This helps minimize patient discomfort and nasal injury.[88] The delivery system should include a "pop-off device" placed close to the airway to protect the patient from overpressurization, thereby limiting excessive volume delivery to the respiratory system.

The term *patient interface device* describes the mechanism by which gas flow from the delivery system is delivered to the airway of the infant. Historically, various interface devices have been applied to administer CPAP to infants. These include enclosure of the head in a plastic pressure chamber, a pressurized plastic bag fitted over the infant's head, face chambers, facemasks, tight-fitting face masks, devices requiring a neck seal, endotracheal tubes, nasopharyngeal tubes, and long and short binasal pharyngeal prongs.[89]

Today, CPAP is most often administered through short binasal prongs, and this method is considered the most effective interface option for delivering CPAP to infants.[89,90] This is attributed primarily to infants being regarded as obligate nose breathers, resulting in CPAP delivering relatively constant airway pressure. Nasal prongs also facilitate mobilization and oral feeding.[90] Because the other methods are used infrequently in the clinical setting, this chapter focuses primarily on short binasal prongs and nasal masks for interfacing with these systems.

Clinicians have often speculated that differences in the level of imposed resistance and hence imposed work of breathing (WOB) between the systems are clinically relevant to infants and may contribute to CPAP failure. Nasal prongs have been reported to have lower resistance to gas flow compared with other commonly used nasal interfaces. These differences are related to the length and internal diameter of the interfaces but are also associated with the delivery system and how CPAP is maintained by this system. The WOB is related to the resistance to gas flow when breathing through the various elements imposed by the CPAP system and interface. The WOB is superimposed on the physiological WOB, which in turn increases the total amount of WOB done by the patient.[91] Imposed expiratory resistance can also affect inspiratory WOB in spontaneously breathing infants.[92] Exhalation is considered active in infants with lung disease, and therefore expiratory resistance is an important consideration.[93] This also becomes important because most infants, particularly premature infants who do not have adequate energy stores and have high caloric requirements, fatigue rapidly.

Early systems that used flow resistors (screw clamp; see Figure 15-1) for exhalation were associated with higher resistance, and hence a higher amount of energy was expended to breathe; currently available systems, on the other hand, use low-resistance threshold-type resistors. In theory, a threshold resistor produces no resistance to exhalation and maintains CPAP by applying an opposing force that is equal to the amount of the desired system pressure. Infant mechanical ventilators have been shown to have higher imposed expiratory resistance compared with endotracheal tube. However, imposed resistance and hence WOB are likely to be lower when breathing through a ventilator with nasal prongs than with an endotracheal tube.[94] The water seal in B-CPAP functions as a pure threshold-type resistor and has been shown to have low imposed expiratory resistance. The IF-CPAP device has been shown in a lung model to have one quarter of the imposed WOB compared with other forms of CPAP.[95] IF-CPAP has also been shown to significantly reduce inspiratory WOB in preterm infants and to improve compliance better compared with a mechanical ventilator CPAP.[96-98] In another study comparing differences in WOB for infants randomized to B-CPAP or IF-CPAP, resistive WOB was lower for infants treated with IF-CPAP; however, these results did not reflect any clinically significant differences in the total inspiratory WOB by the patient.[99]

MECHANICAL VENTILATOR CONTINUOUS POSITIVE AIRWAY PRESSURE

Infant ventilators designed to deliver pressure-control intermittent mandatory ventilation and CPAP were introduced in the mid-1970s. Their contemporary counterparts still offer a simple and efficient method for nasal CPAP delivery to infants. V-CPAP, often described as "conventional CPAP, has been accomplished by placing ventilators in the CPAP mode and setting a constant bias flow rate while interfacing with the system using binasal prongs, a single nasopharyngeal tube, or an endotracheal tube inserted into the nasopharynx. Infant ventilators use exhalation valves to maintain CPAP. The convenience of a blended (air and oxygen) gas source, alarm options, and low cost made this a popular choice among clinicians. The advantage of such a system is that if intubated patients fail V-CPAP, or if a patient is extubated from conventional ventilation, then the ventilator is available at the bedside without having to set up a separate delivery system.

Today, a number of infant ventilators allow noninvasive application of V-CPAP. In these systems CPAP is maintained with a variable demand–flow system. Airway pressure is regulated by servo controlling the instantaneous resistance of the exhalation valve. These ventilators also include the following:

- Highly responsive demand–flow systems
- Leak compensation
- Airway graphics monitoring
- Apnea backup breaths

The interface that is most commonly used with this delivery system uses the Fisher and Paykel nasal prongs (Fisher & Paykel Healthcare, Auckland, New Zealand) (Figure 15-4A) or the Hudson nasal prongs (Hudson RCI/Teleflex, Research Triangle Park, NC) (Figure 15-4B). The prongs are adjusted so that there is never contact between the prongs and the nasal septum.[84] The prong size is established on the basis of weight using a sizing chart provided by the manufacturer (Table 15-2, Hudson nasal prongs), or the head circumference, nasal orifice, and nasal septum size in Fisher and Paykel nasal prongs. The prongs stay in place by attaching the circuitry to a premade hat, using safety pins and rubber bands. A proximal pressure line or "pop-off" can be attached at a Luer adapter at the nasal interface, or this can be plugged.

BUBBLE NASAL CONTINUOUS POSITIVE AIRWAY PRESSURE

B-CPAP (also known as the "water seal" or "bubbly bottle" method) is a simple, safe, inexpensive constant flow delivery system that has been used for nearly

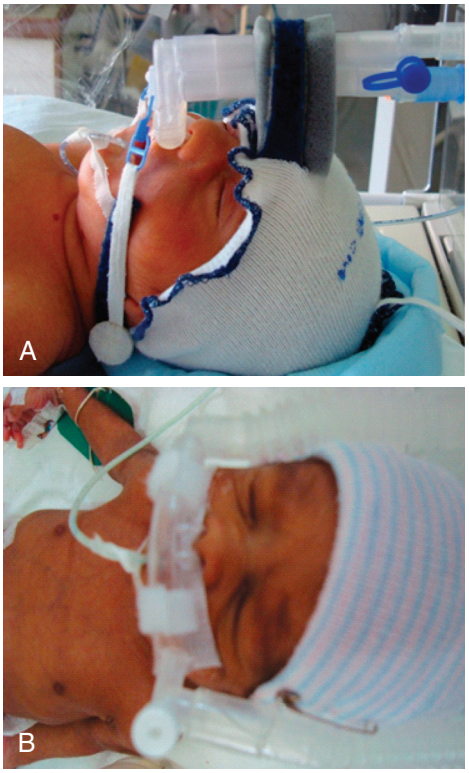


FIGURE 15-4 **A,** Fisher and Paykel infant nasal prong interface with bonnet fixation. **B,** Hudson RCI infant nasal prong interface with bonnet fixation.

Table 15-1 Sizing Chart for Hudson RCI (Teleflex Medical) Infant Nasal Prong

WEIGHT RANGE (g)	SUGGESTED CANNULA SIZE
Less than 700	0
700-1250	1
1250-2000	2
2000-3000	3
More than 3000	4
1-2 years of age	5

four decades to deliver CPAP.[100-103] Table 15-1 is an example of suggested nasal prong size by body weight and manufacturer. This method was implemented by Jen-Tien Wung in the 1970s at Columbia University Medical Center (New York, NY). It is constructed with readily available equipment and materials that can usually be found in most respiratory care equipment storage areas. A commercially available version of this system (Fisher & Paykel Healthcare, Auckland, New Zealand) is currently being used in the United States, Europe, and Australia. Materials include the following (Figure 15-5)[78,87]:

- An infant dual-limb heated wire ventilator circuit
- A humidifier and blended gas source
- A pressure transducer
- A water column filled to 10 cm with either sterile water or a 25% acetic acid solution

Table 15-2 BD Carefusion Infant Flow Nasal Continuous Positive Airway Pressure Bonnet Sizing

BONNET SIZE	BONNET COLOR	TAPE MEASUREMENT (cm)*
000	White	18-20
00	Gray	20-22
0	Pink	22-24
1	Light brown	24-26
2	Yellow	26-28
3	Light blue	28-30
4	Gold	30-32
5	Light green	32-34
6	Light burgundy	34-36
7	Orange	36-38
8	Dark green	38-40
9	Navy	40-42

*Tape measurement indicates the measured head circumference.

A measuring tape is attached to the outside of the water column. The CPAP level is maintained by submerging the distal end of the expiratory circuit straight down into the fluid from the surface of the water line to a measured depth in centimeters, thus creating the amount of CPAP in centimeters of water. If a higher level of CPAP is needed, the tube can be advanced farther down into the fluid column. The flow rate of humidified gas (6 to 10 L/minute) is set to meet the inspiratory flow rate requirements of the patient, maintain the CPAP level, and rinse the system of exhaled carbon dioxide.[87] The pressure measured at the nasal prongs could be slightly higher than the submersion depth of the expiratory tubing below the water surface when higher flow rates are used; therefore, airway pressure should always be monitored at the nasal prong to ensure proper CPAP levels. A high-pressure pop-off can be placed as close to the patient as possible should the expiratory limb become occluded. This system has few alarms or monitoring options, and therefore it is extremely important to evaluate patients frequently, because vital signs may be the only effective alarm for alerting clinicians to airway disconnects, prong occlusion, and mechanical system failure.

Small pressure fluctuations created by the back pressure of bubbles in the underwater seal are transmitted to the airway, thereby producing a noisy component that may enhance lung recruitment and gas mixing in a fashion similar to mechanisms that are present during high-frequency oscillatory ventilation.[104-106]

Subjective accounts of a visible "thoracic wiggle" from these bubble effects are often reported by clinicians caring for infants supported with B-CPAP. The use of higher flow rates can result in more vigorous bubbling and hence higher pressure fluctuations in the

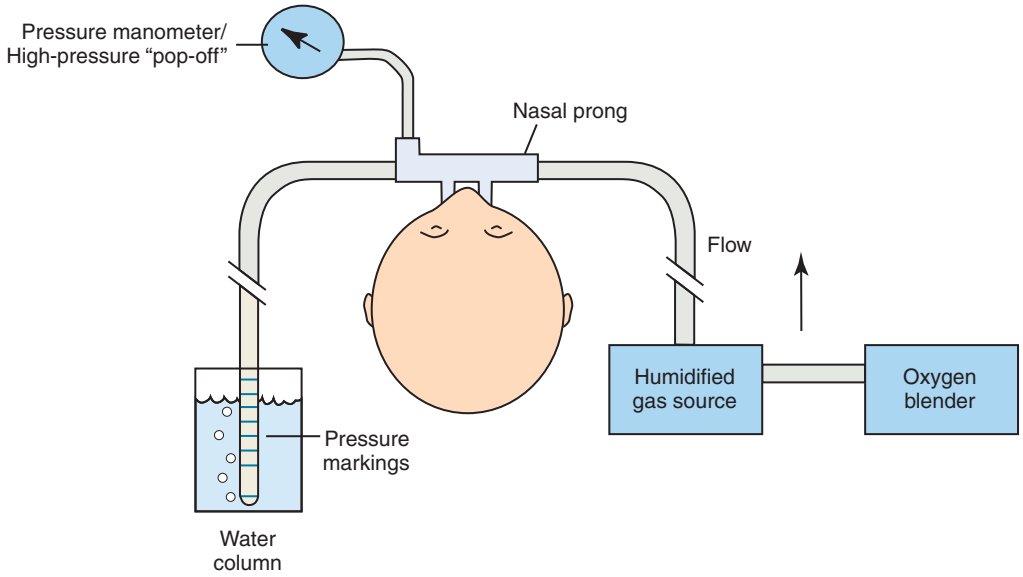


FIGURE 15-5 System for delivering bubble nasal continuous positive airway pressure (CPAP).

delivery system; however, this does not appear to improve gas exchange.[107] In premature animals, the use of B-CPAP has resulted in improvements in gas exchange, lung mechanics, and lung volume, which suggest enhanced alveolar recruitment compared with V-CPAP.[105] B-CPAP may be associated with reduced extubation failure.[108]

INFANT FLOW NASAL CONTINUOUS POSITIVE AIRWAY PRESSURE

IF-CPAP (BD, Yorba Linda, CA) is a commercially available variable flow device that is specifically designed to deliver CPAP in newborns. The "flow driver" provides the source gas (Figure 15-6) and consists of an internalized flow metering system, a blender with an Fio_2 control knob, a digital pressure light-emitting diode (LED), an alarm system, and a pressure relief system.[109] An external auxiliary gas flow meter is used to provide a gas source identical to the set Fio_2 for nebulizers and manual resuscitators. Blended gas is humidified and delivered to the nasal interface "flow generator" (Figure 15-7) using a proprietary patient circuit. Despite setting a constant flow on the flow driver, the geometric design of the flow generator incorporates unique physical properties that allow control of gas delivery to and from the patient and is thus considered variable. The set flow rate is based on fluctuation of the baseline pressure measurement, which is made at the flow generator, as indicated by the LED bars on the front panel of the flow driver. If the nasal prongs or mask (Figure 15-8) are sized and fitted properly, a flow rate of 8 L/minute should maintain a CPAP level of approximately 5 cm H_2O.

The design of the flow generator uses a fluidic flip valve, which is composed of nonmoving parts and provides fresh gas to the infant during inhalation and directs flow away from the infant during exhalation. Gas delivery is accomplished on the basis of the jet entrainment effect, whereby gas flow is provided to each nostril through the fresh gas inlet and passes through twin nasal jet injector nozzles at high velocity,

FIGURE 15-6 Infant Flow driver that can provide continuous positive airway pressure (CPAP) and sigh positive airway pressure (SiPAP). (Courtesy VIASYS Healthcare, Yorba Linda, CA.)

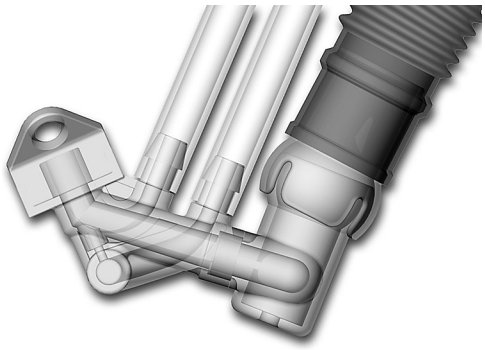


FIGURE 15-7 Infant Flow generator nasal interface device. (Courtesy SensorMedics, Inc., Yorba Linda, CA.)

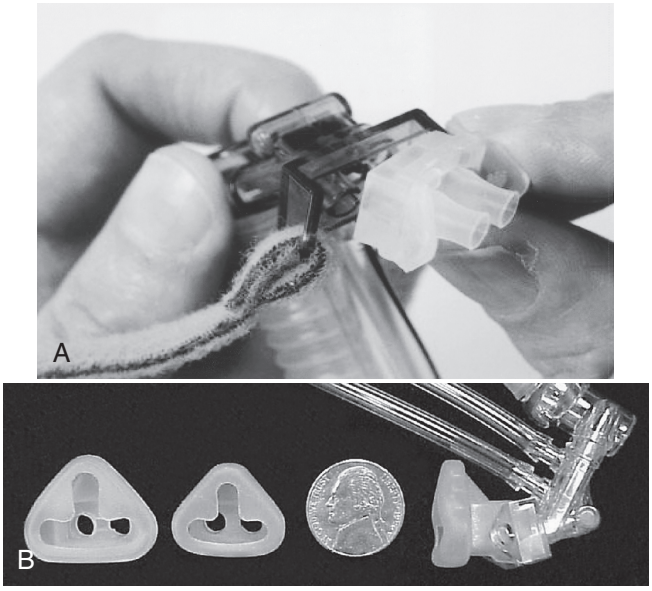


FIGURE 15-8 Silicone nasal prongs **(A)** and masks **(B)** attached to an Infant Flow driver. (A, Courtesy VIASYS Healthcare, Yorba Linda, CA.)

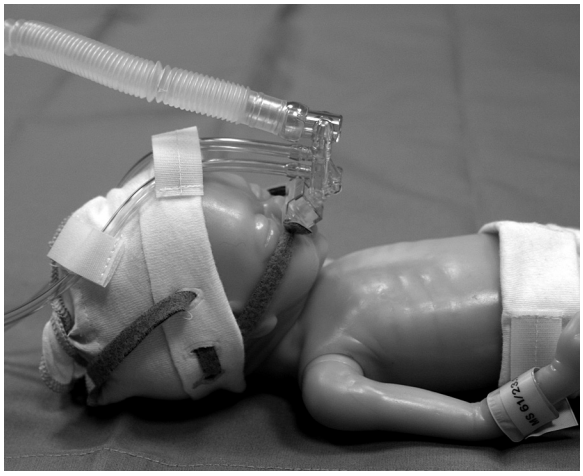


FIGURE 15-9 Proper fixation for the Infant Flow continuous positive airway pressure (CPAP) system. (Courtesy VIASYS Healthcare, Yorba Linda, CA.)

which in turn converts the flow into a constant pressure.[109] If the patient requires any additional inspiratory flow, a Venturi-type effect created by the jet injector nozzles entrains more gas to be delivered. When the infant makes a spontaneous expiratory effort, exhaled gas passes freely and unimpeded by the flow of incoming air. This is accomplished by the Coanda effect, which triggers the "fluidic flip" and redirects incoming flow and exhaled gases through the expiratory channel simultaneously. Once the expiratory effort stops and expiratory flow ceases, the flow immediately switches back to the inspiratory position.[109]

The IF-CPAP system has been shown to deliver more consistent pressure, lowering WOB and being less sensitive to leaks and more effective at alveolar recruitment compared with other forms of CPAP.[96,110] IF-CPAP use has also been shown to reduce the need for supplemental oxygenation in extremely low-birthweight infants after extubation compared with infants randomized to receive V-CPAP with nasal prongs.[111] The ability of the Infant Flow driver to provide consistent pressure at the airway lowers WOB by applying greater stability to the infant respiratory system mechanics for a given change in intrapleural pressure.[95] The decreased variability of the airway pressure and fast response time of the IF-CPAP may also be related to the fact that the flow regulation mechanism is located at the nasal interface device, whereas other CPAP devices (i.e., V-CPAP) regulate flow downstream from the patient (exhalation valve).

IF-CPAP is delivered to infants by using either a proprietary nasal mask or nasal prongs (Figure 15-9). The nasal prongs and masks are made from a soft silicone-based elastomer and are attached directly to the Infant Flow generator, which is then held in place once the interface is fastened by attaching it to a soft cap or bonnet (see Figure 15-9). The thin, soft material that these nasal devices are made of may provide important mechanical effects when using nasal prongs by flaring out during gas inflow, thus increasing the effective internal diameter and decreasing the leak around the prongs. A mask does not rely on a prong entering the nares and may be more beneficial when trying to secure the nasal device onto an infant with craniofacial abnormalities. Nasal prongs have been shown to result in nasal and septal wall skin breakdown, whereas nasal masks have been associated with breakdown low on the septum or at the base of the philtrum.[85] Some clinicians prefer switching back and forth, using both nasal masks and prongs, to eliminate these soft tissue injuries. Figure 15-10 shows the proper measurement techniques, and Table 15-3 presents the sizing chart used to select the proper size bonnet and nasal interface for use with the IF-CPAP device.

HIGH-FLOW NASAL CANNULAS

Nasal cannulas with an outer diameter of 3 mm and flows up to 2 L/minute have been reported to deliver CPAP.[112] Studies of CPAP via nasal cannula have found it to be as effective as conventional CPAP prongs in the treatment of respiratory distress and apnea of prematurity.[113,114]

The pressures delivered with this technique when measured are highly variable and depend on the flow rate, the size of leak around the cannula, and the degree of mouth opening.[112,115] A recent Cochrane review could not find an adequate number of trials and concluded that there was insufficient evidence to establish the safety or effectiveness of high-flow nasal cannulas as a form of respiratory support in preterm infants.[116] Safe and effective use of **high-flow nasal cannulas (HFNCs)** requires careful selection of an appropriate nasal prong/nares ratio even with an integrated pressure relief

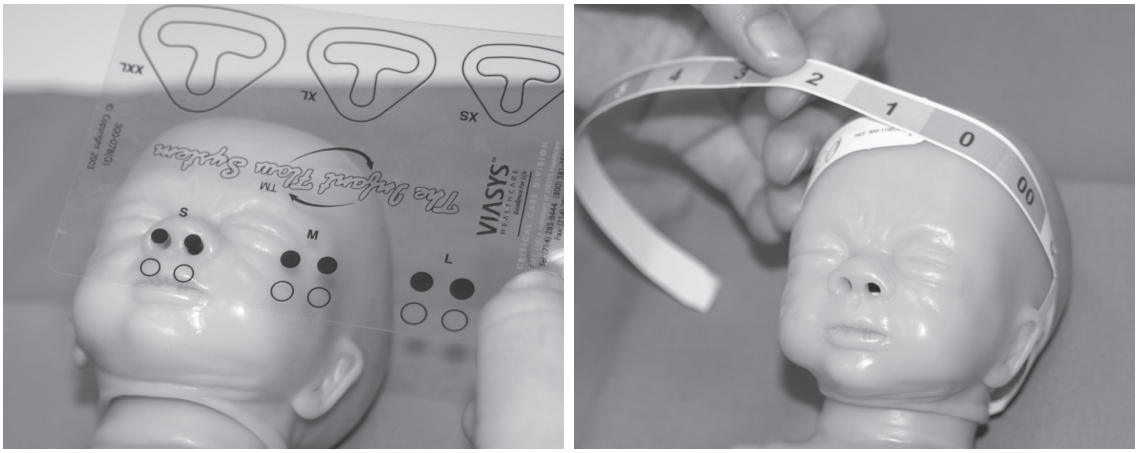


FIGURE 15-10 Nasal prong *(left)* and head circumference *(right)* measurements for the Infant Flow continuous positive airway pressure (CPAP) system. (Courtesy VIASYS Healthcare, Yorba Linda, CA.)

Table 15-3 Example Nasal Skin Breakdown Scoring System for Premature Infants Receiving Continuous Positive Airway Pressure

	ASSESSMENT TIME
Internal nares	0
External nares	1+
Philtrum	0
Bridge	1
Septum	0
Total	2

Key: 0, Normal; 1, pale or pink/red; 2, bleeding, ulcer, eschar; 3, skin tear; +, nasal compression present.
Courtesy B.K. Walsh, D. Kaufman, S. Zanelli, and T. Hicks, University of Virginia Medical Center, Charlottesville, VA.

valve.[117] See Chapter 10 for more details on initial settings.

MANAGEMENT STRATEGIES

INITIATION

CPAP is often used in newborn intensive care to avoid endotracheal intubation and mechanical ventilation. **Mechanical ventilation** in preterm infants is associated with increased risk of sepsis, lung injury, arrested lung development, and chronic lung disease (CLD).[118,119] There is no consensus regarding the most effective management strategy or delivery system to administer CPAP in newborn infants.[94] Management is based more on clinical experience than research trials. In one institution, where elective B-CPAP has been the initial form of support for newborn infants for nearly 4 decades, this practice has resulted in less frequent use of mechanical ventilation and surfactant replacement therapy.[102] This practice has been associated with significant reductions in chronic lung disease compared with other centers that use mechanical ventilation as an initial strategy for managing infants. However, despite the growth of noninvasive CPAP over the past 10 years and regardless of type of CPAP system, Doyle et al. recently reported no significant decline in oxygen dependence (often a definition of CLD) and no significant improvement in lung function at 8 years of age compared with more invasive forms of assisted ventilation.[120] Some institutions support early elective surfactant therapy, brief ventilation, and extubation to nasal CPAP. This practice is also associated with a significant reduction in the need for mechanical ventilation, fewer air leak syndromes, and lower incidence of chronic lung disease compared with a strategy of selective surfactant administration and continued ventilator support.[121]

The steps of initiation include the following:

1. Preparing the circuit, the bubble chamber (in B-CPAP), and the machine
2. Fixing the cap or straps
3. Securing nasal prongs
4. Connecting the circuit
5. Inserting the orogastric tube
6. Setting pressure, Fio_2, and flow

APPLICATION

CPAP is effective at reducing the incidence and duration of severe apneic episodes.[122] Hower, before CPAP can be applied, it is important to emphasize that infants experiencing frequent and sustained apnea or severe respiratory failure should not be considered for this form of support. It is essential that infants have a sufficient stimulus to breathe, because CPAP is intended only for spontaneously breathing infants. Infants who do not respond to CPAP and continue to have frequent unresponsive apnea have failed this form of support.

The primary clinical objectives for managing infants with CPAP are to recruit collapsed lung units, stabilize the lung volume, maintain adequate lung expansion, avoid hyperinflation and apnea, improve gas exchange, and eliminate the need for mechanical

ventilation. This practice requires a team of clinicians who are properly trained in the technical aspects of the CPAP equipment as well as understand the pathophysiology of the infant pulmonary system. This team usually consists of the respiratory therapist and the nurse caring for the patient. Patients receiving CPAP are often more time consuming than patients requiring mechanical ventilation.

CPAP of 4 to 6 cm H_2O is a common starting point for initiating CPAP.[34,123,124] Infants with obstructive lung disease may initially require higher CPAP levels to stent the airways open while allowing adequate ventilation.[37,38] Once CPAP is applied, it may take some time for patients to adjust to breathing through this system. Often, they resist the initial placement of the equipment but then relax once they have become used to it. If the infant continues to appear anxious, agitated, and inconsolable, it is very important to rule out hypoxia and airway obstruction. It is important to adopt "minimal handling" awareness and whenever possible cluster the patient care duties to limit infant stress.

The flow should be minimal to produce bubbling in the bubble chamber. It varies depending upon the pressure set, the lung disease, the weight of the baby, and the leaks in the circuit or from the patient's mouth. In the absence of a blender, first set the total flow and then set the air and the oxygen flow to get the desired Fio_2.

At first the Fio_2 should be set at the same level the patient was receiving before CPAP administration. Higher levels may be used to maintain adequate oxygen saturation or Pao_2.

During the recruitment stage, it is not uncommon for the patient to remain at a higher Fio_2 until the lung volumes are stabilized. Often an increase in Fio_2 may have no effect on oxygenation because of intrapulmonary shunting, and thus additional pressure is required. A 40% increase in Fio_2 during the first 24 hours of nasal CPAP may represent a useful clinical marker to identify infants at high risk for developing a pneumothorax.[68] Physiological changes associated with pneumothorax include decreased arterial blood pressure, increased heart rate, and increased respiratory rate, narrowed pulse pressure; and decreased Pao_2.[69]

Once recruitment occurs, Fio_2 should be weaned promptly to avoid complications caused by hyperoxemia.[125] The CPAP level is generally increased in increments of 1 or 2 cm H_2O; very rarely pressures up to 12 cm H_2O may be required when applying CPAP. The pressure and Fio_2 are increased to attain the desired Pao_2. However, it is best to change only one parameter at a time.

The patient is considered to be approaching stabilization once an adequate level of CPAP is attained. Oxygenation, ventilation, and chest radiograph appearance begin to improve. Reductions in the work of breathing, respiratory rate, and incidence of apnea are also important findings that indicate that the patient is improving.[126] Box 15-4 lists the signs indicating clinical stabilization of patients supported with CPAP. More tolerant guidelines for pH and $Paco_2$ or "permissive hypercapnia" have become widely accepted clinical practices when treating critically ill infants.[127] This alone has likely reduced the number of intubations in infants receiving CPAP. However, it is also important to evaluate ventilation frequently by means of capillary blood gas readings or with a calibrated transcutaneous monitor, because extreme hypercapnia increases the risk for developing intraventricular hemorrhage in small infants.[128]

Box 15-4 Indicators of Stabilization with Continuous Positive Airway Pressure Support

- Comfortable infant
- Normalization of ventilation by evidence of:
  - Reduced respiratory rate
  - $Paco_2$ range of 40 to 60 mm, pH 7.25 to 7.45
  - Minimal or no chest retractions
  - Spo_2 between 88% to 95% on $Fio_2 < 0.4$
  - Improvement in chest radiograph appearance
- Reduction in severity and frequency of apneic episodes

If the patient is not responding to CPAP, it is usually because the lungs are not opening with the amount of support the clinician has chosen. If the CPAP level is set below the opening pressure of the terminal respiratory units, then recruitment is unlikely to occur.[109] Breathing at low FRC can also lead to atelectrauma.[129] Proper assessment of tissue perfusion is vital. Increased intrathoracic pressure may result in worsening hemodynamic status. This is common when patients have low intravascular blood volume or poor cardiac output. Intravenous fluid bolus can help eliminate this problem. If the patient develops apnea that does not require intubation, a loading dose of caffeine citrate of 20 mg/kg followed by a daily maintenance dose of 5 mg/kg (up to 10 mg/kg) can reduce the incidence of apnea.[130]

A rise in $Paco_2$ or fall in Pao_2 after increasing the CPAP pressure may indicate that the optimal CPAP level has been exceeded.[13,131] An increase in mean airway pressure can result in increased alveolar dead space as a result of mechanical compression of the pulmonary microvasculature. If gas exchange worsens in a patient who appeared to be improving, the pressure can first be reduced; otherwise intubation is indicated.

Criteria used to recognize when a patient has failed CPAP and requires intubation and mechanical ventilation should be established by the medical team before placing a patient on CPAP. There are no definitive recommendations at this time, and most institutions rely on anecdotal experience when identifying respiratory failure in infants receiving CPAP support. Box 15-5

Box 15-5 Recognizing Failure of Continuous Positive Airway Pressure Support

Before considering CPAP failure, check the following conditions:

- Baby is not fighting CPAP interface.
- Nasal prongs are of correct size.
- Adequate humidification is present without any condensation in the circuit.
- Adequate pressure and Fio_2 are delivered (check neck position, clear nostrils and airway).

Markers of CPAP failure include the following:

- Increased WOB, nasal flaring, and retractions
- Decreasing pH (<7.25)
- $Paco_2$ greater than 60 mm Hg
- Fio_2 requirement exceeding 0.6 to 0.7 with Pao_2 < 50 to 60 mm Hg or Spo_2 < 88%*
- Nasal CPAP exceeding 8 to 10 cm H_2O
- Frequent apnea with cyanosis and bradycardia (not responding to caffeine therapy)

CPAP, Continuous positive airway pressure; *Fio_2*, fraction of inspired oxygen; *$Paco_2$*, arterial partial pressure of carbon dioxide; *Pao_2*, arterial partial pressure of oxygen; *WOB*, work of breathing.
*Range should be consistent with clinical state and the presence of congenital heart disease or persistent pulmonary hypertension of the newborn.

lists some clinical signs indicating that CPAP has failed and that intubation and mechanical ventilation are necessary. Extremely low birth weight (less than 1000 g) infants born at less than 26 weeks of gestation, are among the patients who most commonly fail nasal CPAP.[45] Other risk parameters include moderate or severe respiratory distress syndrome, septicemia, pneumothorax,[132] need of positive pressure ventilation, alveolar–arterial oxygen gradient ($AaDo_2$) greater than 180 in the first arterial blood gas,[129] lack or partial exposure to antenatal steroids,[133] need for oxygen in resuscitation and maintained in first hours of life, male gender, higher CPAP pressures (more than 5 cm H_2O), and respiratory distress syndrome with criteria for surfactant administration.[134] CPAP is only about 50% effective at eliminating the need for ventilation in infants born before 26 weeks of gestation.[135] Recognizing CPAP failure and the need for intubation and mechanical ventilation is paramount for a neonatal patient, because failure can ensue rapidly as the result of respiratory muscle failure, worsening gas exchange, and apnea.

MONITORING

Monitoring is an essential component in managing patients receiving CPAP. The patient and CPAP system should be assessed frequently and at regular intervals to evaluate the effectiveness of the level of support and plan for subsequent care.

The physical assessment can be helpful when identifying early warning signs of respiratory impairment. Frequent assessment and measurements of vital signs and gas exchange can aid in the early diagnosis of air leak (e.g., pneumothorax) and other complications associated with the use of CPAP. Physical assessment should include documentation of breath sounds, heart rate, blood pressure, skin color, work of breathing, chest rise, level of activity, condition of the nares and nasal septum, secretions, oxygen saturation, transcutaneous carbon dioxide, and periodic arterial blood gas analyses. Brief disconnection from a B-CPAP device may be indicated to properly assess breath sounds. Blood gases should be obtained if there is an acute deterioration in status, but only after the patient becomes stabilized. If the $Paco_2$ correlates closely or trends with the transcutaneous carbon dioxide, blood gas monitoring should be minimized because of the low circulating blood volume in infants and the possibility for contamination with pathogens. Oxygen can be weaned on the basis of measurements obtained with a pulse oximeter.

Equipment monitoring should be incorporated into this assessment to verify proper function and eliminate equipment failure as a variable, should the patient's condition deteriorate.

Equipment monitoring includes assessment of pressure at the patient's airway and verification of the presence of an attached low-pressure or disconnect alarm. However, besides loss of pressure to the patient, back pressure from the resistance across the prongs may prevent the low-pressure or disconnect alarm from sounding. A high-pressure "pop-off" (at least 15 cm H_2O) should be placed in line with the system and assessed for proper function. Other monitors with alarms, such as a pulse oximeter, transcutaneous monitor, or bradycardia alarm, should also be used with a low-pressure, or disconnect, alarm.

When using a B-CPAP device, the frequency of "bubbling" should be evaluated. Continuous bubbling usually indicates adequate gas delivery to the patient. If bubbling ceases during the breath cycle, this may indicate gas loss or a large leak at the patient interface or the patient circuit. Small fluctuations in pressure are common because of the frequency and amplitude of the bubbles; however, if large fluctuations are noted and coincide with the infant's inspiratory phase, then additional flow should be added to the system. Frequent monitoring of the water level height should be done to prevent changes in system pressure caused by condensation and evaporation. Water should be added or suctioned out to accommodate the desired CPAP level.

In the IF-CPAP and mechanical ventilator CPAP systems, low-pressure alarms usually indicate a leak caused by nasal prongs that are too small or an excessive oropharyngeal leak. The oropharynx acts as a safety valve, preventing excessive accumulation of pressure in the airway. Oropharyngeal leaks are more common when using CPAP levels exceeding 8 to 10 cm H_2O. A chin strap, or pacifier, can be helpful at gently sealing the leak and reestablishing the CPAP level.[87] The set flow rate

delivered by the CPAP device should not be increased until large leaks have been identified and resolved. The flow rate should then be adjusted to minimize large fluctuations in the system pressure as measured by a pressure manometer placed at the airway.

A functional manual resuscitator with the proper positive end-expiratory pressure setting as well as intubation equipment should be at the bedside in case the patient requires manual ventilation or intubation. Transcutaneous carbon dioxide monitors should be calibrated on the basis of manufacturer specifications. Humidification devices should also be documented as being on and set at the proper temperature and humidity levels. Water levels should also be frequently evaluated and maintained when using B-CPAP.

Chest radiographs are a valuable clinical tool for estimating lung expansion during the recruitment phase and for visualizing potential air leaks in the lung parenchyma.[136] Chest radiographs can also be helpful in determining whether the patient has any gastric distention from air entering the abdomen, which is more common when using CPAP levels exceeding 10 to 12 cm H_2O. This can decrease respiratory compliance, limit contraction of the diaphragm, and add significantly to respiratory distress. Gastric distention can be alleviated or prevented by inserting an oral gastric tube or by applying suction via a properly size suction catheter.

BEDSIDE CARE AND AIRWAY MANAGEMENT

The proper bedside care of an infant receiving CPAP is perhaps the single most important aspect regarding outcomes and successful use of CPAP therapy.[84] It has also been recognized that these improved outcomes correlate well with the level of skill, familiarity, and experience of the clinicians after implementation of a new CPAP strategy in infants.[123] This includes caregivers who are adequately trained and proficient at troubleshooting and selecting the proper-sized hat and nasal prongs or mask. The prongs should fill the entire nares without blanching the external nares.[84] Selecting prongs that are too small can result in increased resistance and WOB, prong displacement, and excessive leaks.[103]

The fixation technique is also an important aspect of airway care in infants receiving CPAP support. The hat should be tight fitting, covering the ears and extending to the base of the neck.[84] Lateral attachment of the straps should provide equal and gentle tension to avoid pressure points on the skin while securing the nasal interface to the infant.[87] The lack of stabilization and, hence, excessive movement of the prongs could result in worsening nasal injury, airway displacement, and loss of system pressure.

Another important consideration regarding bedside care that relates to airway management includes proper positioning of the infant. Infants can be positioned prone, supine, or on their side and should be turned every 2 to 4 hours.[87] The use of a small folded towel roll beneath the shoulders or chest can help support the infant and help maintain a patent airway.[87]

On occasion, the nasal prongs should be removed from the infant, and delicate suctioning through the mouth and nasopharynx should be done with a 5-Fr suction catheter. Nasal resistance is elevated in neonates compared with adults and is therefore rapidly elevated by a partial airway obstruction caused by mucous accumulation or swelling.[95] Therefore infants who are suctioned usually have noticeable changes in WOB afterward. After suctioning, the nose should be evaluated for any signs of skin breakdown or nasal trauma and the prongs should be checked for the presence of kinking or mucus. Table 15-3 shows a nasal breakdown scoring system used for premature infants requiring CPAP.

The safe and effective delivery of aerosolized medications has been accomplished in-line using various delivery methods.[137] These drugs include bronchodilators, corticosteroids, surfactant, and ribavirin. Often, clinicians remove patients from the CPAP system to deliver bronchodilators. This should be done only if the patient tolerates being without CPAP; otherwise the risks of giving the medications outweigh their intended benefit. In addition to the appropriate airway management, some important key principles like optimal positioning, swaddling and containment of the infant, promoting day–night cycling of lights, minimizing sound levels in the intensive care unit, and involving parents in nursing care may play an important role in improving brain function and subsequent development.[138]

WEANING

Attempts at weaning patients from CPAP should be considered when the patient is stable, has no incidents of apnea, and exhibits acceptable vital signs, blood gas values, and chest radiographic findings. Ideally, the Fio_2 should be weaned aggressively. If infants require oxygen chronically (because of pulmonary hypertension), it is helpful to wean to an oxygen level that can be maintained reasonably with a separate oxygen delivery device. Some institutions wean Fio_2 to 0.21 and then pressure is weaned in increments of 1 to 2 cm H_2O to a level between 3 and 5 cm H_2O. Birth weight may be a significant factor related to the time to successful nasal CPAP (NCPAP) weaning.[139] Several weaning strategies have been described. The most common methods for weaning and withdrawal include (1) decreasing CPAP to a predefined level of airway pressure and then stopping CPAP completely; (2) removing CPAP for a predetermined number of hours each day (also known as "CPAP holidays"[140]) and gradually increasing the amount of time off CPAP each day until it can be stopped completely; and (3) stopping CPAP and starting high-flow heated humidified air (and oxygen if required) via nasal

cannula. A trial is under way comparing the efficacy of bilevel nasal CPAP and conventional CPAP in extubation of infants less than 30 weeks of gestation.[141] A recent randomized controlled trial compared three methods for weaning CPAP in preterm infants. In method 1 (M1), the infant was taken off CPAP with the view to stay off. In method 2 (M2) the infant was cycled on and off CPAP with incremental time off. In method 3 (M3) the infant was cycled on and off CPAP but during off periods was supported by a 2-mm nasal cannula at a flow of 0.5 L/minute. It was inferred that the first method significantly shortened CPAP weaning time, CPAP duration, and oxygen duration; reduced the incidence of bronchopulmonary dysplasia; and shortened admission time. However, further trials are required to confirm these results.[142]

NONINVASIVE INTERMITTENT POSTIVE PRESSURE VENTILATION

Neonates managed with CPAP sometimes fail this form of support and require intubation or reintubation. Nasal intermittent positive pressure ventilation (NIPPV) is a method of augmenting CPAP by delivering ventilator breaths via the nasal prongs or mask to improve effectiveness without the need for invasive ventilation. Older pediatric patients with chronic respiratory failure have benefited from NIPPV. NIPPV use in neonates has been shown to reduce the incidence of intubation from respiratory failure and the need for reintubation within 48 hours but appears to have no effect on chronic lung disease or on mortality compared with CPAP alone.[142] There is no evidence that synchronization or breath delivery type produces better results, but more research is needed. (See Chapter 16 for more details of how these modes work.)

INFANT FLOW SIGH POSITIVE AIRWAY PRESSURE

Infant Flow "sigh" positive airway pressure (IF-SiPAP) (BD, Yorba Linda, CA) is a new device that uses the Infant Flow driver design and a new flow generator (see Figure 15-6) that provides pressure controlled intermittent mandatory ventilation. Mandatory breaths are time triggered and time cycled while allowing unrestricted, unassisted, spontaneous breathing. This is accomplished by setting the baseline CPAP level, followed by a slow, unsynchronized secondary pressure (sigh breath) set at approximately 2 to 3 cm H_2O higher than the baseline pressure. The inspiratory time is set at about 1 to 3 seconds. The respiratory rate controls the frequency of the intermittent "sigh" breaths. The infant is thus allowed to breathe spontaneously throughout the complete cycle of the sigh breath. Figure 15-11

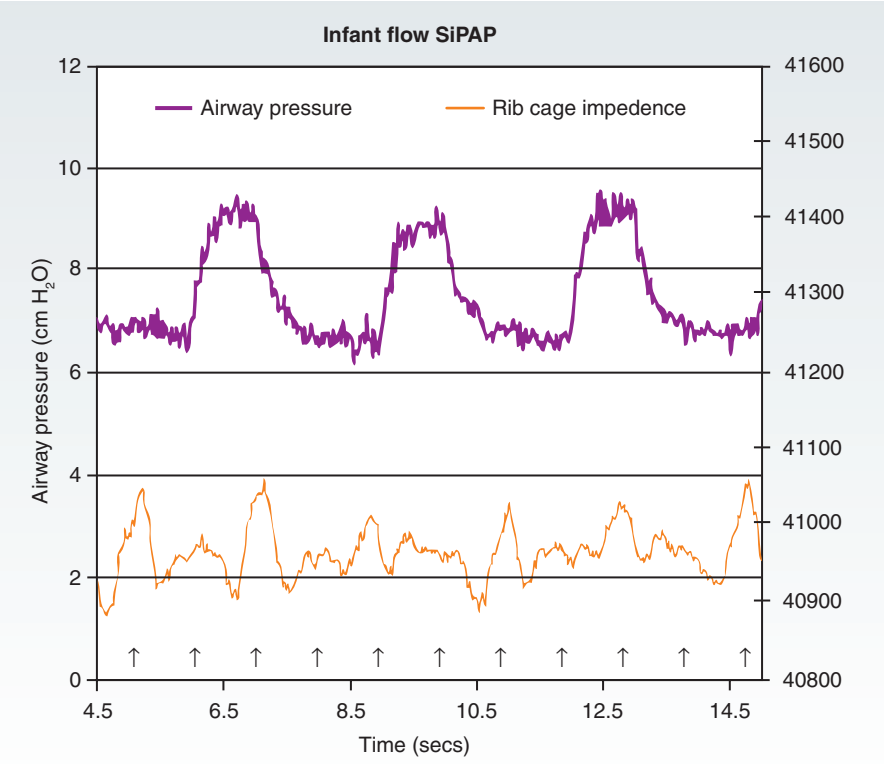


FIGURE 15-11 Infant Flow sigh positive airway pressure *(SiPAP):* spontaneous breathing measurements made in a low-birth-weight infant. Airway pressure was obtained at the nasal interface, and rib cage impedance (relative volume change) measurements were obtained with respiratory impedance plethysmography bands. The *arrows* indicate spontaneous breathing efforts made by the patient.

shows the sequence of spontaneous breathing of a low-birth-weight infant during the pressure sighs created by the IF-SiPAP.

This concept is not intended to serve as a noninvasive pressure support mode, but rather to aid in the recruitment and stabilization of unstable alveoli and thus preserve FRC. Unlike pressure support, the small delta pressure is held in the lung longer and the patient is not allowed to terminate the breath on the basis of certain criteria; rather, the patient breathes spontaneously throughout the entire respiratory cycle. In theory, these "sigh" breaths should also improve gas exchange and work of breathing and serve as a stimulant for apneic infants. The application of spontaneous breathing, compared with the absence of spontaneous breathing, during a sustained pressure-hold has been shown to promote reopening of atelectatic lung regions and improve end-expiratory lung volume.[143]

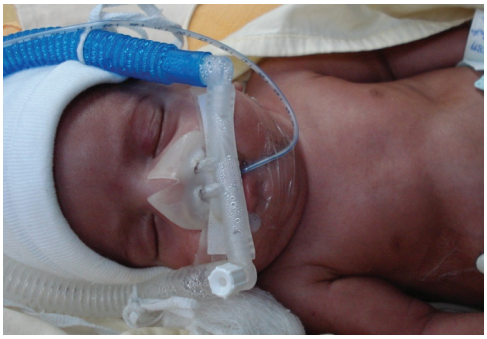


FIGURE 15-12 Infant comfortably positioned on continuous positive airway pressure (CPAP).

To date, there is only one published report that shows that the use of bilevel nasal CPAP results in significant improvements in gas exchange compared with standard nasal CPAP (Figure 15-12) in preterm infants.[144]

Key Points

- CPAP opens alveoli, thus increasing the FRC of the lung, resulting in more efficient gas exchange.
- The primary indications for CPAP in preterm infants are respiratory distress syndrome, apnea of prematurity, delivery room prophylactic CPAP, after extubation from mechanical ventilation, and surfactant administration followed by NCPAP. The contraindications of CPAP include choanal atresia, cleft palate, tracheoesophageal fistula, and preoperative diaphragmatic hernia.
- The delivery system for CPAP can be a ventilator, B-CPAP device, or flow driver. Endotracheal tubes, nasopharyngeal prongs, and long and short binasal prongs are the common interfaces used for CPAP delivery.
- Among the delivery systems available, current evidence does not support a single device for CPAP delivery. A short binasal prong, however, is the most effective interface option for delivering CPAP to infants.
- There is no consensus regarding the most effective management strategy to administer CPAP in newborn infants. Management is based more on clinical experience than research trials.
- Monitoring and bedside care with supportive management are the key parameters that decide success with CPAP. Stabilization is judged as a comfortable infant with reduced respiratory rate and minimal or no chest retractions, in addition to other important key features.
- Pneumothorax, pulmonary interstitial emphysema, pneumomediastinum, and pneumatocele are the possible complications of CPAP application.
- The proper bedside care of an infant receiving CPAP is perhaps the single most important aspect influencing outcomes and successful use of CPAP therapy.
- Weaning should be considered when the patient is stable; has no incidents of apnea; and exhibits acceptable vital signs, gas exchange, and chest radiograph findings. Some institutions wean to an Fio_2 level of 0.21 and then pressure is weaned in increments of 1 to 2 cm H_2O to a level between 3 and 5 cm H_2O.

Assessment Questions

See Evolve Resources for answers.

1. The most common interface used to deliver CPAP to spontaneously breathing infants is:
   - **A.** Infant hood
   - **B.** Nasal prongs
   - **C.** Nasopharyngeal endotracheal tube
2. Physiological effects of CPAP include the following except:
   - **A.** Improved respiratory system compliance and resistance
   - **B.** Stabilization of the chest wall
   - **C.** Increased mucus production
   - **D.** Less lung injury than with mechanical ventilators
3. CPAP is contraindicated in infants with which of the following congenital anomalies?
   - **A.** Preoperative congenital diaphragmatic hernia
   - **B.** Postoperative heart surgery
   - **C.** Postoperative congenital diaphragmatic hernia
4. CPAP levels greater than 8 cm H_2O are commonly associated with which of the following conditions?
   - **A.** Gastric distention
   - **B.** Oropharyngeal leaks
   - **C.** Acute pulmonary edema
   - **D.** Both A and B

5. Which of the following clinical indicators best describes methods for detecting early pneumothorax while monitoring infants receiving nasal CPAP?
   A. Persistent coughing and nasal flaring
   B. Widened pulse pressure
   C. An increased Fio_2 over the first day of CPAP support
   D. A significant increase in respiratory distress
   E. Diminished bilateral breath sounds
6. The following factors are essential when constructing a B-CPAP system except:
   A. A positive end-expiratory pressure/exhalation valve
   B. Hudson nasal prongs
   C. A blended gas source
7. Early attempts to create systems to provide CPAP to spontaneously breathing infants were aimed at trying to mimic which of the following important physiological factors that affect gas delivery to the lung?
   A. Nasal flaring
   B. Chest rise
   C. Work of breathing
   D. Grunting
8. The most important aspect of CPAP that can impact the outcome and success of CPAP is:
   A. The device being used to generate CPAP
   B. Suctioning and airway clearance techniques
   C. Proper bedside care and level of experience of clinicians using the CPAP device
   D. The physician writing the orders
9. The proper arrangement for any nasal CPAP system includes all of the following except:
   A. The hat should be loose fitting, covering the nose and extending to the base of the neck.
   B. Lateral attachment should provide gentle tension on the nasal interface.
   C. The prongs should be properly sized to eliminate migration from the nares.
   D. The hat should be tight fitting, covering the ears and extending to the base of the neck.
10. All of the following devices are considered acceptable for measuring and delivering nasal CPAP safely to infants except:
    A. V-CPAP
    B. B-CPAP
    C. IF-SiPAP
    D. High-flow nasal cannula

REFERENCES

1. Courtney SE, Barrington KJ. Continuous positive airway pressure and noninvasive ventilation. *Clin Perinatol*. 2007;34(1):73-92, vi.
2. Gregory GA, Kitterman JA, Phibbs RH, Tooley WH, Hamilton WK. Treatment of the idiopathic respiratory-distress syndrome with continuous positive airway pressure. *N Engl J Med*. 1971;284(24):1333.
3. Bancalari E, Gerhardt T, Monkus E. Simple device for producing continuous negative pressure in infants with IRDS. *Pediatrics*. 1973;52(1):128.
4. Chernick V, Vidyasagar D. Continuous negative chest wall pressure in hyaline membrane disease: one year experience. *Pediatrics*. 1972;49(5):753.
5. Bancalari E, Garcia OL, Jesse MJ. Effects of continuous negative pressure on lung mechanics in idiopathic respiratory distress syndrome. *Pediatrics*. 1973;51(3):485.
6. Kattwinkel J, Fleming D, Cha CC, Fanaroff AA, Klaus MH. A device for administration of continuous positive airway pressure by the nasal route. *Pediatrics*. 1973;52(1):131.
7. Richardson CP, Jung AL. Effects of continuous positive airway pressure on pulmonary function and blood gases of infants with respiratory distress syndrome. *Pediatr Res*. 1978; 12(7):771.
8. Saunders RA, Milner AD, Hopkin IE. The effects of continuous positive airway pressure on lung mechanics and lung volumes in the neonate. *Biol Neonate*. 1976;29(3–4):178.
9. Greenspan JS, Abbasi S, Bhutani VK. Sequential changes in pulmonary mechanics in the very low birth weight (less than or equal to 1000 grams) infant. *J Pediatr*. 1988;113(4): 732.
10. Locke R, Greenspan JS, Shaffer TH, Rubenstein SD, Wolfson MR. Effect of nasal CPAP on thoracoabdominal motion in neonates with respiratory insufficiency. *Pediatr Pulmonol*. 1991;11(3):259.
11. Elgellab A, Riou Y, Abbazine A, et al. Effects of nasal continuous positive airway pressure (NCPAP) on breathing pattern in spontaneously breathing premature newborn infants. *Intensive Care Med*. 2001;27(11):1782.
12. Heldt GP. Development of stability of the respiratory system in preterm infants. *J Appl Physiol*. 1988;65(1):441.
13. Landers S, Hansen TN, Corbet AJ, Stevener MJ, Rudolph AJ. Optimal constant positive airway pressure assessed by arterial alveolar difference for CO2 in hyaline membrane disease. *Pediatr Res*. 1986;20(9):884.
14. Magnenant E, Rakza T, Riou Y, et al. Dynamic behavior of respiratory system during nasal continuous positive airway pressure in spontaneously breathing premature newborn infants. *Pediatr Pulmonol*. 2004;37(6):485.
15. Durand M, McCann E, Brady JP. Effect of continuous positive airway pressure on the ventilatory response to CO_2 in preterm infants. *Pediatrics*. 1983;71(4):634.
16. Kamper J, Wulff K, Larsen C, Lindequist S. Early treatment with nasal continuous positive airway pressure in very low-birth-weight infants. *Acta Paediatr*. 1993;82(2): 193.
17. De Klerk AM, De Klerk RK. Nasal continuous positive airway pressure and outcomes of preterm infants. *J Paediatr Child Health*. 2001;37(2):161.
18. Narendran V, Donovan EF, Hoath SB, Akinbi HT, Steichen JJ, Jobe AH. Early bubble CPAP and outcomes in ELBW preterm infants. *J Perinatol*. 2003;23(3):195.

19. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med*. 2001;163(7):1723.
20. Jobe AH, Kramer BW, Moss TJ, Newnham JP, Ikegami M. Decreased indicators of lung injury with continuous positive expiratory pressure in preterm lambs. *Pediatr Res*. 2002; 52(3):387.
21. Ho JJ, Subramaniam P, Henderson-Smart DJ, Davis PG. Continuous distending pressure for respiratory distress syndrome in preterm infants. *Cochrane Database Syst Rev*. 2002; (2):CD002271.
22. Krouskop RW, Brown EG, Sweet AY. The early use of continuous positive airway pressure in the treatment of idiopathic respiratory distress syndrome. *J Pediatr*. 1975;87(2):263.
23. Harris H, Wilson S, Brans Y, Wirtschafter D, Cassady G. Nasal continuous positive airway pressure. Improvement in arterial oxygenation in hyaline membrane disease. *Biol Neonate*. 1976;29(3–4):231.
24. Yu VY, Rolfe P. Effect of continuous positive airway pressure breathing on cardiorespiratory function in infants with respiratory distress syndrome. *Acta Paediatr Scand*. 1977; 66(1):59.
25. Polin RA, Sahni R. Newer experience with CPAP. *Semin Neonatol*. 2002;7(5):379.
26. Miller MJ, DiFiore JM, Strohl KP, Martin RJ. Effects of nasal CPAP on supraglottic and total pulmonary resistance in preterm infants. *J Appl Physiol*. 1990;68(1):141.
27. Gaon P, Lee S, Hannan S, Ingram D, Milner AD. Assessment of effect of nasal continuous positive pressure on laryngeal opening using fibre optic laryngoscopy. *Arch Dis Child Fetal Neonatal Ed*. 1999;80(3):F230.
28. Miller RW, Pollack MM, Murphy TM, Fink RJ. Effectiveness of continuous positive airway pressure in the treatment of bronchomalacia in infants: a bronchoscopic documentation. *Crit Care Med*. 1986;14(2):125.
29. Miller MJ, Carlo WA, Martin RJ. Continuous positive airway pressure selectively reduces obstructive apnea in preterm infants. *J Pediatr*. 1985;106(1):91.
30. Jones RA. Apnoea of immaturity. 1. A controlled trial of theophylline and face mask continuous positive airways pressure. *Arch Dis Child*. 1982;57(10):761.
31. Henderson-Smart DJ, Subramaniam P, Davis PG. Continuous positive airway pressure versus theophylline for apnea in preterm infants. *Cochrane Database Syst Rev*. 2001;(4): CD001072.
32. Robertson NJ, Hamilton PA. Randomised trial of elective continuous positive airway pressure (CPAP) compared with rescue CPAP after extubation. *Arch Dis Child Fetal Neonatal Ed*. 1998;79(1):F58.
33. Kattwinkel J. Neonatal apnea: pathogenesis and therapy. *J Pediatr*. 1977;90(3):342.
34. Kurz H. Influence of nasopharyngeal CPAP on breathing pattern and incidence of apnoeas in preterm infants. *Biol Neonate*. 1999;76(3):129.
35. Speidel BD, Dunn PM. Effect of continuous positive airway pressure on breathing pattern of infants with respiratory-distress syndrome. *Lancet*. 1975;1(7902):302.
36. Davis S, Jones M, Kisling J, Angelicchio C, Tepper RS. Effect of continuous positive airway pressure on forced expiratory flows in infants with tracheomalacia. *Am J Respir Crit Care Med*. 1998;158(1):148.
37. Panitch HB, Allen JL, Alpert BE, Schidlow DV. Effects of CPAP on lung mechanics in infants with acquired tracheobronchomalacia. *Am J Respir Crit Care Med*. 1994;150(5 Pt 1): 1341.
38. Weigle CG. Treatment of an infant with tracheobronchomalacia at home with a lightweight, high-humidity, continuous positive airway pressure system. *Crit Care Med*. 1990;18(8):892.
39. American Association for Respiratory Care (AARC). Application of continuous positive airway pressure to neonates via nasal prongs or nasopharyngeal tube. *Respir Care*. 1994; 39(8):817.
40. Kiciman NM, Andréasson B, Bernstein G, et al. Thoracoabdominal motion in newborns during ventilation delivered by endotracheal tube or nasal prongs. *Pediatr Pulmonol*. 1998;25(3):175.
41. Jonson B, Ahlström H, Lindroth M, Svenningsen NW. Continuous positive airway pressure: modes of action in relation to clinical applications. *Pediatr Clin North Am*. 1980;27(3):687.
42. Buckmaster AG, Arnolda GR, Wright IM, Henderson-Smart DJ. CPAP use in babies with respiratory distress in Australian special care nurseries. *J Paediatr Child Health*. 2007;43(5): 376.
43. Davis PG, Henderson-Smart DJ. Nasal continuous positive airways pressure immediately after extubation for preventing morbidity in preterm infants. *Cochrane Database Syst Rev*. 2003;(2):CD000143.
44. Sandri F, Plavka R, Ancora G, et al. Prophylactic or early selective surfactant combined with nCPAP in very preterm infants. *Pediatrics*. 2010;125(6):e1402.
45. Finer NN, Carlo WA, Duara S, et al. Delivery room continuous positive airway pressure/positive end-expiratory pressure in extremely low birth weight infants: a feasibility trial. *Pediatrics*. 2004;114(3):651.
46. Sandri F, Ancora G, Lanzoni A, et al. Prophylactic nasal continuous positive airways pressure in newborns of 28-31 weeks gestation: multicentre randomised controlled clinical trial. *Arch Dis Child Fetal Neonatal Ed*. 2004;89(5):F394.
47. Han VK, Beverley DW, Clarson C, et al. Randomized controlled trial of very early continuous distending pressure in the management of preterm infants. *Early Hum Dev*. 1987; 15(1):21-32.
48. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med*. 2010; 362(21):1970.
49. Subramaniam P, Henderson-Smart DJ, Davis PG. Prophylactic nasal continuous positive airways pressure for preventing morbidity and mortality in very preterm infants. *Cochrane Database Syst Rev*. 2005;(3):CD001243.
50. Rojas MA, Lozano JM, Rojas MX, et al. Very early surfactant without mandatory ventilation in premature infants treated with early continuous positive airway pressure: a randomized, controlled trial. *Pediatrics*. 2009;123(1):137.
51. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet J-M, Carlin JB. Nasal CPAP or intubation at birth for very preterm infants. *N Engl J Med*. 2008;358(7):700.
52. Stevens TP, Blennow M, Soll RF. Early surfactant administration with brief ventilation vs selective surfactant and continued mechanical ventilation for preterm infants with or at risk for RDS. *Cochrane Database Syst Rev*. 2002;(2): CD003063.
53. Tapia JL, Urzua S, Bancalari A, et al. Randomized trial of early bubble continuous positive airway pressure for very low birth weight infants. *J Pediatr*. 2012;161(1):75-80.e1.
54. Jeena P, Pillay P, Adhikari M. Nasal CPAP in newborns with acute respiratory failure. *Ann Trop Paediatr*. 2002; 22(3):201.
55. Yurdakok M, Ozek E. Transient tachypnea of the newborn: the treatment strategies. *Curr Pharm Des*. 2012;18(21): 3046.
56. Lin HC, Su BH, Lin TW, Tsai CH, Yeh TF. System-based strategy for the management of meconium aspiration syndrome: 198 consecutive cases observations. *Acta Paediatr Taiwan*. 2005;46(2):67.
57. Fox WW, Berman LS, Downes Jr JJ, Peckham GJ. The therapeutic application of end-expiratory pressure in the meconium aspiration syndrome. *Pediatrics*. 1975;56(2):214.
58. Goldsmith JP. Continuous positive airway pressure and conventional mechanical ventilation in the treatment of

meconium aspiration syndrome. *J Perinatol*. 2008;28(suppl 3): S49.
59. Robertson NR. Prolonged continuous positive airways pressure for pulmonary oedema due to persistent ductus arteriosus in the newborn. *Arch Dis Child*. 1974;49(7):585.
60. Gregory GA, Edmunds Jr LH, Kitterman JA, Phibbs RH, Tooley WH. Continuous positive airway pressure and pulmonary and circulatory function after cardiac surgery in infants less than three months of age. *Anesthesiology*. 1975;43(4):426.
61. Cogswell JJ, Hatch DJ, Kerr AA, Taylor B. Effects of continuous positive airway pressure on lung mechanics of babies after operation for congenital heart disease. *Arch Dis Child*. 1975;50(10):799.
62. Buyukpamukcu N, Hicsonmez A. The effect of C.P.A.P. upon pulmonary reserve and cardiac output under increased abdominal pressure. *J Pediatr Surg*. 1977;12(1):49.
63. Verder H, Albertsen P, Ebbesen F, et al. Nasal continuous positive airway pressure and early surfactant therapy for respiratory distress syndrome in newborns of less than 30 weeks' gestation. *Pediatrics*. 1999;103(2):E24.
64. Verder H, Robertson B, Greisen G, et al. Surfactant therapy and nasal continuous positive airway pressure for newborns with respiratory distress syndrome. Danish-Swedish Multicenter Study Group. *N Engl J Med*. 1994;331(16): 1051.
65. Kribs A, Vierzig A, Hünseler C, et al. Early surfactant in spontaneously breathing with nCPAP in ELBW infants—a single centre four year experience. *Acta Paediatr*. 2008;97(3):293.
66. Horbar JD, Badger GJ, Carpenter JH, et al. Trends in mortality and morbidity for very low birth weight infants, 1991- 1999. *Pediatrics*. 2002;110(1 Pt 1):143.
67. Keszler M, Ryckman FC, McDonald Jr JV, et al. A prospective, multicenter, randomized study of high versus low positive end-expiratory pressure during extracorporeal membrane oxygenation. *J Pediatr*. 1992;120(1):107.
68. Goldsmith JP. Continuous positive airway pressure and conventional mechanical ventilation in the treatment of meconium aspiration syndrome. *J Perinatol*. 2008;28(suppl 3): S49.
69. Migliori C, Campana A, Cattarelli D, Pontiggia F, Chirico G. [Pneumothorax during nasal-CPAP: a predictable complication?]. *Pediatr Med Chir*. 2003;25(5):345.
70. Ogata ES, Gregory GA, Kitterman JA, Phibbs RH, Tooley WH. Pneumothorax in the respiratory distress syndrome: incidence and effect on vital signs, blood gases, and pH. *Pediatrics*. 1976;58(2):177.
71. Hall RT, Rhodes PG. Pneumothorax and pneumomediastinum in infants with idiopathic respiratory distress syndrome receiving continuous positive airway pressure. *Pediatrics*. 1975;55(4):493.
72. Gessler P, Toenz M, Gugger M, Pfenninger J. Lobar pulmonary interstitial emphysema in a premature infant on continuous positive airway pressure using nasal prongs. *Eur J Pediatr*. 2001;160(4):263.
73. Gürakan B, Tarcan A, Arda IS, Coşkun M. Persistent pulmonary interstitial emphysema in an unventilated neonate. *Pediatr Pulmonol*. 2002;34(5):409.
74. De Bie HMA, Van Toledo-Eppinga L, Verbeke JIML, Van Elburg RM. Neonatal pneumatocele as a complication of nasal continuous positive airway pressure. *Arch Dis Child Fetal Neonatal Ed*. 2002;86(3):F202.
75. Wong W, Fok TF, Ng PC, Chui KM, To KF. Vascular air embolism: a rare complication of nasal CPAP. *J Paediatr Child Health*. 1997;33(5):444.
76. Palmer KS, Spencer SA, Wickramasinghe YA, Wright T, Southall DP, Rolfe P. Effects of positive and negative pressure ventilation on cerebral blood volume of newborn infants. *Acta Paediatr*. 1995;84(2):132.
77. Tulassay T, Machay T, Kiszel J, Varga J. Effects of continuous positive airway pressure on renal function in prematures. *Biol Neonate*. 1983;43(3–4):152.
78. Furzan JA, Gabriele G, Wheeler JM, Fixler DE, Rosenfeld CR. Regional blood flows in newborn lambs during endotracheal continuous airway pressure and continuous negative pressure breathing. *Pediatr Res*. 1981;15(5):874.
79. Jaile JC, Levin T, Wung JT, Abramson SJ, Ruzal-Shapiro C, Berdon WE. Benign gaseous distension of the bowel in premature infants treated with nasal continuous airway pressure: a study of contributing factors. *AJR Am J Roentgenol*. 1992;158(1):125.
80. Moritz B, Fritz M, Mann C, Simma B. Nasal continuous positive airway pressure (n-CPAP) does not change cardiac output in preterm infants. *Am J Perinatol*. 2008;25(2):105.
81. De Paoli AG, Morley C, Davis PG. Nasal CPAP for neonates: what do we know in 2003? *Arch Dis Child Fetal Neonatal Ed*. 2003;88(3):F168.
82. Bonta BW, Uauy R, Warshaw JB, Motoyama EK. Determination of optimal continuous positive airway pressure for the treatment of IRDS by measurement of esophageal pressure. *J Pediatr*. 1977;91(3):449.
83. Peck DJ, Tulloh RM, Madden N, Petros AJ. A wandering nasal prong—a thing of risks and problems. *Paediatr Anaesth*. 1999;9(1):77.
84. Loftus BC, Ahn J, Haddad Jr J. Neonatal nasal deformities secondary to nasal continuous positive airway pressure. *Laryngoscope*. 1994;104(8 Pt 1):1019.
85. McCoskey L. Nursing Care Guidelines for prevention of nasal breakdown in neonates receiving nasal CPAP. *Adv Neonatal Care*. 2008;8(2):116.
86. Yong SC, Chen SJ, Boo NY. Incidence of nasal trauma associated with nasal prong versus nasal mask during continuous positive airway pressure treatment in very low birthweight infants: a randomised control study. *Arch Dis Child Fetal Neonatal Ed*. 2005;90(6):F480.
87. Lee SY, Lopez V. Physiological effects of two temperature settings in preterm infants on nasal continuous airway pressure ventilation. *J Clin Nurs*. 2002;11(6):845.
88. Bonner KM, Mainous RO. The nursing care of the infant receiving bubble CPAP therapy. *Adv Neonatal Care*. 2008;8(2): 78-95; quiz 96-97.
89. De Paoli AG, Davis PG, Faber B, Morley CJ. Devices and pressure sources for administration of nasal continuous positive airway pressure (NCPAP) in preterm neonates. *Cochrane Database Syst Rev*. 2008;(1):CD002977.
90. Davis P, Davies M, Faber B. A randomised controlled trial of two methods of delivering nasal continuous positive airway pressure after extubation to infants weighing less than 1000 g: binasal (Hudson) versus single nasal prongs. *Arch Dis Child Fetal Neonatal Ed*. 2001;85(2):F82.
91. Banner MJ, Kirby RR, Blanch PB. Differentiating total work of breathing into its component parts. Essential for appropriate interpretation. *Chest*. 1996;109(5):1141.
92. Moomjian AS, Schwartz JG, Wagaman MJ, Shutack JG, Shaffer TH, Fox WW. The effect of external expiratory resistance on lung volume and pulmonary function in the neonate. *J Pediatr*. 1980;96(5):908.
93. Emeriaud G, Beck J, Tucci M, Lacroix J, Sinderby C. Diaphragm electrical activity during expiration in mechanically ventilated infants. *Pediatr Res*. 2006;59(5):705.
94. De Paoli AG, Morley CJ, Davis PG, Lau R, Hingeley E. In vitro comparison of nasal continuous positive airway pressure devices for neonates. *Arch Dis Child Fetal Neonatal Ed*. 2002;87(1):F42.
95. Pandit PB, Courtney SE, Pyon KH, Saslow JG, Habib RH. Work of breathing during constant- and variable-flow nasal continuous positive airway pressure in preterm neonates. *Pediatrics*. 2001;108(3):682.

96. Courtney SE, Pyon KH, Saslow JG, Arnold GK, Pandit PB, Habib RH. Lung recruitment and breathing pattern during variable versus continuous flow nasal continuous positive airway pressure in premature infants: an evaluation of three devices. *Pediatrics*. 2001;107(2):304.
97. Lee KS, Dunn MS, Fenwick M, Shennan AT. A comparison of underwater bubble continuous positive airway pressure with ventilator-derived continuous positive airway pressure in premature neonates ready for extubation. *Biol Neonate*. 1998;73(2):69.
98. Liptsen E, Aghai ZH, Pyon KH, et al. Work of breathing during nasal continuous positive airway pressure in preterm infants: a comparison of bubble vs variable-flow devices. *J Perinatol*. 2005;25(7):453.
99. Chernick V. Continuous distending pressure in hyaline membrane disease: of devices, disadvantages, and a daring study. *Pediatrics*. 1973;52(1):114.
100. Kaur C, Sema A, Beri RS, Puliyel JM. A simple circuit to deliver bubbling CPAP. *Indian Pediatr*. 2008;45(4):312.
101. Avery ME, Tooley WH, Keller JB, et al. Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. *Pediatrics*. 1987;79(1):26.
102. Kahn DJ, Courtney SE, Steele AM, Habib RH. Unpredictability of delivered bubble nasal continuous positive airway pressure: role of bias flow magnitude and nares-prong air leaks. *Pediatr Res*. 2007;62(3):343.
103. Pillow JJ, Travadi JN. Bubble CPAP: is the noise important? An in vitro study. *Pediatr Res*. 2005;57(6):826.
104. Pillow JJ, Hillman N, Moss TJM, et al. Bubble continuous positive airway pressure enhances lung volume and gas exchange in preterm lambs. *Am J Respir Crit Care Med*. 2007;176(1):63.
105. Suki B, Alencar AM, Sujeer MK, et al. Life-support system benefits from noise. *Nature*. 1998;393(6681):127.
106. Morley CJ, Lau R, De Paoli A, Davis PG. Nasal continuous positive airway pressure: does bubbling improve gas exchange? *Arch Dis Child Fetal Neonatal Ed*. 2005;90(4):F343.
107. Moa G, Nilsson K, Zetterström H, Jonsson LO. A new device for administration of nasal continuous positive airway pressure in the newborn: an experimental study. *Crit Care Med*. 1988;16(12):1238.
108. Yadav S, Thukral A, Sankar MJ, et al. Bubble vs conventional continuous positive airway pressure for prevention of extubation failure in preterm very low birth weight infants: a pilot study. *Indian J Pediatr*. 2012;79(9):1163.
109. Wiswell TE, Srinivasan P. Continuous positive airway pressure [Internet]. In: Goldsmith JP, Karotkin EH, eds. *Assisted Ventilation of the Neonate*. 4th ed. Philadelphia: WB Saunders; 2003, 127 [cited 2012. Sep 15].
110. Stoll BJ, Gordon T, Korones SB, et al. Late-onset sepsis in very low birth weight neonates: a report from the National Institute of Child Health and Human Development Neonatal Research Network. *J Pediatr*. 1996;129(1):63.
111. Thomson MA, Yoder BA, Winter VT, Giavedoni L, Chang LY, Coalson JJ. Delayed extubation to nasal continuous positive airway pressure in the immature baboon model of bronchopulmonary dysplasia: lung clinical and pathological findings. *Pediatrics*. 2006;118(5):2038.
112. Locke RG, Wolfson MR, Shaffer TH, Rubenstein SD, Greenspan JS. Inadvertent administration of positive end-distending pressure during nasal cannula flow. *Pediatrics*. 1993;91(1):135.
113. Sreenan C, Lemke RP, Hudson-Mason A, Osiovich H. High-flow nasal cannulae in the management of apnea of prematurity: a comparison with conventional nasal continuous positive airway pressure. *Pediatrics*. 2001;107(5):1081.
114. Saslow JG, Aghai ZH, Nakhla TA, et al. Work of breathing using high-flow nasal cannula in preterm infants. *J Perinatol*. 2006;26(8):476.
115. Kubicka ZJ, Limauro J, Darnall RA. Heated, humidified high-flow nasal cannula therapy: yet another way to deliver continuous positive airway pressure? *Pediatrics*. 2008;121(1):82.
116. Wilkinson D, Andersen C, O'Donnell CP, De Paoli AG. High flow nasal cannula for respiratory support in preterm infants. *Cochrane Database Syst Rev*. 2011;(5):CD006405.
117. Sivieri EM, Gerdes JS, Abbasi S. Effect of HFNC flow rate, cannula size, and nares diameter on generated airway pressures: an in vitro study. *Pediatr Pulmonol*. May 2013;48(5):506-514.
118. Hillman NH, Moss TJM, Kallapur SG, et al. Brief, large tidal volume ventilation initiates lung injury and a systemic response in fetal sheep. *Am J Respir Crit Care Med*. 2007;176(6):575.
119. Martin RJ, Nearman HS, Katona PG, Klaus MH. The effect of a low continuous positive airway pressure on the reflex control of respiration in the preterm infant. *J Pediatr*. 1977;90(6):976.
120. Doyle LW, Carse E, Adams AM, et al. Ventilation in extremely preterm infants and respiratory function at 8 years. *N Engl J Med*. 2017;377(4):329-337.
121. Stevens TP, Harrington EW, Blennow M, Soll RF. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. *Cochrane Database Syst Rev*. 2007;(4):CD003063.
122. Lindner W, Vossbeck S, Hummler H, Pohlandt F. Delivery room management of extremely low birth weight infants: spontaneous breathing or intubation? *Pediatrics*. 1999;103(5 Pt 1):961.
123. Thia LP, McKenzie SA, Blyth TP, Minasian CC, Kozlowska WJ, Carr SB. Randomised controlled trial of nasal continuous positive airways pressure (CPAP) in bronchiolitis. *Arch Dis Child*. 2008;93(1):45.
124. Flynn JT, Bancalari E, Snyder ES, et al. A cohort study of transcutaneous oxygen tension and the incidence and severity of retinopathy of prematurity. *N Engl J Med*. 1992;326(16):1050.
125. Miller JD, Carlo WA. Safety and effectiveness of permissive hypercapnia in the preterm infant. *Curr Opin Pediatr*. 2007;19(2):142.
126. Fabres J, Carlo WA, Phillips V, Howard G, Ambalavanan N. Both extremes of arterial carbon dioxide pressure and the magnitude of fluctuations in arterial carbon dioxide pressure are associated with severe intraventricular hemorrhage in preterm infants. *Pediatrics*. 2007;119(2):299.
127. Clark RH, Gerstmann DR, Jobe AH, Moffitt ST, Slutsky AS, Yoder BA. Lung injury in neonates: causes, strategies for prevention, and long-term consequences. *J Pediatr*. 2001;139(4):478.
128. Schmidt B, Roberts RS, Davis P, et al. Long-term effects of caffeine therapy for apnea of prematurity. *N Engl J Med*. 2007;357(19):1893.
129. Andréasson B, Lindroth M, Svenningsen NW, et al. Measurement of ventilation and respiratory mechanics during continuous positive airway pressure (CPAP) treatment in infants. *Acta Paediatr Scand*. 1989;78(2):194.
130. Ammari A, Suri M, Milisavljevic V, et al. Variables associated with the early failure of nasal CPAP in very low birth weight infants. *J Pediatr*. 2005;147(3):341.
131. AARC clinical practice guideline: Patient-ventilator system checks. American Association for Respiratory Care. *Respir Care*. 1992;37(8):882.
132. Boo NY, Zuraidah AL, Lim NL, Zulfiqar MA. Predictors of failure of nasal continuous positive airway pressure in treatment of preterm infants with respiratory distress syndrome. *J Trop Pediatr*. 2000;46(3):172.

133. Koti J, Murki S, Gaddam P, Reddy A, Reddy MDR. Bubble CPAP for respiratory distress syndrome in preterm infants. *Indian Pediatr*. 2010;47(2):139.
134. Rocha G, Flôr-de-Lima F, Proença E, et al. Failure of early nasal continuous positive airway pressure in preterm infants of 26 to 30 weeks gestation. *J Perinatol*. 2013;33(4):297-301.
135. Giedion A, Haefliger H, Dangel P. Acute pulmonary X-ray changes in hyaline membrane disease treated with artificial ventilation and positive end-expiratory pressure (PEP). *Pediatr Radiol*. 1973;1(3):145.
136. Greenough A, Premkumar M, Patel D. Ventilatory strategies for the extremely premature infant. *Paediatr Anaesth*. 2008;18(5):371.
137. Jardine LA, Inglis GD, Davies MW. Strategies for the withdrawal of nasal continuous positive airway pressure (NCPAP) in preterm infants. *Cochrane Database Syst Rev*. 2011;(2):CD006979.
138. Als H, Duffy FH, McAnulty G, et al. NIDCAP improves brain function and structure in preterm infants with severe intrauterine growth restriction. *J Perinatol*. 2012;32(10):797.
139. Rastogi S, Rajasekhar H, Gupta A, Bhutada A, Rastogi D, Wung JT. Factors affecting the weaning from nasal CPAP in preterm neonates. *Int J Pediatr*. 2012;2012:416073.
140. Shoemaker MT, Pierce MR, Yoder BA, DiGeronimo RJ. High flow nasal cannula versus nasal CPAP for neonatal respiratory disease: a retrospective study. *J Perinatol*. 2007;27(2):85.
141. Victor S. EXTUBATE: a randomised controlled trial of nasal biphasic positive airway pressure vs. nasal continuous positive airway pressure following extubation in infants less than 30 weeks' gestation: study protocol for a randomised controlled trial. *Trials*. 2011;12:257.
142. Todd DA, Wright A, Broom M, et al. Methods of weaning preterm babies <30 weeks gestation off CPAP: a multicentre randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed*. 2012;97(4):F236.
143. Lemyre B, Davis PG, De Paoli AG, Kirpalani H. Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for preterm neonates after extubation. *Cochrane Database Syst Rev*. 2017;2:CD003212.
144. User experience network. Supply gas failure alarm on Cardinal Health Infant Flow SiPAP units may not activate. *Health Devices*. 2009;38(7):232.
145. Migliori C, Motta M, Angeli A, Chirico G. Nasal bilevel vs. continuous positive airway pressure in preterm infants. *Pediatr Pulmonol*. 2005;40(5):426.

Noninvasive Mechanical Ventilation of the Infant and Child

16

Brian K. Walsh

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. Describe the effects of noninvasive ventilation (NIV) on respiratory function.
2. Differentiate the effects of NIV from continuous positive airway pressure (CPAP) on respiratory function.
3. Identify pediatric respiratory disorders amenable to a trial of NIV.
4. Identify clinical scenarios in children less amenable to a trial of NIV.
5. Explain the inspiratory pressure support feature of commercial bilevel pressure ventilators.
6. Discuss how adjustments in inspiratory and expiratory positive airway pressures affect respiratory function.
7. Recall the principles of interface selection to optimize the effectiveness and comfort of NIV.
8. Discuss common complications and contraindications to NIV.

Key Terms

noninvasive ventilation (NIV)
negative pressure–assisted ventilation (NPAV)
continuous positive airway pressure (CPAP)
high-flow nasal cannula (HFNC)
inspiratory positive airway pressure (IPAP)
expiratory positive airway pressure (EPAP)

DEFINITIONS AND INTRODUCTION

Methods of respiratory assistance that do not require an indwelling artificial airway are collectively termed *noninvasive* (Box 16-1). This chapter addresses noninvasive ventilation in children in general, but the focus is primarily on **noninvasive ventilation (NIV).** Interest in NIV treatment in infants and children over the past 3 decades has grown, in part because of the pervasive belief that NIV is a safe alternative to invasive assisted ventilation via endotracheal tube. Although the cumulative experience with NIV treatment of children in acute settings is promising, the evidence that NIV is superior to standard treatment in preventing intubation is inconclusive. A trial of NIV treatment may delay intubation and actually worsen clinical outcomes, as suggested by its use in adults with simple community-acquired pneumonia.[1] Improved survival of children with severe lung injury who are left with long-term respiratory dysfunction has fostered the use of NIV in the pediatric intensive care unit. NIV is used in this setting to facilitate early extubation and transition

Box 16-1 Noninvasive Ventilation: Broad Purpose and Definitions

The broad purpose of noninvasive ventilation is to treat respiratory dysfunction and restore respiratory gas exchange in a range of clinical settings.

Noninvasive ventilation (NIV): A method of respiratory assistance that involves an external interface and a cyclical positive pressure device.

Negative pressure–assisted ventilation (NPAV): A method of respiratory assistance based on intermittent application of subatmospheric pressure external to the chest wall through a tank or mold.

Continuous positive airway pressure (CPAP): A method of respiratory assistance based on application of a distending flow via an external interface to attain a defined constant positive pressure.

High-flow nasal cannula (HFNC): A means of respiratory assistance that uses a soft nasal cannula interface and high humidified flow source to raise the intraluminal pharyngeal pressure.

to ambulatory care. The evidence in support of NIV as a means of early extubation in children with severe lung disease is not conclusive.[2] NIV is also commonly used in the emergency department and general care areas of the hospital to treat children with acute respiratory distress.[3] The safety and effectiveness of NIV therapy in children outside the intensive care unit (ICU) for acute respiratory disorders have not been well studied or validated despite this common practice.

NIV treatment of infants and children with chronic respiratory disorders in the outpatient setting has also steadily grown. Caregivers of children with chronic respiratory failure managed at home by tracheostomy and positive pressure ventilation often seek NIV as a means to tracheal decannulation to ameliorate the social disadvantages associated with tracheostomy.[4] There are no clear guidelines for monitoring children treated with NIV in either the hospital or ambulatory setting. These and other issues pertaining to the use of NIV in pediatric patients are addressed in this chapter.

FACTORS FOR THE RESPIRATORY CARE PROFESSIONAL TO CONSIDER BEFORE STARTING NIV IN A CHILD

Foremost, the clinician should assess the age and pattern of respiratory dysfunction in the child and the clinical setting to decide whether a trial of NIV is warranted. Are sedation and electronic monitoring going to be necessary? A second consideration is whether the available equipment for NIV has the necessary performance features to meet the ventilatory demands of the child. Commercially available bilevel pressure ventilators with inspiratory pressure support are designed to respond to the mechanical properties and respiratory time constants of adults,[5] and tidal volume by NIV is dependent on the level of respiratory impedance.[6] Furthermore, small children and infants with respiratory distress often cannot attain the predefined levels of inspiratory flow or pressure required to trigger the inspiratory support feature. After initiation of NIV, the child must be assessed immediately to be certain that the work of breathing has decreased and there is sufficient improvement in respiratory gas exchange.

OBJECTIVES OF NONINVASIVE VENTILATION AND CONTINUOUS POSITIVE AIRWAY PRESSURE

The broad objectives of assisted ventilation are addressed elsewhere (see Chapter 17). The primary objectives of NIV in children with acute respiratory distress are to decrease the work of breathing and improve respiratory gas exchange (Box 16-2). To determine the effectiveness of NIV in achieving these objectives, the respiratory therapy professional must complete a thorough examination of the child. Children with acute respiratory distress typically breathe rapidly and shallowly, use the accessory muscles of respiration, and present with thoracic or abdominal retractions. Therefore, the therapist's primary objective is to evaluate the work of breathing before and after initiation of NIV and document in the medical record that the goals of treatment have been achieved.

Children with respiratory failure from neuromuscular weakness or central alveolar hypoventilation may not demonstrate the signs and symptoms of respiratory distress despite severe derangement in respiratory gas exchange. In such patients and in young infants, an arterial blood gas is necessary to assess the degree of respiratory dysfunction and to determine the effectiveness of NIV. A venous blood gas is often used to assess the acid–base status of a child in the acute setting but is not a reliable estimate of respiratory gas exchange. Thus arterial or capillary blood samples are the preferred method of collection. The attending physician of record should be notified when, in the opinion of the therapist, a child has failed a trial of noninvasive ventilation.

Box 16-2 Objectives of Noninvasive Ventilation in Pediatric Patients with Respiratory Distress

The primary objectives of NIV are to decrease the work of breathing and improve respiratory gas exchange.

- Decreased work of breathing, as indicated by the following:
  - Decreased respiratory rate
  - Decreased retractions
  - Decreased use of accessory muscles of breathing
- Improved respiratory gas exchange, indicated by the following:
  - Decreased arterial $Paco_2$
  - Increased arterial Pao_2
  - Increased arterial pH
- Increased functional residual capacity
- Increased patency of the oral-pharyngeal airway and decreased intrinsic auto-positive end-expiratory pressure

The clinical objectives of **continuous positive airway pressure (CPAP)** therapy are similar to those of NIV but through different mechanisms. An appropriate level of CPAP must increase end-expiratory lung volume (functional residual capacity) and thereby improve oxygenation. CPAP therapy may or may not improve tidal volume and alveolar ventilation, depending on its effects on lung mechanics. In children and neonates with restrictive respiratory dysfunction and decreased lung compliance, CPAP therapy can raise tidal volume if it improves compliance. However, in children with lung overexpansion from air trapping and increased compliance, CPAP therapy may actually decrease tidal volume by causing overdistention and decreased compliance. Two clinical trials have compared intermittent nasal NIV to CPAP in neonates with respiratory distress syndrome.[7,8] A significant decrease in treatment failure, defined as the need for rescue invasive ventilation, was found in NIV-treated infants, but NIV did not decrease the prevalence of chronic lung disease. In daily practice, CPAP is likely as good a choice as NIV in situations in which the predominant respiratory derangement is hypoxemia from ventilation–perfusion inequality but the child has adequate alveolar ventilation. NIV is preferred when hypoventilation is present and the child has sufficient inspiratory effort to trigger the inspiratory pressure support function of the NIV device.

NIV can be applied to children with both acute and chronic respiratory disorders to achieve other benefits on lung function (see Box 16-2). Children with restrictive lung disorders, including atelectasis, pneumonia, neuromuscular weakness, and morbid obesity, typically present with hypoxemia and a reduction in functional residual capacity. Both NIV and CPAP are effective in this setting to restore end-expiratory lung volume. NIV is offered to patients with chronic hypoventilation disorders as a clinical benefit used at night to reduce the severity of daytime symptoms associated with chronic hypercarbia—headache and fatigue.[9] The daytime $Paco_2$ (arterial partial pressure of carbon dioxide) should decrease 1 to 2 weeks after initiation of nocturnal NIV treatment. This is likely explained by decreased blood pH through nocturnal carbon dioxide elimination, diminution of renal bicarbonate reabsorption, and restoration of the central ventilatory responsiveness to changes in pH. Intermittent NIV treatment in pediatric patients with chronic hypoventilation disorders effectively improves daytime carbon dioxide elimination for at least a period of 1 year, and this improvement is associated with a decrease in total serum levels of bicarbonate.[10,11]

Likewise, in children with intermittent or chronic upper airway obstruction, NIV or CPAP can raise the intraluminal pharyngeal and hypopharyngeal pressures to impede collapse and maintain the patency of the laryngeal inlet. Assessment of the effectiveness of NIV or CPAP in both these functions is important and involves a detailed respiratory examination and appropriate monitoring of gas exchange. The sleep laboratory is an ideal location to assess the effectiveness of NIV and CPAP in the treatment of upper airway dysfunction and sleep-disordered breathing. There is an important role for the respiratory therapist in optimal interface selection, adjustment, and monitoring of NIV in the polysomnography laboratory.

OBJECTIVES OF HIGH-FLOW NASAL CANNULA

High-flow nasal cannula (HFNC) systems are commonly used to treat acute respiratory distress. HFNC treatment is often selected as an alternative to NIV and CPAP to avoid the relative discomfort of a mask interface. The goal is to administer a threshold level of nasal gas flow to raise the intraluminal nasopharyngeal pressure sufficiently to increase functional residual capacity and maintain upper airway patency. The effectiveness of HFNC in meeting these objectives is not well studied in children.[12] In premature infants, the minimal level of HFNC treatment to improve respiratory status was found in one systematic review to be greater than 2 L/minute.[13] In a study of infants with bronchiolitis, nasopharyngeal pressures increased linearly (0.45 cm H_2O for each 1 L/minute increase) with HFNC rates up to 6 L/minute.[14] In an uncontrolled study of children in the ICU, treatment with HFNC was associated with acute improvement in respiratory distress and aeration on chest film.[15] Children presenting to the emergency department with acute respiratory distress treated with HFNC per an institutional protocol had a significant reduction in intubation rates compared with children not treated in this way during an earlier period, but this observation was retrospective and not controlled.[16] Table 16-1 describes estimated HFNC flow rates in which patients may be at a higher risk of failure, and therefore closer monitoring should be provided. For more details on suggested flow settings, refer to Chapter 10.

Table 16-1 Patients at Risk for Noninvasive Ventilation or High-Flow Nasal Cannula Failure

	NONINVASIVE VENTILATION	HIGH-FLOW NASAL CANNULA
Oxygenation	P/F < 300 S/F < 264 Fio_2 > 0.4 with an Spo_2 of 88%-97%	Age: <1 yr: >2 L/minute 1-5 yrs: >4 L/minute 5-10 yrs: >6 L/minute >10 yrs: >8 L/minute
Ventilation	Delta pressure > 15 OR PIP > 20	<1 yr: >6 L/minute 1-5 yrs: >10 L/minute 5-10 yrs: >14 L/minute >10 yrs: >20 L/minute

EXPERIENCE WITH NONINVASIVE VENTILATION TREATMENT IN PEDIATRIC RESPIRATORY DISORDERS

ACUTE RESPIRATORY FAILURE

NIV is widely used in the ICU setting to treat infants and children with acute respiratory distress associated with a broad spectrum of disorders (Box 16-3). Whereas the cumulative evidence is highly supportive of an early trial of NIV in adults with acute cardiogenic pulmonary edema[17] and acute exacerbations of chronic obstructive pulmonary disease,[18] evidence in support of NIV treatment in adults with acute asthma is not conclusive.[19] Furthermore, there is no comparable level of evidence to support or refute NIV use in acute respiratory disorders of children. This topic was last reviewed in 2011,[20] and the fundamental question from that review is the same today: Does NIV treatment prevent or just delay intubation in children with acute respiratory distress at risk for respiratory failure? The physiological benefits of NIV in children with acute respiratory failure associated with hypercarbia were recently described.[21] Use of NIV led to a 33% increase in tidal volume and a 56% decrease in the diaphragmatic pressure–time product. These changes indicate a significant decrease in work of breathing and improved respiratory gas exchange. Unfortunately, short-term physiologic improvements after NIV use in children with acute respiratory distress have not been linked to improved clinical outcomes confirmed by controlled trials. The studies to date are observational and include children with diverse causes of respiratory distress.

In a recent observational study of 151 small children in acute respiratory failure who were treated with NIV, there were clear improvements in gas exchange and work of breathing, but the study was uncontrolled and the intubation failure rate was nearly 25%.[22] Risk factors for NIV failure (i.e., need for intubation) were premature birth and pneumonia. Improvements in oxygenation occurred in both the NIV success and NIV failure groups in the first 4 hours of treatment, but indices in the work of breathing improved only in the NIV success group. A 5-year review of NIV use in children in the ICU setting again supported its effectiveness (77% success rate in preventing intubation), but these observations were both uncontrolled and retrospective.[23] These reports do highlight disorders for which NIV treatment in children was not effective, including acute respiratory distress syndrome (ARDS).[23,24] Since these reports and the growth of NIV in ARDS, the PALICC developed guidelines on the use of NIV.[25] In a case series, NIV was used with mixed results in children with respiratory distress from status asthmaticus,[20] acute chest syndrome,[25] and congenital heart disease.[26] With acute asthma, NIV may be an effective adjunct therapy to improve lung function when applied in combination with nebulized bronchodilators.[27] An important note on the interpretation of these reports for the respiratory care professional is the need for sedation to comfortably apply NIV in the acute setting, especially for children with status asthmaticus.[20]

Box 16-3 Acute Respiratory Disorders of Infancy and Childhood Amenable to Treatment with Noninvasive Ventilation

- Bronchiolitis[a]
- Pneumonia[a]
- Status asthmaticus[a]
- Postextubation respiratory distress[a]
- Early phase of ARDS
- Acute respiratory distress after bone marrow transplantation
- Acute chest syndrome
- Congenital heart disease
- Pulmonary edema
- Fat or bone marrow embolism
- Acute pulmonary hemorrhage
- Near-drowning lung injury
- Acute lung aspiration syndromes

[a]Indicates a less than low noninvasive ventilation failure rate.

Guide for the Practicing Respiratory Care Professional: Acute Respiratory Distress

The practicing respiratory professional should consider several factors before initiating a trial of NIV in an infant or child with acute respiratory distress (Box 16-4). Foremost, the therapist must evaluate the setting and available resources to monitor and treat the child. Monitoring requirements and availability of skilled ancillary personnel are as important with NIV as they are for a child who requires intubation and mechanical ventilation. Table 16-1 describes estimated NIV settings in which patients may be at higher risk of failure, and therefore closer monitoring should be provided. Case reports do not support a trial of NIV in patients with cardiovascular instability and fulminant respiratory failure—for example, children with rapidly evolving hypoxemia from ARDS.[23] Pediatric disorders that lead to a low likelihood of successful response to NIV include ARDS, status asthmaticus, pulmonary hemorrhage with

Box 16-4 Factors Informing the Success or Failure of Noninvasive Ventilation in the Treatment of Acute Respiratory Distress in Children

- Assignment of skilled personnel to monitor and manage critically ill children
- Availability of appropriate noninvasive ventilation equipment and monitoring devices
- Level of postnatal development and status of airway protective reflexes
- Exclusion of children with rapidly evolving hypoxemia: cardiovascular instability, acute respiratory distress syndrome, severe asthma

hemoptysis, and sepsis with cardiovascular instability. NIV should not be initiated based on the assumption that it will necessarily decrease the likelihood of endotracheal intubation, and thus should be restricted to a practice environment also conducive to immediate airway management and critical care support of the child. Consideration should also be given to whether the child will need sedation to tolerate NIV. Agitation with placement of the mask interface is an important cause of treatment failure in children with status asthmaticus treated with NIV.[20]

CHRONIC RESPIRATORY FAILURE

NIV is often used to treat children with chronic respiratory disorders in two settings—as rescue therapy, based on the belief that it can prevent endotracheal intubation in acute exacerbations, and as a long-term clinical benefit. In a recent European review, outpatient NIV use in children was concentrated among a few centers specializing in pediatric respiratory care.[28] Long-term use of NIV can provide substantial clinical benefit to children with a range of respiratory disorders complicated by chronic respiratory failure (Box 16-5).[29-32] The physiologic benefits of NIV treatment in the ambulatory setting were reviewed earlier in this chapter. Perhaps the most successful experience with NIV as a rescue therapy is its use in acute exacerbations of hypercarbic respiratory failure in children with chronic neuromuscular disorders.[33] Children with myelomeningocele are at risk for a number of life-threatening respiratory complications for which NIV has been used effectively in combination with other respiratory therapies.[34] In children with advanced cystic fibrosis (CF) lung disease, long-term NIV has been successful as a bridge therapy to lung transplantation.[35] In a single uncontrolled case series, long-term NIV use was associated with stabilization of lung function in advanced CF lung disease,[36] but the short-term use of NIV was no more beneficial than standard therapies in clearing airway secretions.[37] Nonetheless, in a systematic review of available trials of NIV, the current recommendation is to consider its use as an adjunct therapy for airway secretion clearance in patients with CF lung disease.[38]

Box 16-5 Pediatric Chronic Respiratory Disorders Amenable to Long-Term Noninvasive Ventilation Treatment

- Chronic respiratory failure associated with neuromuscular weakness or chest wall dysfunction
- Cerebral palsy and other severe neurobehavioral abnormalities
- Respiratory complications of myelomeningocele
- Advanced cystic fibrosis lung disease (as a bridge to transplantation)
- Alternative to tracheostomy in congenital central alveolar hypoventilation syndrome

Standard treatment for congenital central alveolar hypoventilation syndrome (CCHS) is long-term assisted ventilation via tracheostomy, with or without supplemental diaphragmatic pacing. CCHS is an especially high-risk disorder when considering treatment with NIV because of the failure of autonomic ventilatory drive during quiet sleep. These children are at high risk for central hypoventilation. Nonetheless, because of the social and medical disadvantages of tracheostomy, caregivers of children with CCHS increasingly seek noninvasive modes of ventilation as a means to facilitate tracheal decannulation.[11,30] NIV has been used to treat children with CCHS with standard mask interfaces and as a bridge to long-term treatment with **negative pressure–assisted ventilation (NPAV)**.[39] With regard to effective settings, a recent modification of the pressure-support mode to facilitate assured volume delivery was used to treat a teenager with CCHS.[40]

Guide for the Practicing Respiratory Care Professional: Chronic Disorders

Respiratory care professionals involved in the treatment with NIV of children with chronic respiratory disorders should make sure that appropriate monitoring is in place. In the home setting, NIV should be viewed as a treatment with probable clinical benefit, and not for the purpose of life support. Hence monitoring requirements may be less stringent in the home setting than in the hospital but, most importantly, are determined by the acuity of the child's condition. The selection of a comfortable mask interface that fits appropriately is especially important for long-term NIV use in children. In about one-fifth of children, an interface change is necessary, primarily because of patient discomfort.[41] CCHS is a special disorder in which careful monitoring is necessary whenever the child is asleep. The device used to apply NIV must be set to deliver effective and consistent minute ventilation, and a backup ventilatory rate is mandatory. The sleep laboratory is an ideal setting to assess the adequacy of meeting these goals in children, and such studies should be done on a regular basis. A best practice advisory is available from the American Academy of Sleep Medicine to adjust NIV settings via polysomnography in adults and children with stable alveolar hypoventilation syndromes.[42] Although there are certainly neonates with CCHS who have been treated with NIV alone since birth, the safety of this practice as an alternative to standard treatment with regard to long-term developmental and cardiopulmonary outcomes has not been rigorously studied.

OBSTRUCTIVE SLEEP APNEA SYNDROME AND MORBID OBESITY

NIV is often selected as an alternative to nasal CPAP in children with complicated obstructive sleep apnea syndrome (OSAS) and in children with obesity hypoventilation syndrome. The advantage of NIV in

these disorders is the pressure support function, which will assist the respiratory muscles during inspiration to overcome resistance imposed by a collapsed upper airway and stiff chest wall. Although there are no clear guidelines, selection of NIV over CPAP for children with OSAS is typically made in cases of OSAS complicated by alveolar hypoventilation and hypercarbia. OSAS often complicates a restrictive pattern of respiratory dysfunction in a number of so-called *overlap syndromes*, including cerebral palsy, myelomeningocele, Down syndrome, and morbid obesity. In these disorders, NIV confers a distinct advantage over CPAP to decrease the work of the respiratory muscles, increase tidal volume, and thereby reverse alveolar hypoventilation. A distinct pattern of periodic central apnea during sleep is an important complication of sleep-disordered breathing in congestive heart failure patients. Application of a sufficient level of CPAP to reduce the apnea-hypopnea index in heart failure patients below 15 events per hour was associated with improved cardiac function.[43] NIV is widely touted as a means to improve nocturnal ventilation and sleep quality in patients with obesity hypoventilation syndrome. However, in a recent controlled trial, although NIV did improve daytime carbon dioxide elimination, it did not alter a panel of inflammatory and metabolic disturbances in obesity hypoventilation syndrome.[44]

NONINVASIVE VENTILATION WITH POSITIVE-PRESSURE DEVICES

PRESSURE-CONTROL MODES

NIV is accomplished in children using either pressure-control or volume-control modes.[28] "Bilevel" ventilators (or modes) deliver pressure-control continuous spontaneous ventilation or pressure-control intermittent mandatory ventilation (IMV). An innovation pioneered by Respironics is a mode called "spontaneous/timed." It is classified as a form of pressure-control intermittent mandatory ventilation, but in contrast to conventional forms of IMV, spontaneous breaths (inspiration is both triggered and cycled by the patient) suppress mandatory breaths (inspiration is triggered or cycled by the machine) as long as the spontaneous breath rate is higher than the set mandatory rate. The purpose of this feature is to improve patient–ventilator synchrony, because spontaneous breaths allow the patient to influence both the frequency and inspiratory time of assisted breaths. As with any pressure-control mode, tidal volume is dependent on the compliance and resistance of the respiratory system and the gradient between the inspiratory and expiratory pressure adjustments.[6,45] Most bilevel ventilators available for commercial use are adept at delivering sufficient flow to reach the targeted level of inspiratory pressure.[5] These devices also have a flow compensation feature so that small leaks around the interface or through the mouth do not seriously impair performance. However, the capacity of NIV devices to compensate for severe leaks is limited, and the result is greater patient–ventilation asynchrony, cited as a common reason for NIV failure in the acute setting.[29]

Other features that are standard on bilevel ventilators include an **expiratory positive airway pressure (EPAP)** adjustment, backup ventilatory rate, and mode selection. Some devices introduced recently feature an integrated blender to titrate supplemental oxygen delivery (such as the BiPAP Vision ventilator support system; Philips Respironics, Murrysville, PA). Other more recent adaptations of bilevel ventilators include integrated alarm systems, graphic displays, memory chip for record events, and internal battery packs.

Regulatory Issues with Bilevel Ventilators

Despite widespread publications citing their effectiveness and safety, the US Food and Drug Administration (FDA) does not approve bilevel devices as an invasive mode of mechanical ventilation in children. Instead, these devices are in the FDA category of noncontinuous ventilator and as such are primarily intended to augment patient ventilation. The position of most managed care agencies and home respiratory vendors is that bilevel positive airway pressure with backup rate is not appropriate for use with a tracheostomy or as a substitute for an FDA-approved portable home ventilator. Although this has not been an issue for inpatient application, it is a major impediment for outpatient use. Most home care companies require that physicians sign an indemnification agreement releasing them from liability should the device fail.

Adaptive Servoventilation

The adaptive servoventilator (AutoSet CS; ResMed, Sydney, Australia) is a modified bilevel pressure ventilator suitable for NIV. The device provides a baseline level of ventilatory support (end-inspiratory pressure of 9 cm H_2O) superimposed on 5 cm H_2O CPAP. It monitors the patient's minute ventilation and calculates a target of 90% of this value. If the unassisted minute ventilation decreases, the ventilator increases inspiratory pressure to attain the target.[46] If the subject suddenly becomes apneic, the device will trigger mandatory breaths and increase the inspiratory pressure amplitude from a minimum of 4 cm H_2O up to whatever is required to maintain ventilation at 90% of the long-term average. The main goal of adaptive servoventilation (ASV) is to treat periodic breathing, or Cheyne Stokes respiration (CSR), which is the most common breathing pattern in 25% to 40% of patients with chronic heart failure (CHF). However, studies of ASV have shown mixed results in adults, and this mode may have potential deleterious effects in patients with severe CHF who have predominantly CSR.[46] Although the use of ASV in children is limited, its design features are amenable to long-term disorders complicated by central alveolar hypoventilation,

including Chiari malformation, myelomeningocele, and even CCHS.

Proportional Assist Ventilation

Proportional assist ventilation (PAV) is a form of pressure-control continuous spontaneous ventilation. Unlike PSV, which uses a preset inspiratory pressure, PAV provides inspiratory pressure in proportion to the patient's spontaneous breathing effort as determined by instantaneous feedback from an in-line pneumotachometer.[47] One form of PAV (as originally described and on the Draeger VN500 ventilator) provides assistance by supporting preset values for elastic load (elastance times volume) and resistive load (resistance times flow). In a form of PAV called *PAV+* (Medtronics PB980 ventilator), the operator sets the actual level of work of breathing to be supported, and the ventilator maintains this at a constant level even as lung mechanics change. PAV has the potential to enhance patient–ventilator synchrony. PAV performed better with regard to patient preference and some physiological variables than standard PSV by nasal mask in a comparison trial of adults with acute respiratory failure.[48]

Neurally Adjusted Ventilatory Assist

Neurally adjusted ventilatory assist (NAVA) is a form of pressure-control continuous spontaneous ventilation and, like PAV, is designed to make inspiratory pressure proportional to inspiratory effort.[49] However, NAVA is unique among modes in that triggering, cycling, and pressure control are based on signals from a special nasogastric tube that measures the electrical activity of the diaphragm. Because NAVA does not rely on pressure or flow signals for control, it is impervious to leaks. This makes it a possibly ideal mode for NIV. Lee et al. recently reported that NAVA improved patient–ventilator synchrony and diaphragmatic unloading in preterm infants during noninvasive nasal ventilation even in the presence of large air leaks.[50]

Volume-Control Modes

NIV can be accomplished through portable ventilators designed to deliver volume-control modes (i.e., preset tidal volume and flow). The features of these ventilators are reviewed. The potential advantages of volume-control modes for NIV include superior performance when used in the synchronized intermittent mandatory ventilation mode for patients with significant neuromuscular weakness or central hypoventilation who may not trigger bilevel ventilators. However, this limitation of standard bilevel ventilators may be overcome with modern devices with the technical features to provide ASV and PAV or NAVA.

Major drawbacks of portable control ventilators for NIV in pediatric patients include their relative size, limited portability, and, most importantly, limited attainment of high levels of inspiratory flow to support spontaneous respiratory efforts. Newer generations of portable ventilators are smaller and provide flow rates that support spontaneous breathing, including pressure support.

To appropriately adjust a volume-control mode for NIV, the delivered tidal volume should be approximately twice that of the child's physiological tidal volume to accommodate the dead space of the nasopharynx and conducting airways. Setting the tidal volume above the physiologic range and adjusting the peak inspiratory pressure until the required tidal volume is achieved can accomplish this. This method, originally referred to as *pressure plateau ventilation*, is commonly used for invasive long-term mechanical ventilation in pediatric patients.[51] Probably because of enhanced patient comfort and lower cost with pressure-device NIV, there is a modern trend away from volume-regulated and toward pressure-supported devices to accomplish NIV in the ambulatory setting.[52]

NONINVASIVE VENTILATION WITH NEGATIVE-PRESSURE DEVICES

NPAV is a form of respiratory assistance in which subatmospheric pressure is applied intermittently through a cuirass or tank (iron lung) device external to the chest wall. Expiration occurs as the pressure around the chest wall is allowed to return to atmospheric levels. This method of assisted ventilation has a long tradition of being effective in pediatric patients with hypoventilation associated with acquired neurological injury from trauma or infection and chronic restrictive lung disorders.[53,54] However, large tank ventilators are difficult to transport and have gradually fallen out of use. Instead, modern cuirass devices (United Hayek RTC, London, UK) are FDA-approved and are being used on a limited basis. The advantage of these devices is a beneficial effect on cardiac filling pressures and volumes, a benefit found even in healthy individuals.[55] In a highly novel application, negative pressure applied to the abdomen in combination with nasal CPAP has been studied as an effective means of recruiting atelectatic lung, although this approach has not been used in humans.[56] An important drawback of NPAV is significant disruption of sleep in patients with neuromuscular disorders and poor control of the muscle group supporting the upper airway. In these patients, treatment with NPAV can be complicated by recurrent episodes of obstructive apnea or hypopnea culminating in transient hypoxemia.

NONINVASIVE VENTILATION ADJUSTMENT: MODES AND PRESSURE TITRATION

MODES

Most bilevel pressure-control ventilators suitable for NIV feature CPAP, spontaneous, timed, and spontaneous/timed operating modes (Box 16-6). In the CPAP mode,

Box 16-6 Noninvasive Ventilation Modes

CPAP: Continuous flow with no inspiratory pressure assist or rate
Spontaneous: Patient-triggered inspiratory pressure assist with no backup rate
Timed: Device-initiated pulse of preset positive pressure at a set rate
Spontaneous/Timed: Patient-triggered inspiratory pressure assist and timed mode cycling in the event of prolonged apnea

these devices provide constant flow to maintain a target level of CPAP. Inspiratory pressure support is not provided. In the spontaneous mode, the ventilator starts inspiration in response to the patient's spontaneous inspiratory effort. The ventilator delivers flow to reach and maintain the preset **inspiratory positive airway pressure (IPAP).** Inspiration cycles off after the inspiratory flow decays to a preset threshold, usually expressed as a percentage of peak inspiratory flow. In the timed mode, the ventilator time triggers inspirations at a preset frequency. In the spontaneous/timed mode, the flow-trigger feature is activated and mandatory breaths are time triggered only when the spontaneous breath rate is lower than the set mandatory rate (i.e., spontaneous breaths suppress mandatory breaths to improve patient–ventilator synchrony).

Guide for the Practicing Respiratory Care Professional: Noninvasive Ventilation Adjustment

Pediatric patients are typically managed with NIV in the spontaneous/timed mode. The chief advantage of this mode is patient comfort. This results when the child's inspiratory efforts are assisted with the inspiratory pressure support feature. Significant barriers to effective NIV in pediatric patients treated with NIV are ineffective triggering[57-58] and patient–ventilator asynchrony.[29] The best way for the practicing therapist to promote effective triggering and prevent asynchrony with NIV is to minimize leaks around the mask interface. In the presence of a significant leak, the inspiratory pressure target is never reached, resulting in a long inflation time as the unit delivers massive amounts of inspiratory flow in an attempt to attain the preset inspiratory pressure. This may require application of an oral-nasal mask in a child with significant mouth leak. Some modern bilevel ventilators (VPAP III ST, ResMed, Poway, CA; BiPAP Vision, Philips Respironics) designed for NIV feature an adjustable inflation time that can be set to prevent this problem. There is little published experience with pediatric patients treated with NIV exclusively in the timed mode. Recent guidelines recommend consideration of the timed mode or use of a backup rate in children with evidence of central alveolar hypoventilation.[42] In this mode the ventilator essentially functions as a time-cycled, pressure-limited device. It is important for therapists to be aware that many ventilators available for NIV in children have significant performance limitations—hence the need for appropriate bedside assessment and monitoring.[59]

PRESSURE TITRATION

With modern bilevel pressure ventilators, the IPAP adjustment determines the target distending airway pressure attained during ventilator inflations (Box 16-7). The IPAP must be set above the EPAP to raise the child's tidal volume, "unload" the respiratory muscles, and decrease respiratory distress. The difference between IPAP and EPAP determines the maximum passive tidal volume; the actual tidal volume is dependent on the duration of the pressure difference (inspiratory time), respiratory system resistance and compliance, and inspiratory effort (if any). Detailed guidelines for the adjustment of NIV settings in the polysomnography laboratory are provided by the American Academy of Sleep Medicine.[42] Although modern bilevel devices are capable of achieving IPAP levels of 30 cm H_2O, children younger than 12 years typically do not tolerate pressures higher than 20 cm H_2O without some type of sedation.[20] There may be a delay of several hours before a step increase in IPAP achieves a reduction in $Paco_2$. In this event, other factors can be used to determine the effectiveness in NIV (Table 16-2). In day-to-day clinical practice, an IPAP setting of between 8 and 12 cm H_2O is typically sufficient to achieve the goals of NIV in pediatric patients.

The EPAP adjustment with NIV primarily determines the end-expiratory lung volume and maintains the stability of the upper airway. In a typical pediatric application of NIV, EPAP levels of 6 to 8 cm H_2O are effective in improving oxygenation and preventing obstructive apnea. Most children, regardless of the setting or indication, poorly tolerate EPAP levels above 10 cm H_2O.

Over titration of airway pressures is a common mistake when NIV is attempted in pediatric patients. In children with normal lung compliance, typically those with neuromuscular lung diseases, optimal results are seen at relatively low distending pressures. Raising the pressure to compensate for leaks around the nasal mask or through the mouth often is poorly tolerated in children and can lead to central hypoventilation. The mechanism behind this is uncertain, but it is also seen in adult patients with obesity hypoventilation syndrome treated with nasal CPAP.[60]

Box 16-7 Noninvasive Ventilation Pressure Adjustments

Inspiratory positive airway pressure (IPAP): Determines the tidal volume
Expiratory positive airway pressure (EPAP): Raises end-expiratory lung volume and impedes upper airway collapse

Table 16-2 Methods to Determine the Clinical Effectiveness of Noninvasive Ventilation

OUTCOME EXPECTED	METHODS AND LIMITATIONS
Decrease in work of breathing	*Physical examination:* Acute decrease in respiratory rate, retractions, and use of accessory muscles. Not reliable in young infants and children with neuromuscular and central disorders.
Improvement in respiratory gas exchange	*Pulse oximetry:* Acute improvement in Sa_{O_2}. Not a reliable metric in the assessment of hypoventilation. Interpretation obscured by concurrent O_2 treatment. *Blood gas sampling:* Increase in pH, decrease in Pa_{CO_2}, increase in Pa_{O_2}; invasive—Pa_{CO_2} may not decrease for hours if at all in some disorders. *End-tidal CO_2 monitoring:* Acute reduction in end-tidal CO_2. High background flow in NIV circuit can wash out expired CO_2. *Transcutaneous CO_2 monitoring:* Subacute reduction in transcutaneous CO_2 monitoring; accuracy dependent on careful electrode placement; changes lag minutes behind change in actual Pa_{CO_2}.
Increase in FRC	*Routine chest radiography:* Increased lung expansion, decreased atelectasis; difficult to accomplish during therapy; changes can lag days behind.
Maintenance of upper airway patency	*Sleep polysomnography:* Subacute reductions in the number of airway-occlusive episodes decrease with the degree of thoracoabdominal asynchrony. Not amenable to acute clinical setting.

FRC, Functional residual capacity; *NIV,* noninvasive ventilation; Pa_{CO_2}, arterial partial pressure of carbon dioxide; Pa_{O_2}, arterial partial pressure of oxygen; Sa_{O_2}, arterial oxygen saturation.

In NPAV, the applied subatmospheric pressure is decreased incrementally to raise the tidal volume. A significant hazard in exposing patients with neuromuscular disorders to intermittent external subatmospheric pressures while leaving the head and neck exposed to ambient atmospheric pressure is episodic obstructive apnea and hypopnea. In clinical practice this can be minimized by concomitant nasal CPAP therapy with NPAV.

INTERFACE SELECTION AND FIT

Interface devices appropriate for NIV include nasal masks, nasal-oral masks, and nasal plugs or pillows.[41] Recent advances in interface design have led to assisted ventilation with a helmet device. Administration of CPAP via a helmet was compared with conventional mask interface in children with acute respiratory distress and was well tolerated, with some physiological advantages.[61] One study in adults compared different interfaces and showed that although nasal masks are more acceptable to patients, facial masks and nasal plugs delivered higher minute ventilation with better carbon dioxide elimination than nasal masks.[62]

In most clinical scenarios, the nasal mask is the preferred interface in pediatric patients (Box 16-8). Newer-generation nasal masks have a soft gel cushion (e.g., the Phantom nasal mask, SleepNet, Manchester, NH) that conforms to the contours of the face and forehead and are thus more comfortable. These models also minimize air leaks and facial trauma. However, in critically ill patients, even small oral air leaks are undesirable. Nasal-oral masks should be considered when absolute avoidance of an oral air leak is necessary. However, nasal-oral masks may pose a significant risk of aspiration of gastric contents in the event of emesis and also may increase anxiety in young children. Under these conditions, sedation is often necessary, and the child should not be fed.

Nasal masks are commercially available in a wide range of sizes and shapes to fit children and adolescents. However, soft nasal masks are not widely available for small infants, and in one case series children younger than 2 years treated with NIV required custom-made masks. Custom masks may also be indicated for children with midfacial syndromes associated with maxillary hypoplasia. The nasal mask should fit snugly around the nasal margins. When the mask is too large, significant tension on the head straps is necessary to prevent mask leaks, thereby promoting dermal ulceration at the nasal bridge. Long-term intermittent NIV by means of a nasal mask may impair maxillary bone growth.[63] This concern, although not clearly supported by available evidence, is considered significant by caregivers of children treated with NIV.

Nasal plugs or pillows can be substituted for nasal masks in children who complain of discomfort with the nasal mask. Nasal plugs or pillows are not used as

Box 16-8 Guide to Interface Selection in Pediatric Patients Treated with Noninvasive Ventilation

- Consider the setting: Acute respiratory distress versus long-term use for a chronic disorder.
- Consider the acuity: A complete seal is important if gas exchange is compromised by leak.
- Soft nasal masks are more comfortable, better tolerated, and have a relative safety advantage.
- Nasal-oral masks are indicated when a complete seal is necessary and the child is in acute distress.
- The most common error in pediatrics is to select an overly large mask in the interest of comfort. These pose greater risks of leak and skin irritation.

often, because most children eventually adapt to the nasal mask very well. They may have some role in treating teenagers, because they place no pressure on the face and do not interfere with vision.

MONITORING THE PATIENT AND VENTILATOR CIRCUIT

Selection of patient and ventilator monitors with NIV is based primarily on the clinical setting and the acuity of the patient. In critically ill children, NIV serves a life-support function. The optimal location for patients receiving NIV depends on the capacity for adequate monitoring, staff skill, experience with and knowledge of the equipment used, and awareness of potential complications. The patient should thus be monitored for arterial oxygen saturation (Sao_2), arterial blood gases, work of breathing, development of hemodynamic instability or altered mental status, and failure to tolerate the device. Each monitor device should have alarm limits set by an experienced respiratory therapist.

Often, NIV is used for stable patients with respiratory dysfunction as a clinical benefit. A hospital ward, sleep laboratory, or step-down unit is an appropriate setting for NIV in this capacity. A pulse oximeter alone may be sufficient for monitoring, provided the child is clinically stable and not likely to decompensate in the event of equipment failure or removal of the interface. Novel monitoring of compliance, leak, and selected physiological variables is available through software integrated into modern bilevel devices. In one observational study, this type of monitoring provided helpful information for the clinician in regard to respiratory events but was prone to artifacts—hence the need for independent validation.[64]

Intermittent NIV can be accomplished safely at home without any patient or ventilator monitors. However, children with stable long-term disorders treated with NIV in the home setting have frequent episodes of hypercarbia in the absence of hypoxemia.[65] In nearly all of these children with hypercarbic episodes, daytime capillary arterialized carbon dioxide levels were normal in nearly all of them. Thus routine continuous carbon dioxide monitoring is advised for children at risk for hypoventilation and treated with NIV. This is often a challenge with NIV because of dilution of exhaled carbon dioxide by the continuous flow present between the nasal opening and mask interface. An alternative to nasal sampling devices is the recent introduction of ear carbon dioxide monitoring systems, but these have not been adequately studied in children in the ambulatory setting.

COMPLICATIONS OF AND CONTRAINDICATIONS TO NONINVASIVE VENTILATION

COMPLICATIONS

Pediatric patients are at relatively higher risk for complications to NIV as a result of unique physiological differences from adults (Table 16-3). Because NIV is often used in the long-term treatment of young children, it may well affect the postnatal growth of the midface and jawbone. Long-term NIV use is associated with facial flattening in most children and retraction of the mandible in some.[66] An important confounding issue is whether children at risk for midfacial hypoplasia are more likely to be treated with NIV and whether the disorders themselves promote abnormal facial growth versus the effects of the mask interface *per se.* Whatever the mechanism, this is an important cosmetic consideration and should be shared with the child's caregivers in advance of a course of long-term NIV. A fatal complication of NIV has been reported in an adult patient who died from hypoventilation and failure of the battery pack device.[67]

Table 16-3 Factors Unique to Pediatric Patients That Promote Complications of NIV

COMPLICATION	FACTOR UNIQUE TO CHILDREN
Aspiration	Immaturity of airway protective reflexes
Reflux	Impaired gastroesophageal sphincter function during infancy
Upper airway obstruction	Anatomical factors, difficulty clearing secretions
Large oral leak	Tendency to mouth breathe
Agitation	Anxiety, incomplete understanding, developmental disorders

Approximately half of children experience one or more minor complications of NIV. The most common minor complication reported is skin irritation as a result of the nasal mask (48%), leading to skin necrosis in up to 8%.[66] Other minor but important side effects of NIV in children include nasal dryness or discomfort, epistaxis, and eye irritation. One study found that prolonged use of maintenance steroids was an additional risk factor for development of skin ulcers during NIV.[68] Epistaxis can be prevented by humidification, whereas conjunctival irritation can be prevented by selection of an appropriate size nasal mask.

CONTRAINDICATIONS

The only absolute contraindication to a trial of NIV in pediatric patients with acute respiratory distress is cardiovascular instability. Relative contraindications include nasopharyngeal obstruction, massive hemoptysis, poor clearance of or profuse oral secretions, and extreme agitation or anxiety.

FUTURE OF NONINVASIVE VENTILATION IN PEDIATRICS

A major impediment for the future of NIV in infants and children is the reluctance of companies that manufacture

Clinical Highlight

CS is an 11-year-old girl with advanced CF lung disease and CF-associated diabetes. She was hospitalized four times in the past year for treatment of pulmonary exacerbations with systemic broad-spectrum antibiotics, chest physiotherapy, inhaled hypertonic saline, and inhaled Colistin. CS's sputum is infected with pan-resistant *Burkholderia cepacia,* and despite the hospitalizations, her FEV_1 has decreased over time to 20% of predicted levels. Her Sa_{O_2} in room air is 85% but increases to 95% with 2 L/minute nasal cannula oxygen. A recent echocardiogram showed moderate pulmonary artery hypertension with enlargement of the right ventricle. CS was referred to a regional center for evaluation for lung transplant. However, she was not listed for transplant and was asked to return for reevaluation in 6 months. In the interim, CS developed morning headaches. A capillary blood gas in room air showed a pH of 7.41, Pa_{CO_2} of 53 torr, and Pa_{O_2} of 74 torr. Because of the headaches, pulmonary hypertension, and hypercarbia, CS was offered nocturnal NIV as a bridge therapy during the transplant evaluation period. She preferred a face mask interface and was treated with a pressure-targeted bilevel device adjusted to the spontaneous/timed mode, a backup rate of 12 breaths per minute, IPAP of 14 cm, EPAP of 8 cm, and Fi_{O_2} of 0.21. After a few months of NIV, the patient's morning headaches cleared, her pulmonary artery pressure as estimated by echocardiogram stabilized, and her body mass index reached a plateau. The plan is to continue nocturnal NIV pending evaluation for lung transplantation.

Adolescent with advanced cystic fibrosis lung disease treated with face mask NIV.

bilevel ventilators to seek FDA approval of their devices for pediatric patients. This is primarily because of the cost of FDA approval and the relatively low volume of units expected to be sold in the pediatric market. The result is that clinicians who care for children with chronic hypoventilation disorders and are attracted to NIV as an alternative to invasive tracheostomy with positive pressure ventilation become involved in funding disputes and legal conflicts with companies that dispense durable medical equipment.

Despite these constraints, the future for NIV in pediatric patients is promising. Smaller interfaces and flow-triggered, pressure-targeted units suitable for small children are appearing for home use. Modern bilevel units already can achieve target inspiratory pressure of 30 cm H_2O and are equipped with independent oxygen adjustment settings. These units also come with a maximal inspiratory time setting to prevent prolonged inflations in the presence of uncompensated leaks. PAV, a method of assisted ventilation that is responsive to the resistive and elastic properties of the respiratory system, can be administered by means of a nasal mask. This method of assisted ventilation is well beyond preliminary trials in adults and may have significant advantages over NIV with current bilevel devices. At present, NIV treatment should be restricted to carefully selected children and centers equipped with the appropriate equipment and experienced personnel. Randomized trials comparing early NIV versus standard treatment in well-characterized patient populations are needed to clearly define the role of NIV in children.

Key Points

- NIV is a noninvasive mode of respiratory assistance administered by an external interface device for the purposes of improving alveolar ventilation and oxygenation, decreasing the spontaneous work of breathing, and relieving respiratory distress.
- In contrast to CPAP, NIV in most applications will raise the child's tidal volume and hence increase carbon dioxide elimination.
- Various respiratory disorders of childhood may be treated with NIV, but the available evidence best supports NIV use in some forms of acute respiratory distress and long term for treatment of chronic restrictive disorders.
- NIV is less effective in children with cardiopulmonary instability and severe lung injury, such as evolving ARDS. Its use in children with acute asthma, though promising, is not supported by clinical studies.
- In bilevel pressure devices suitable for use with NIV, the inspiratory pressure support feature is triggered when the child makes a spontaneous inspiratory effort and can therefore decrease the work of breathing.
- The tidal volume attained during NIV is positively correlated with the pressure gradient between the IPAP and EPAP settings.

- The optimal interface for NIV in most children is a soft nasal mask that fits snugly over the child's nose and does not require undue tension on the attachment straps to remain in place.
- The most common complication of NIV in children is skin irritation at the interface margins, but serious life-threatening complications have also been reported.

Assessment Questions

See Evolve Resources for answers.

1. An absolute contraindication to a trial of NIV in a child with respiratory distress is:
   - **A.** Status asthmaticus
   - **B.** Absence of a nasogastric tube to ventilate the stomach
   - **C.** Cardiovascular instability
   - **D.** Tracheoesophageal fistula
2. True or false:
   The required level of monitoring for a child with long-term respiratory failure treated with nocturnal NIV in the ambulatory setting as a probable clinical benefit should include a cardiorespiratory monitor and pulse oximeter.
3. The following pediatric respiratory disorders may be treated with a trial of NIV in the acute setting *except:*
   - **A.** ARDS with sepsis
   - **B.** Bronchiolitis
   - **C.** Acute exacerbation of cystic fibrosis lung disease
   - **D.** Pneumonia in a child with muscular dystrophy
4. True or false:
   Current evidence supports a trial of NIV to prevent endotracheal intubation and invasive mechanical ventilation in children with acute respiratory distress.
5. You are called by the floor nurse to evaluate a child with cerebral palsy and pneumonia being treated with NIV who is agitated. The child's heart rate is elevated and he is moving around the bed. The best response in this situation is to:
   - **A.** Reassure the nurse and the child's parents that NIV takes some time to get used to and simply observe the child over time.
   - **B.** Notify the attending physician that the child is not tolerating NIV and needs to be sedated so that the NIV can be effective.
   - **C.** Do a complete respiratory examination, paying attention to the child's work of breathing and vital signs before and after application of NIV.
   - **D.** Replace the nasal mask interface with a full-face mask interface that covers the mouth and nose so as to prevent oral leak.

REFERENCES

1. Ferrer M, Cosentini R, Nava S. The use of non-invasive ventilation during acute respiratory failure due to pneumonia. *Eur J Intern Med*. 2012;23:420.
2. Keenan SP, Powers C, McCormack DG, Block G. Noninvasive positive-pressure ventilation for postextubation respiratory distress: a randomized controlled trial. *JAMA*. 2002; 287:3238.
3. Thys F, Roeseler J, Delaere S, et al. Two-level non-invasive positive pressure ventilation in the initial treatment of acute respiratory failure in an emergency department. *Eur J Emerg Med*. 1999;6(3):207.
4. Make BJ, Hill NS, Goldberg AI, et al. Management of pediatric patients requiring long-term ventilation. *Chest*. 1998;113: 289S.
5. Kacmarek RM. Characteristics of pressure-targeted ventilators used for noninvasive positive pressure ventilation. *Respir Care*. 1997;42:380.
6. Adams AB, Bliss PL, Hotchkiss J. Effects of respiratory impedance on the performance of bilevel pressure ventilators. *Respir Care*. 2000;45:390.
7. Meneses J, Bhandari V, Alves JG. Nasal intermittent positive pressure ventilation versus nasal continuous positive airway pressure for preterm infants with respiratory distress syndrome: a systematic review and meta-analysis. *Arch Pediatr Adolesc Med*. 2012;166:372.
8. Gizzi C, Papoff P, Campelli M, Cerasaro C, Agostino R, Moretti C. Surfactant and noninvasive ventilation for preterm infants. *Acta Biomed*. 2012;83(suppl 1):24.
9. Hill NS, Eveloff SE, Carlisle CC, Goff SG. Efficacy of nocturnal nasal ventilation in patients with restrictive thoracic disease. *Am Rev Respir Dis*. 1992;145:365.
10. Teague WG. Long term mechanical ventilation in infants and children. In: Hill NS, ed. *Long-term Mechanical Ventilation*. New York: Marcel Dekker; 2001:177.
11. Teague WG, Harsch A, Lesnick B. Non-invasive positive pressure ventilation as a long-term treatment for pediatric patients with chronic hypoventilation disorders. *Am J Respir Crit Care Med*. 1999;159:297[abstract].
12. Lee JH, Rehder KJ, Williford L, Cheifetz IM, Turner DA. Use of high flow nasal cannula in critically ill infants, children, and adults: a critical review of the literature. *Intensive Care Med*. 2013;39(2):247-257.
13. Manley BJ, Dold SK, Davis PG, Roehr CC. High-flow nasal cannulae for respiratory support of preterm infants: a review of the evidence. *Neonatology*. 2012;102:300-308.
14. Arora B, Mahajan P, Zidan MA, Sethuraman U. Nasopharyngeal airway pressures in bronchiolitis patients treated with high-flow nasal cannula oxygen therapy. *Pediatr Emerg Care*. 2012;28:1179-1184.
15. Spentzas T, Minarik M, Patters AB, Vinson B, Stidham G. Children with respiratory distress treated with high-flow nasal cannula. *J Intensive Care Med*. 2009;24:323-328.
16. Wing R, James C, Maranda LS, Armsby CC. Use of high-flow nasal cannula support in the emergency department reduces the need for intubation in pediatric acute respiratory insufficiency. *Pediatr Emerg Care*. 2012;28:1117-1123.
17. Vital FM, Saconato H, Ladeira MT, et al. Non-invasive positive pressure ventilation (CPAP or bilevel NIV) for

cardiogenic pulmonary edema. *Cochrane Database Syst Rev*. 2008;(3):CD005351.
18. Ram FS, Picot J, Lightowler J, Wedzicha JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2004;(1):CD004104.
19. Ram FS, Wellington S, Rowe BH, Wedzicha JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma. *Cochrane Database Syst Rev*. 2005;(1):CD004360.
20. Najaf-Zadeh A, Leclerc F. Noninvasive positive pressure ventilation for acute respiratory failure in children: a concise review. *Ann Intensive Care*. 2011;1(1):15.
21. Essouri S, Durand P, Chevret L, et al. Physiological effects of noninvasive positive ventilation during acute moderate hypercapnic respiratory insufficiency in children. *Intensive Care Med*. 2008;34:2248.
22. Abadesso C, Nunes P, Silvestre C, Matias E, Loureiro H, Almeida H. Non-invasive ventilation in acute respiratory failure in children. *Pediatr Rep*. 2012;4(2):e16. doi:10.4081/pr.2012.e16.
23. Essouri S, Chevret L, Durand P, Haas V, Fauroux B, Devictor D. Noninvasive positive pressure ventilation: five years of experience in a pediatric intensive care unit. *Pediatr Crit Care Med*. 2006;7:329.
24. Mayordomo-Colunga J, Medina A, Rey C, et al. Predictive factors of non-invasive ventilation failure in critically ill children: a prospective epidemiological study. *Intensive Care Med*. 2009;35:527.
25. Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med*. 2015;16(5):428-439.
26. Padman R, Henry M. The use of bilevel positive airway pressure for the treatment of acute chest syndrome of sickle cell disease. *Del Med J*. 2004;76:199.
27. Gupta P, Kuperstock JE, Hashmi S, et al. Efficacy and predictors of success of noninvasive ventilation for prevention of extubation failure in critically ill children with heart disease. *Pediatr Cardiol*. 2012;34(4):964-977.
28. Galindo-Filho VC, Dornelas de Andrade A, Brandão DC, et al. Noninvasive ventilation coupled with nebulization during asthma crises: a randomized controlled trial. *Respir Care*. 2013;58(2):241-249.
29. Fauroux B, Boffa C, Desguerre I, Estournet B, Trang H. Long-term noninvasive mechanical ventilation for children at home: a national survey. *Pediatr Pulmonol*. 2003;35:119.
30. Hess DR. The growing role of noninvasive ventilation in patients requiring prolonged mechanical ventilation. *Respir Care*. 2012;57:900.
31. Teague WG. Non-invasive positive pressure ventilation: current status in paediatric patients. *Paediatr Respir Rev*. 2005;6:52.
32. Fauroux B, Lofaso F. Domiciliary non-invasive ventilation in children. *Rev Mal Respir*. 2005;22:289.
33. Matsui S, Nakagawa G, Takei S, et al. The effect of noninvasive positive pressure ventilation in children with severe motor and intellectual disabilities with respiratory insufficiency. *No To Hattatsu*. 2012;44:284.
34. Piastra M, Antonelli M, Caresta E, Chiaretti A, Polidori G, Conti G. Noninvasive ventilation in childhood acute neuromuscular respiratory failure: a pilot study. *Respiration*. 2006;73:791.
35. Kirk VG, Morielli A, Gozal D, et al. Treatment of sleep-disordered breathing in children with myelomeningocele. *Pediatr Pulmonol*. 2000;30:445.
36. Padman R, Nadkarmi V, Von Nessen S, et al. Noninvasive positive pressure ventilation in end-stage cystic fibrosis: a report of seven cases. *Respir Care*. 1994;39:736.
37. Fauroux B, Le Roux E, Ravilly S, Bellis G, Clément A. Long-term noninvasive ventilation in patients with cystic fibrosis. *Respiration*. 2008;76:168.
38. Placidi G, Cornacchia M, Polese G, Zanolla L, Assael BM, Braggion C. Chest physiotherapy with positive airway pressure: a pilot study of short-term effects on sputum clearance in patients with cystic fibrosis and severe airway obstruction. *Respir Care*. 2006;51:1145.
39. Moran F, Bradley JM, Piper AJ. Non-invasive ventilation for cystic fibrosis. *Cochrane Database Syst Rev*. 2009;21:CD002769.
40. Tibballs J, Henning RD. Noninvasive ventilatory strategies in the management of a newborn infant and three children with congenital central hypoventilation syndrome. *Pediatr Pulmonol*. 2003;36:544.
41. Vagiakis E, Koutsourelakis I, Perraki E, et al. Average volume-assured pressure support in a 16-year-old girl with congenital central hypoventilation syndrome. *J Clin Sleep Med*. 2010;6:609.
42. Ramirez A, Delord V, Khirani S, et al. Interfaces for long-term noninvasive positive pressure ventilation in children. *Intensive Care Med*. 2012;38:655.
43. Berry RB, Chediak A, Brown LK, et al. Best clinical practices for the sleep center adjustment of non-invasive positive pressure ventilation (NIV) in stable chronic alveolar hypoventilation syndromes. *J Clin Sleep Med*. 2010;6:491.
44. Arzt M, Floras JS, Logan AG, et al. Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP). *Circulation*. 2007;115:3173.
45. Borel JC, Tamisier R, Gonzalez-Bermejo J, et al. Noninvasive ventilation in mild obesity hypoventilation syndrome: a randomized controlled trial. *Chest*. 2012;141:692.
46. Strumpf DA, Carlisle CC, Millman RP, et al. An evaluation of the Respironics BiPAP bilevel CPAP device for delivery of assisted ventilation. *Respir Care*. 1990;35:415.
47. Rabec C, Emeriaud G, Amadeo A, Fauroux B, Georges M. New modes in non-invasive ventilation. *Paediatr Respir Rev*. 2016;18:73-84.
48. Younes M, Puddy A, Roberts D, et al. Proportional assist ventilation: results of an initial clinical trial. *Am Rev Respir Dis*. 1992;145:121.
49. Gay PC, Hess DR, Hill NS. Noninvasive proportional assist ventilation for acute respiratory insufficiency: comparison with pressure support ventilation. *Am J Respir Crit Care Med*. 2001;164:1606.
50. Sinderby C, Navalesi P, Beck J, et al. Neural control of mechanical ventilation in respiratory failure. *Nat Med*. 1999;5(12):1433-1436.
51. Lee J, Kim HS, Jung YH, et al. Non-invasive neurally adjusted ventilatory assist in preterm infants: a randomised phase II crossover trial. *Arch Dis Child Fetal Neonatal Ed*. 2015;100(6):F507-F513.
52. Keens TG, Jansen MT, DeWitt PK. Home care for children with chronic respiratory failure. *Semin Respir Med*. 1990;11:269.
53. Janssens JP, Derivaz S, Breitenstein E, et al. Changing patterns in long-term noninvasive ventilation: a 7-year prospective study in the Geneva Lake area. *Chest*. 2003;123:67.
54. Hartmann H, Jawad MH, Noyes J, Samuels MP, Southall DP. Negative extra thoracic pressure ventilation in central hypoventilation syndrome. *Arch Dis Child*. 1994;70:418.
55. Linton DM. Cuirass ventilation: a review and update. *Crit Care Resusc*. 2005;7(1):22.
56. McBride WT, Ranaldi G, Dougherty MJ, et al. The hemodynamic and respiratory effects of cuirass ventilation in healthy volunteers: Part 1. *J Cardiothorac Vasc Anesth*. 2012;26:868.

57. Chierichetti M, Engelberts D, El-Khuffash A, Babyn P, Post M, Kavanagh BP. Continuous negative abdominal distension augments recruitment of atelectatic lung. *Crit Care Med*. 2012;40:1864.
58. Nava S, Ceriana P. Patient-ventilator interaction during noninvasive positive pressure ventilation. *Respir Care Clin N Am*. 2005;11:281.
59. Cuvelier A, Achour L, Rabarimanantsoa H, Letellier C, Muir JF, Fauroux B. A noninvasive method to identify ineffective triggering in patients with noninvasive pressure support ventilation. *Respiration*. 2010;80:198.
60. Fauroux B, Leroux K, Desmarais G, et al. Performance of ventilators for noninvasive positive pressure ventilation in children. *Eur Respir J*. 2008;31:1300.
61. Piper AJ, Sullivan CE. Effects of short-term NIPPV in the treatment of patients with severe obstructive sleep apnea and hypercapnia. *Chest*. 1994;105:434.
62. Chidini G, Calderini E, Cesana BM, Gandini C, Prandi E, Pelosi P. Noninvasive continuous positive airway pressure in acute respiratory failure: helmet versus facial mask. *Pediatrics*. 2010;126(2):e330.
63. Navales P, Fanfulla F, Frigerio P, Gregoretti C, Nava S. Physiologic evaluation of noninvasive mechanical ventilation delivered with three types of masks in patients with chronic hypercapnic respiratory failure. *Crit Care Med*. 2000;28: 1785.
64. Villa MP, Pagani J, Ambrosio R, Ronchetti R, Bernkopf E. Mid-face hypoplasia after long-term nasal ventilation. *Am J Respir Crit Care Med*. 2002;166:1142.
65. Pasquina P, Adler D, Farr P, Bourqui P, Bridevaux PO, Janssens JP. What does built-in software of home ventilators tell us? An observational study of 150 patients on home ventilation. *Respiration*. 2012;83:293.
66. Paiva R, Krivec U, Aubertin G, Cohen E, Clément A, Fauroux B. Carbon dioxide monitoring during long-term noninvasive respiratory support in children. *Intensive Care Med*. 2009; 35:1068.
67. Fauroux B, Lavis JF, Nicot F, et al. Facial side effects during noninvasive positive pressure ventilation in children. *Intensive Care Med*. 2005;31:965.
68. Lechtzin N, Weiner CM, Clawson L. A fatal complication of noninvasive ventilation. *N Engl J Med*. 2001;344:533.
69. Jones DJ, Braid GM, Wedzicha JA. Nasal masks for domiciliary positive pressure ventilation: patient usage and complications. *Thorax*. 1994;49:811.

Invasive Mechanical Ventilation of the Neonate and Pediatric Patient

17

Brian K. Walsh, Robert L. Chatburn

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. Explain when mechanical ventilation is indicated in neonates and pediatric patients.
2. Describe the fundamentals of mechanical ventilator operation.
3. Describe and execute the management of patients undergoing mechanical ventilation.
4. Identify complications associated with mechanical ventilation.
5. Explain various approaches for minimizing complications with ventilators.
6. Compare differences in operation between pressure, volume, and adaptive control breath types.
7. Provide reasons why one mode of ventilation would be chosen over another for certain conditions.
8. Determine initial ventilator settings for various patient sizes.
9. Recognize factors that could improve the interaction between the patient and the mechanical ventilator.
10. Define and discuss various weaning strategies.
11. Define *conventional* and *high-frequency ventilation.*
12. Describe how gas is delivered and exhaled during high-frequency jet ventilation.
13. Describe how gas is delivered and exhaled during high-frequency oscillatory ventilation.
14. Describe the relative roles frequency and tidal volume play during high-frequency ventilation.
15. Explain the relationship between lung volume and oxygenation during high-frequency ventilation.
16. Identify mechanical ventilation strategies for a given pathophysiology.

Neonatal and pediatric mechanical ventilation (MV) presents some of the most clinically challenging situations in respiratory care. The neonatal and pediatric population encompasses a broad range of weights, ages, sizes, and diseases; therefore ventilator practices can vary widely. In this chapter, a *neonate* is defined as any newborn infant younger than 44 weeks of gestation and a *pediatric patient* represents any child older than 1 month of age. We also identify **conventional ventilation** (CV) as ventilation modes that provide 150 or fewer breaths per minute and **high-frequency ventilation** (HFV) as modes that provide more than 150 breaths per minute.

It is often said that children are not small adults, and infants are not small children. That is true for most clinical applications and many basic lung mechanics and the design of modes of ventilation. For example, compared with adults, pediatric patients have incomplete airway cartilage, increased airway resistance, higher chest wall compliance related to incomplete rib cage ossification, lower functional residual capacity (FRC) related to fewer alveoli, more reliance on the diaphragm, higher risk for pulmonary vascular remodeling, and a higher metabolic rate.[1] Hence thorough knowledge of these subjects serves all patients needing MV. Most of the concepts presented in this chapter are the same for both neonatal and pediatric applications; however, there are other situations that are unique to the neonatal or pediatric patient.

There is currently no consensus regarding optimal ventilator strategies for this patient population.[2] A tremendous amount of research is needed to determine best practices for managing neonatal and pediatric patients receiving ventilatory support. To manage neonatal and pediatric MV effectively, the clinician must combine the principles described in this chapter with the knowledge of how airway anatomy and pulmonary pathophysiology are affected by various diseases. It is beyond the scope of this chapter to provide an in-depth review of ventilator equipment or guidelines for disease-specific ventilator management. These aspects are more than adequately covered elsewhere in this book and by ventilator manufacturers' online resources for clinicians.

Several exciting technologies have been developed for the respiratory care of newborns and pediatric patients. These new tools range from enhancements in the pharmacologic management of distinct cardiopulmonary disorders to tremendous strides in MV. Critical to the successful application of these new treatments is the development of disease-specific strategies, which include ways in which some therapies may positively interact with others. CMV and HFV continue to play important roles in this growth.

The link between MV, oxygen, and subsequent acute and chronic lung disease was made in both pediatric and adult patients shortly after the introduction of CMV into clinical practice.[3,4] At that time, understanding of the mechanisms of these injuries was limited to the observed interactions between oxygen, pressure, and time.[5] The various techniques of HFV emerged during the 1980s from efforts to develop methods of managing respiratory failure that would minimize the negative pulmonary consequences of ventilatory support. More recent trials indicate that ventilating adult patients with acute respiratory distress syndrome (ARDS) with higher tidal volumes contributes to further lung damage.[6] Although the most common mode for ventilating neonates is some form of pressure-control intermittent mandatory ventilation, accumulating evidence supports more advanced modes used in this population.[7,8]

This chapter reviews (1) basic concepts of CMV and HFV, (2) current understanding of mechanisms of gas exchange for CMV and HFV, (3) basic approaches of each mode of ventilation, (4) basic disease-specific strategies, and (5) special patient care considerations. This chapter also introduces the emerging understanding of the interaction between modes of ventilation, monitoring, and strategies.

GOALS AND OBJECTIVES

There are three basic goals of MV, regardless of the patient population[9]:

1. Safety
   a. Ensure adequate gas exchange.
   b. Provide lung protection (minimize atelectrauma and volutrauma).
2. Comfort
   a. Maximize patient–ventilator synchrony.
   b. Ensure an adequate work supply by the ventilator in response to the work support demand by the patient.
3. Liberation
   a. Minimize duration of ventilation.
   b. Minimize risk of adverse events.

Specific clinical objectives include the desire to increase oxygenation, correct respiratory acidosis, reduce respiratory distress, prevent or reverse atelectasis, reduce respiratory muscle fatigue, manage intracranial pressure, lower oxygen consumption, and stabilize the chest wall for adequate lung expansion. Box 17-1 lists clinical situations in which MV is indicated.

GENERAL TYPES OF VENTILATION

The real challenge in learning about MV is understanding the taxonomy of modes rather than the "knobology" of specific ventilators. This chapter divides ventilation strategies (not modes) into three

Box 17-1 Clinical Indications for (but Not Limited to) Conventional Ventilation

CATEGORY	SPECIFIC FINDINGS OR VALUES
Inadequate/absent respiratory effort	Absent, weak, or intermittent spontaneous effort Frequent (>6 events/hour) or severe apnea requiring PPV
Excessive work of breathing (relative)	Marked retractions, severe tachypnea, stridor, or airway obstruction
High oxygen requirement	Fio_2 > 0.40-0.60, S/F ratio < 264, P/F ratio < 300
Severe respiratory acidosis	pH <7.2 and not improving, Pco_2 >60
Moderate or severe respiratory distress *and* contraindications for noninvasive support	Intestinal obstruction; intestinal perforation; recent gastrointestinal surgery; ileus; CDH
Postoperative period	Residual effect of anesthetic agents; fresh abdominal incision; need for continued muscle relaxation (e.g., fresh tracheostomy)

Fio_2, Fraction of inspired oxygen.

main groups based on the preset ventilatory frequency, CMV, and HFV.

CONVENTIONAL VENTILATION

The United States Food and Drug Administration (FDA) limits the preset ventilatory frequency of mechanical ventilators to 150 breaths per minute. This is an arbitrary limit, and normal breathing (even for premature infants) does not reach this value. Nevertheless, CMV is the establishment of a relatively normal pattern of frequency and tidal volume for the required minute ventilation of a patient (modified by any disease process) (Figure 17-1A).

HIGH-FREQUENCY VENTILATION

HFV is a general term used to describe MV using tidal volumes less than or equal to the dead space volume and delivered at higher than normal breathing rates. Tidal volume, dead space volume, and breathing rate all vary with patient age and size (tidal and dead space volumes vary inversely with increasing age, whereas breathing rate varies directly). The FDA has chosen to define HFV devices as those that provide breathing rates exceeding 150 breaths per minute. These ventilators operate at breathing rates of 4 to 15 Hz (1 Hz = 60 breaths per minute or 1 cycle per second) and deliver the requisite small tidal volumes. This HFV discussion is limited to devices currently cleared by the FDA for use in neonates or pediatric patients (many more devices are available outside the United States). Several types of HFV devices have been tested and reported in the literature. They differ functionally by the way each breath is generated, their relationship to conventional ventilator settings (if any), the range of

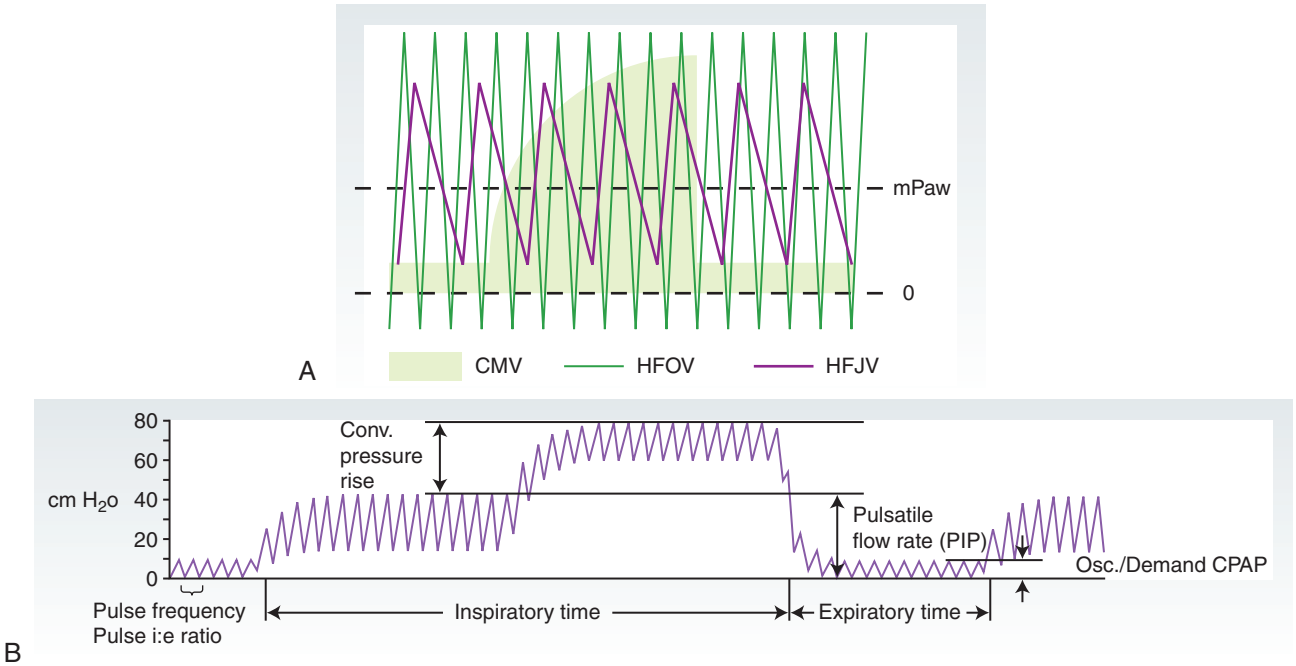


FIGURE 17-1 Low-frequency, high-frequency oscillatory ventilation (HFOV) and high-frequency jet ventilation (HFJV). **A,** Pressure time waveform of *HFOV* and *HFJV* with conventional ventilation *(CV)* in the background for comparison. **B,** Pressure time waveform of high frequency intrapulmonary percussive ventilation (HFIPV). Settings on HFIPV are clearly labeled. *CPAP,* Continuous positive airway pressure; mPaw, mean, airway pressure.

breathing rates, and the nature of the expiratory portion of the respiratory cycle (see Figure 17-1A).

High-Frequency Jet Ventilation

High-frequency jet ventilation (HFJV) was the first type of HFV developed for neonates. The first and only commercial device for HFJV of infants is called the Life Pulse and is manufactured by Bunnell Incorporated (Salt Lake City, UT). In general, HFJV devices deliver short-pulsed jets of gas into the airway opening (see Figure 17-1A). Delivered tidal volumes are a combination of the volume of the jet pulse and entrainment volumes that are "dragged" along with each jet. Original techniques using a modified triple-lumen endotracheal tube (ETT) and using catheters placed in a standard ETT have been described. Modern adaptations use a special connector that replaces the ETT adapter to allow the combination of the HFJV and CMV (Figure 17-2). The Bunnell ventilator combines CMV breaths and positive end-expiratory pressure (PEEP) (using a separate ventilator) with jet breaths and relies on passive chest recoil for expiration. It controls flow delivery to maintain set inspiratory pressures and delivers a mode that is a form of PC-IMV Pressure control-intermittent mandatory ventilation (PC-IMV).

High-Frequency Intrapulmonary Percussive Ventilation

High-frequency intrapulmonary percussive ventilation (HFIPV) delivers short bursts of gas to a modified jet entrainment device called a *sliding Venturi valve.* There is only one manufacturer of HFIPPV devices (Percussionaire Corporation, Sandpoint, ID), and there are several different models. Unlike the Bunnel jet ventilator, the Percussionaire device does not require a separate CMV device. On the other hand, inspiratory pressures are open-loop controlled, meaning that peak inspiratory pressure is a function of the patient's lung mechanics for any given set of ventilator parameters. Intrapulmonary percussive ventilation is defined by the manufacturer as "a cyclic method of controlled percussive intrapulmonary (sub tidal) breath stacking, increasing the existing Functional Residual Capacity (FRC) of the pulmonary structures to a selected level (pulsatile equilibrium) at which point repetitive sub tidal volume delivery does not further increase lung volumes. Each percussive inspiratory interval (timed in seconds) is associated with percussive, diffuse intrapulmonary gas mixing concomitant with aerosol delivery; followed by passive exhalation of a Gross Tidal Volume to a selected baseline." The manufacturer defines volumetric diffusive ventilation as "a cyclic method of precisely controlling the intrapulmonary delivery of successive (aggregate) sub tidal volumes to a selected equilibrium (increase in lung volume) ultimately reaching an Oscillatory Apneustic Plateau (Oscillatory Equilibrium), followed by the passive exhalation of a gross tidal volume down to a programmed static and/or pulsatile baseline." A further explanation of this rather complex mode is beyond the scope of this book (see Figure 17-1B).

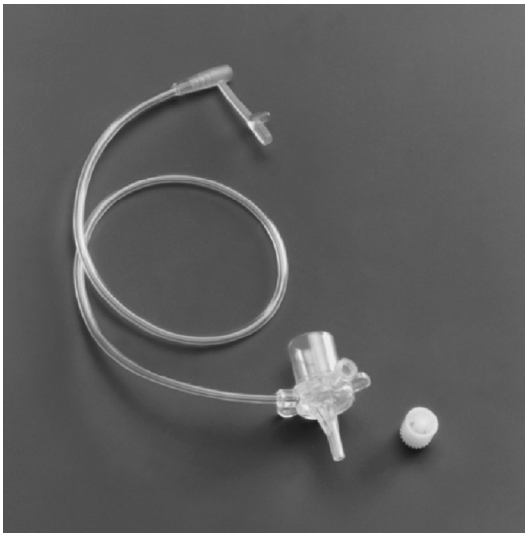


FIGURE 17-2 LifePort endotracheal tube (ETT) adapter. Jet pulses are delivered through the side lumen of the ETT, and servocontrol over jet pressures is maintained by feedback from pressures sampled at the distal ETT lumen. Connection to a conventional ventilator is provided at the proximal ETT opening. This ETT adapter is made specifically for use with this device. (Courtesy Bunnell Inc., Salt Lake City, UT.)

High-Frequency Oscillatory Ventilation

Of all HFV techniques, **high-frequency oscillatory ventilation (HFOV)** has been the most used and studied. There is only one HFOV device on the market in the United States (3100A HFOV, Vyaire Medical). Other HFOV devices have been described in the literature, but their designs are beyond the scope of this chapter. Common to all HFOV devices is the provision of extremely small tidal volumes and very high breathing rates of 3 to 15 Hz, as well as the presence of continuous distending pressure (CDP) or mean airway pressure (mPaw). The outward flow of expiratory gases is enhanced by the active exhalation phase of the piston cycle. This last feature distinguishes HFOV from all other HFV methods. All current devices use a standard ETT, allowing precise control over mPaw. But like HFIPV the pressure amplitude is open-loop controlled and therefore a function of lung mechanics. Ventilator output is delivered to the proximal ETT (at the ETT circuit connection). Because the ETT behaves as a low-pass filter at these rapid breathing rates, pulmonary structures experience markedly dampened phasic pressures.

EVIDENCE FOR HIGH-FREQUENCY VENTILATION

Neonatal Patients

The bulk of clinical data regarding appropriate application of HFV devices has been acquired from neonatal humans and animals. From these studies, two clear indications for HFV use during either routine or rescue circumstances have evolved.[10-12] They include diffuse homogeneous lung disease (or the atelectasis-prone lung) in which CMV management is failing or may lead to increased risk of pulmonary morbidity, and existing pulmonary air leak syndromes (e.g., pneumothorax and pulmonary interstitial emphysema [PIE]). Diffuse homogeneous lung disease includes natural surfactant deficiency (respiratory distress syndrome), shock lung in the newborn, and diffuse pneumonia. Other diagnoses, including congenital pulmonary hypoplasia (both the congenital diffuse variety and that associated with congenital diaphragmatic hernia), may be additional indications. The efficacy of HFV for pulmonary hypoplasia is promising but not yet clearly established.[17]

Each of these lung diseases has been successfully managed with extracorporeal membrane oxygenation (ECMO).[18] The role of pre-ECMO HFV has been the subject of wide debate, with at least one published report describing a 50% reduction in the need for ECMO among infants referred to an ECMO center and who met ECMO criteria and began HFOV on admission.[19] However, there are also data that imply an increased risk of pulmonary morbidity among infants who avoided ECMO by using HFV. The timing of HFV intervention, the parameters determining HFV failure, and the decision to discontinue HFV and initiate ECMO are currently empirical.[20]

HFV continues to be indicated for infants in whom air leak syndromes develop but the incidence of intractable air leak has decreased. This is probably the result of surfactant use, improved ventilatory techniques and devices, and better patient monitoring. Other conditions common to the neonate but not clearly benefited by HFV include particulate meconium aspiration, congenital lobar emphysema, bronchopulmonary dysplasia, and viral pneumonia. Further data from controlled trials with defined patient populations and treatment strategies are needed to offer clearer recommendations about HFV use in these conditions (Box 17-2).

Pediatric Patients

Controlled trials in pediatric patients have been fairly limited.[21] However, as would be anticipated, proper strategic HFV use has had positive results in children with ARDS and pulmonary air leak. In general, HFOV is applied as a rescue therapy in those failing CMV. An additional interesting HFV application is HFJV use during and after cardiac surgery, especially for children undergoing right ventricular outflow tract diversion or repair. At least two groups of investigators have reported improved hemodynamic measurements in children managed with the HFJV in both intraoperative and postoperative environments.[22,23] The ability to provide adequate ventilation with low mean and peak pressures in children with otherwise normal lungs offers a substantial advantage of HFJV over HFOV and CMV. Furthermore, this feature makes HFJV a more efficacious method of treating traumatic or acquired bronchopleural fistulas than other forms of respiratory support.

Box 17-2 Clinical Indications for (but Not Limited to) High-Frequency Ventilation

CATEGORY	SPECIFIC FINDINGS OR VALUES	TYPE OF HIGH-FREQUENCY VENTILATION SUGGESTED
Failure of conventional ventilation	OI > 15, PIP > 28 cm H_2O, PEEP > 8 cm H_2O in neonates or > 12 cm H_2O in pediatrics	HFOV
Air leak syndromes	PIE on chest radiograph Pneumothorax not easily resolved with chest tube Bronchopleural fistulas	HFOV/HFJV
Postoperative cardiac conditions with or without secondary lung disease where a higher $mP_{\overline{AW}}$ could hinder hemodynamics	Increasing mPaw worsens hemodynamics	HFJV
Severe respiratory acidosis	pH <7.2 and not improving, P_{CO_2} >65	HFOV
Airway debris	Inhalation burn injury, lung diseases with copious secretions	HFPV

F_{IO_2}, fraction of inspired oxygen; *HFJV*, high-frequency jet ventilation; *HFPV*, high-frequency percussive ventilation; *HFOV*, high-frequency oscillatory ventilation; *OI*, oxygenation index; *$mP_{\overline{AW}}$*, mean airway pressure; *PEEP*, positive end-expiratory pressure; *PIE*, pulmonary interstitial emphysema; *PIP*, peak inspiratory pressure.

Case Study 1

You are called to assist with a full-term neonate who was transferred to your facility for further evaluation. The patient is the son of a diabetic mother who tested positive for group B streptococcus infection. He is 5 kg, has received one dose of surfactant, and has extremely low lung volumes on AP chest radiograph. The transport team has the infant on CMV, pressure control rate of 60, peak inspiratory pressure (PIP) of 32, PEEP of 10, and fraction of inspired oxygen (FiO_2) of 1.0. These ventilator settings are producing a peripheral capillary oxygen saturation (SpO_2) of 85%, with admission blood gas values of 7.15/65/66/23. What mode of ventilation would you suggest for this patient and why?

See Evolve Resources for answers.

MODES OF MECHANICAL VENTILATION

A *mode of ventilation* is defined as a predetermined pattern of interaction between a patient and a ventilator. However, there is no standardization in the industry regarding either naming modes or explaining their operation. Because different manufacturers employ different nomenclature to describe often closely related modes of ventilation, communication between users of different devices has become increasingly difficult.

As evidence of the need for a systematic approach, at last count, there are about 290 names of modes on 33 ventilators in the United States alone. This is comparable to using many drugs by trade name only and not by their generic or chemical names and no classification system. That is the situation with ventilator modes today. In addition, many ventilators are designed to span the entire age range from preterm newborn to adults and have a variety of modes that have never been evaluated in newborn infants. A classification system is important to be able to identify which modes are the same and which are different. Then clinicians can identify the technologic capabilities of different ventilators for both purchasing decisions[13] and clinical application. Indeed, having identified the modes themselves, practitioners can then compare their specific features to determine which modes best meet the clinical goals of MV for a particular patient at a particular time. Thus three basic skills (mode classification, goal selection, and mode selection) make up a rational framework for mastering the art and science of MV.[9]

TEN MAXIMS FOR UNDERSTANDING MODES OF CONVENTIONAL VENTILATION

This section defines basic terms related to MV in general, with specific applications to neonatal ventilation highlighted. To explain these terms in context, the chapter describes 10 basic technologic concepts (maxims) that underlie all modes of ventilation. Taken together, they make up a classification system applicable to any mode on any ventilator.

1. Defining a Breath

A breath is defined as one cycle of positive flow (inflation) and negative flow (expiration) in terms of the flow-time curve (Figure 17-3).

2. Defining an Assisted Breath

A breath is assisted if the ventilator inflation provides some or all of the work of breathing. Graphically, this corresponds to airway pressure increasing above baseline during inspiration.

3. Assistance With Volume or Pressure Control

A ventilator assists breathing using either pressure control or volume control based on the equation of motion for the respiratory system. A simplified version,

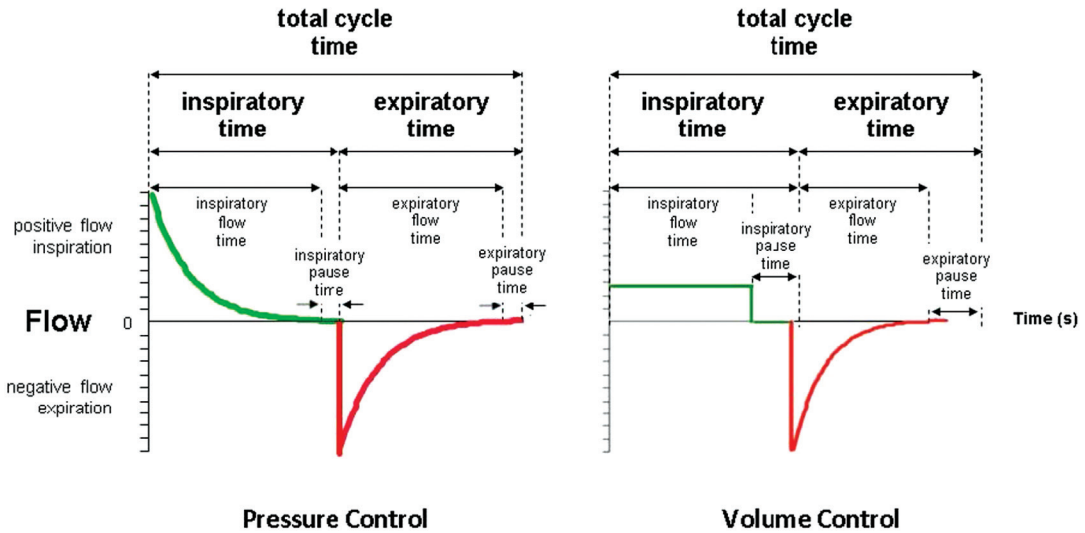


FIGURE 17-3 A ventilator cycle is defined in terms of the flow-time curve. Important timing parameters related to ventilator settings are labeled. (Reproduced with permission from Mandu Press, Ltd.)

assuming passive inspiration and no auto-PEEP (incomplete expiration prior to the initiation of the next breath causes progressive air trapping), is as follows:

$$P(t) = EV(t) + R\dot{V}(t)$$

This equation relates pressure *(P, above PEEP)*, tidal volume *(V)*, and flow in the ETT ($\dot{V}$) as continuous functions of time *(t)* with the parameters of elastance *(E)* and resistance *(R)*. If any one of the functions (*P, V,* or $\dot{V}$) is predetermined, the other two may be derived. Auto-PEEP is the pressure associated with the gas trapped in the lungs during expiration at the time when the next breath begins.

The term *control variable* refers to what is predetermined or preset during a ventilator cycle. The concept of a control variable provides a means to divide all modes of ventilation into three main groups.

Volume control (VC) means that *both* tidal volume and inspiratory flow (variables on the right-hand side of the equation) are preset. In journal articles on neonatal and pediatric MV, you will often see the following terms used interchangeably to mean VC: "volume targeted," "volume limited," and "volume preset." **Pressure control (PC) ventilation** means that inflation pressure (the variable on the left-hand side of the equation) is preset. In practice, this means one of two things: either (1) the peak inflation pressure is preset (i.e., airway pressure rises to some target value and remains there until inflation time is complete) or (2) inflation pressure is controlled by the ventilator so that it is proportional to the patient's inspiratory effort. Journal articles on neonatal and pediatric MV often use the following terms interchangeably to mean pressure control: "pressure controlled," "pressure limited," and "pressure preset."

Time control (TC) is a general category of ventilator modes for which flow, volume, and pressure are all dependent on respiratory system mechanics. Because no parameters of the pressure, volume, or flow waveforms are preset, the only control of the cycle is the timing. Examples of this are HFOV (Vyaire 3100 ventilator) and volumetric diffusive respiration (Percussionaire ventilator). Characteristic waveforms for VC and PC are shown in Figure 17-5.

4. Trigger and Cycle Events

Breaths delivered by a ventilator are classified according to the criteria that **trigger** (start) and cycle (stop) an inflation. The most basic trigger variable during MV is time, as in the case of a preset inflation frequency (the period between inflations is 1/f). Other trigger variables include a preset apnea interval and various indicators of inspiratory effort (e.g., changes in baseline pressure or flow, or electrical signals derived from diaphragm movement). The most common cycle variable is a preset inflation time (time-cycled ventilation). Other cycle variables include pressure (e.g., peak airway pressure), volume (volume-cycled), flow (e.g., percent of peak inflation flow; flow-cycled), and electrical signals derived from diaphragm movement.

5. Machine Versus Patient Trigger and Cycle Events

Trigger and cycle events can be either patient or ventilator initiated. Inflation can be patient-triggered or patient-cycled by a signal representing inspiratory effort (e.g., changes in baseline airway pressure, changes in baseline bias flow, or the electrical signal derived from diaphragm activity, as with neurally adjusted ventilatory assist [NAVA]).[14,15]

Patient triggering means starting inflation based on a patient signal independent of a ventilator-generated trigger signal. Proper triggering can reduce work of breathing, allows the patient to be more comfortable, reduces oxygen consumption, and can result in a shorter duration of ventilation.[16] There are three common trigger variables used in neonatal and pediatric ventilation: flow, pressure, and electrical activity of the diaphragm (NAVA). Flow triggering is the one most commonly used in the neonatal patient population, but NAVA is gaining popularity at present because its sensitivity is not degraded by leaks (e.g., around an uncuffed ETT).

To accomplish flow triggering, a flow sensor can be placed at the airway opening to sense inspiratory effort by measuring inspiratory flow. There are two basic types of flow sensors used with ventilators. One is called a *pneumotachometer.* It has a flow-resistive element such as a screen or plastic flap in the flow path. The pressure on both sides of the resistor is conducted to pressure sensors in the ventilator through small-diameter tubing. The difference between the two pressures is proportional to flow. The second type of flow sensor is called a *hot wire anemometer.* Very thin wires are placed in the flow path and heated. The flow carries away the heat. Therefore, the amount of energy required to maintain the heat in the wires is proportional to flow. Flow sensors add dead space to the airway, and the potential increase in tidal volume associated with synchronized intermittent mandatory ventilation (SIMV) may be negated by an increase in carbon dioxide retention. Flow sensors may also be affected by secretions and require frequent cleaning. Flow sensing and triggering can also be done with the internal ventilator flow sensor and can be sensitive enough for most patients. With these improvements in making the ventilator more receptive to patient effort, problems associated with secretions, condensation, system or patient leaks, and active cardiac pulsation could lead to erroneous triggering of the ventilator (autocycling) (Table 17-1).

To accomplish pressure triggering, a pressure sensor is used to measure a drop in pressure in the ventilator circuit resulting from an inspiratory effort. For the pressure in the circuit to drop to less than the trigger threshold, (determined by the sensitivity setting), approximately

Table 17-1 Synchronizing Systems for Mechanical Ventilators

TYPE	SOURCE	ADVANTAGES AND DISADVANTAGES
Flow sensor	Pneumotachometer (heated wire, variable orifice, differential pressure)	Fast response; provides volume measurement; adds dead space; affected by secretions
Pressure sensor	Proximal airway, ventilator demand valve	No dead space; requires good patient effort; low transit time
Electrical activity of the diaphragm (EAdi)	Nasogastric tube with electrodes that determine the electrical activity of the diaphragm	No dead space; unaffected by secretions, auto-PEEP, and leaks; requires catheter (invasive); no volume measurement

2 mL of volume must be displaced from the circuit. This often accounts for a large portion of neonatal tidal volume and thus is not well tolerated. Thus a low-birthweight infant may not consistently produce the level of effort necessary to trigger the ventilator. Furthermore, for pressure triggering, the response time tends to be slow because of a delay from the progression of the pressure drop through the ventilator tubing (at the speed of sound). Because of this, synchronization is difficult to achieve at patient trigger rates greater than 35 to 40 breaths per minute.

NAVA uses a nasogastric tube with specialized sensors that obtain signals from the electrical activity of the diaphragm (EAdi) to control the timing and pressure of the ventilation delivered. In theory, this form of triggering and support is particularly useful for patients with gas trapping and auto-PEEP who have high work of breathing as a result of triggering. Furthermore, this form of triggering is not affected by leaks and secretions; therefore, autocycling and hypocapnia in newborns can be eliminated. However, this modality is invasive, and placement of the nasogastric tube could be initially uncomfortable for the patient, though it may lead to increased synchrony and earlier liberation.

Case Study 2

You are called by your nursing colleague to assess a patient requiring MV who does not appear to be comfortable just before sedation. Your initial assessment reveals that the child does not appear to be triggering the ventilator. What steps would you take to solve this problem?

See Evolve Resources for answers.

Ventilator triggering means starting inflation based on a signal (usually time) from the ventilator, independent of a patient trigger signal.

Patient cycling means ending the inflation based on signals representing the patient-determined components of the equation of motion (i.e., elastance or resistance and including effects related to inspiratory effort). Note that flow cycling (as used in the mode called *pressure support*) is a form of patient cycling, because the rate of flow decay to the cycle threshold, and hence the inflation time, is determined by patient mechanics (i.e., the time constant and effort).

Ventilator cycling means ending inflation independent of signals representing the patient-determined components of the equation of motion.

6. Spontaneous Versus Mandatory Breaths

Breaths are classified as spontaneous or mandatory based on their trigger and cycle events. A spontaneous breath is one in which the patient retains substantial control over timing (frequency and inspiratory time). It may or may not be assisted by the ventilator. Thus, in terms of trigger and cycle events, a spontaneous breath is one in which inspiration is both triggered and cycled by the patient. Anything else is a mandatory breath.

A mandatory breath is one during which the patient has lost some control over timing. That means inspiration is either triggered or cycled by the ventilator (or both) independent of patient breathing efforts. By definition, a mandatory breath is an assisted breath.

7. Breath Sequences

There are only three possible sequences of mandatory or spontaneous breaths: continuous mandatory ventilation (CMV), intermittent mandatory ventilation (IMV), and continuous spontaneous ventilation (CSV). CMV is commonly known as **"assist/control" (AC) ventilation,** and every inspiratory effort triggers a mandatory breath; For intermittent breaths the mandatory breaths may or may not be triggered by the patient; thus we have IMV (time triggered) or SIMV (patient triggered). In CSV, mandatory breaths are not provided. The breath sequence that is offered is continuous positive airway pressure (CPAP) when no pressure support is set or pressure support (PSV) (Figure 17-4) when the patient triggers the ventilator (spontaneous effort).

8. Ventilatory Patterns

A ventilatory pattern is a control variable paired with a breath sequence. Thus, with two main control variables (ignoring TC for simplicity) and three breath sequences, there are five major ventilatory patterns: VC-CMV (commonly known as *VC-AC*), VC-IMV, PC-CMV (commonly known as *PC-AC*), PC-IMV, and PC-CSV. In principle, the combination VC-CSV is not possible, because volume control implies a preset tidal volume, which implies machine cycling, and machine

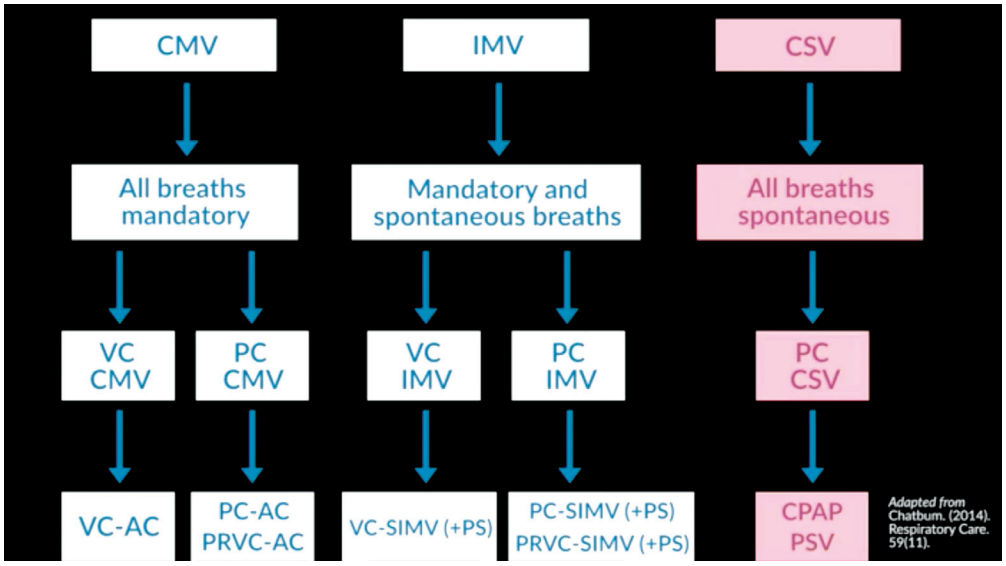


FIGURE 17-4 There are only three possible sequences of mandatory or spontaneous breaths: continuous mandatory ventilation *(CMV),* intermittent mandatory ventilation *(IMV),* and continuous spontaneous ventilation *(CSV). AC,* Assist/control; *CPAP,* continuous positive airway pressure; *PC,* pressure control; *PRVC,* pressure regulated volume control; *PS, PSV,* pressure support ventilation; *SIMV,* synchronized intermittent mandatory ventilation; *VC,* volume control. (Adapted from Robert L Chatburn et al: A Taxonomy for Mechanical Ventilation: 10 Fundamental Maxims. *Respiratory Care* Nov 2014, 59 (11) 1747-1763; DOI:10.4187/respcare.03057.)

cycling makes every inflation mandatory, not spontaneous (see Maxim 6).

9. Targeting Schemes

Within each ventilatory pattern there are several types that can be distinguished by their targeting schemes. A targeting scheme is a model of the relationship between operator inputs and ventilator outputs to achieve a specific ventilatory pattern, usually in the form of a feedback control system.[17] Targets can be set for parameters during a breath (within-breath targets). These parameters relate to the pressure, volume, and flow waveforms (Figure 17-5). Examples of such targets include peak inspiratory flow and tidal volume

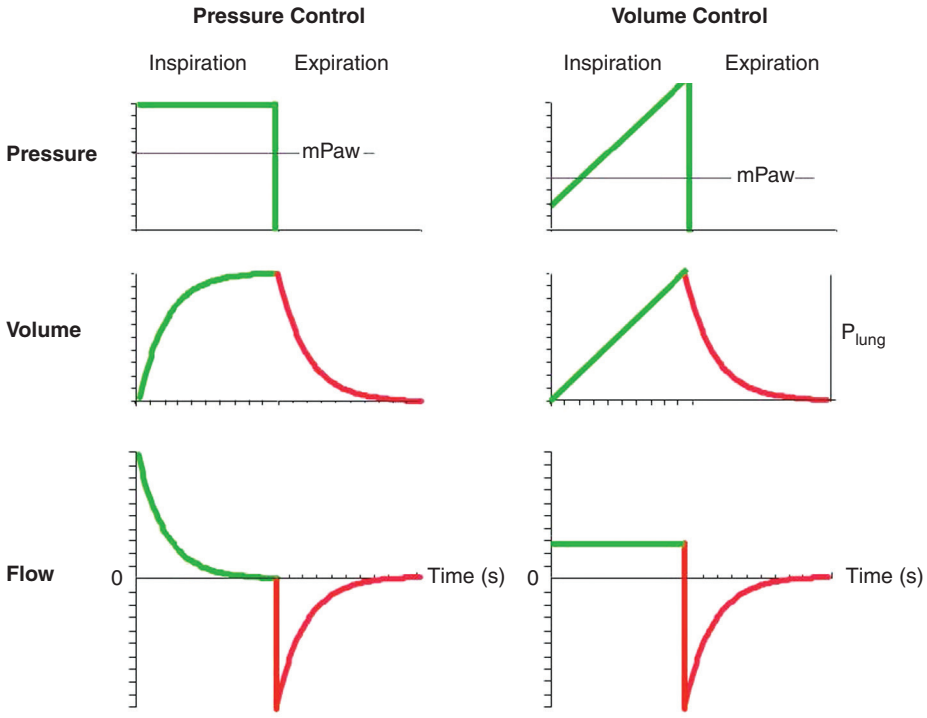


FIGURE 17-5 Characteristic waveforms for volume control and pressure control. Note that mean airway pressure (mPaw) is less for volume control than for pressure control given the same tidal volume and inspiratory time. (Reproduced with permission from Mandu Press, Ltd.)

or inspiratory pressure and rise time (i.e., slope of the pressure wave [set-point targeting], pressure, volume, and flow [dual targeting]) and constant of proportionality between inflation pressure and patient effort (servo targeting), as in proportional assist ventilation (PAV)[18] and NAVA. [19]

Targets can be set to operate over a range of breaths (between-breath targets) to modify the within-breath targets and the overall ventilatory pattern. In neonatal ventilation, the between-breath target is typically tidal volume (for pressure control using adaptive targeting). For pediatric and adult ventilation, between-breath targets include work rate of breathing and minute ventilation (for optimal targeting) and combined end tidal Pco_2, tidal volume, and frequency values describing a "zone of comfort" (for intelligent targeting, such as SmartCarePS or IntelliVent-ASV).

The targeting scheme (or combination of targeting schemes) is what distinguishes one ventilatory pattern from another. There are currently seven basic targeting schemes that account for the wide variety seen in different modes of ventilation (Box 17-3).

Box 17-3 Seven Basic Targeting Schemes

Set-point: A targeting scheme where the operator sets all the parameters of the pressure waveform (pressure control modes) or volume and flow waveforms (volume control modes). The ventilator does not adjust any targets automatically.

Dual: A targeting scheme that allows the ventilator to switch between volume control and pressure control *during a single inspiration* (not currently used for neonatal ventilation).

Biovariable: A targeting scheme that allows the ventilator to automatically set the inspiratory pressure (or tidal volume) randomly to mimic the variability observed during normal breathing (not currently used for neonatal ventilation).

Servo: A targeting scheme in which the output of the ventilator (e.g., inspiratory pressure) automatically follows a varying input (e.g., inspiratory effort). Current examples for neonatal and pediatric ventilation are NAVA and PAV.

Adaptive: A targeting scheme that allows the ventilator to automatically set one target (e.g., pressure within an inspiration) to achieve another target (e.g., tidal volume). Modes that use pressure control with adaptive targeting are often referred to in the literature as "volume targeted" or "volume guarantee" modes.

Optimal: A targeting scheme that automatically adjusts the targets of the ventilatory pattern to either minimize or maximize some overall performance characteristic (e.g., work rate of breathing; not currently used for neonatal ventilation but applicable to pediatric patients).

Intelligent: A targeting scheme that automatically adjusts the targets of the ventilatory pattern using artificial intelligence programs such as fuzzy logic, rule-based expert systems, and artificial neural networks (not currently used for neonatal ventilation but applicable to pediatric patients).

10. Mode Classification

A mode of ventilation is classified according to its control variable, breath sequence, and targeting scheme(s). Thus, the ventilator mode taxonomy has four hierarchical levels:

Control variable (pressure or volume, for the primary breaths)
Breath sequence (CMV, IMV, or CSV)
Primary targeting scheme (for CMV or CSV)
Secondary targeting scheme (for IMV)

The "primary breath" is either the only breath type (mandatory breaths for CMV and spontaneous breaths for CSV) or the mandatory breath (for IMV). We consider it primary because if the patient becomes apneic, it is the only factor keeping the patient alive. The targeting schemes can be represented by single lowercase letters: set-point, s; dual, d; servo, r; bio-variable, b; adaptive, a; optimal, o; intelligent, i.

Translating the name of a mode into a mode classification using the taxonomy is a simple three-step procedure:

Step 1: Identify the primary control variable. If the inspiratory pressure is preset or if pressure is proportional to inspiratory effort, then the control variable is pressure. On the contrary, if the operator sets *both* tidal volume *and* flow, then the control variable is volume. (If only one of these is preset, then the control variable is pressure.)

Step 2: Identify the breath sequence.

Step 3: Identify the targeting schemes for the primary and (if applicable) secondary breaths.

For example, the mode commonly called *time cycled pressure limited* in the neonatal literature is classified as follows: (1) inspiratory pressure is preset, so the control variable is pressure; (2) inspiratory time is preset, indicating machine cycling and thus the presence of mandatory breaths, plus allowance for spontaneous breaths between mandatory breaths, indicating the sequence is IMV; (3) all targets are operator preset, so the targeting scheme is set-point. Hence the "tag" (classification abbreviation) for this mode is PC-IMVs. In contrast, for a mode called *volume support,* the operator sets a target tidal volume, but flow is not preset; hence the control variable is pressure. Every inspiration is both patient-triggered (pressure or flow) and patient-cycled (% of peak flow), hence the breath sequence is CSV. Finally, the ventilator automatically adjusts the inspiratory pressure between breaths to achieve (on average) the operator set target expired tidal volume. Hence the classification would be PC-CSVa.

MANAGING VENTILATOR SETTINGS

CONVENTIONAL VENTILATION

Clinical protocols guiding decisions to implement MV techniques should be in place in each institution before these devices are used. Personnel involved in patient

management must demonstrate proficiency in the use of the device and clinical expertise to ensure patient safety. Active training programs within each institution should be mandatory and include a demonstration by personnel that they understand ventilator controls and circuit design, basic troubleshooting, and management strategies. Before the initiation of MV, each device and circuit should be inspected to ensure proper calibration and function. Specific care should be taken to ensure that (1) proper gas temperature and humidity are present, (2) ventilator and circuit position is such that a smooth transition can occur, and (3) initial settings are lower than anticipated requirements to allow a slow increase toward desired levels and prevent inadvertent injury. Finally, other appropriate primary therapies (e.g., surfactant replacement for surfactant deficiency and vasopressor support for impaired myocardial function) and good pulmonary toilet should be optimized along with ventilatory management.

Proper management of ventilator settings requires monitoring of noninvasive metrics arterial blood gases, chest radiographs, and ventilator waveforms along with physical assessment of the patient.

Indications for Mechanical Ventilation

As mentioned earlier, there are three general goals for MV: safety, comfort, and liberation. In contrast, indications for MV are specific signs and symptoms observed during the course of patient assessment that suggest that a machine is needed to ensure that the general goals of safety and comfort are maintained. Because of the wide range of clinical conditions, weights, and gestational ages of neonatal patients, no simple formula exists to define indications for intubation and MV. In general, reasonable indications include inadequate or absent respiratory effort, clinical signs of impending respiratory failure, a high and rising Pco_2 level, persistent high oxygen requirement (Fio_2 greater than 0.40-0.60), and excessive work of breathing despite optimized noninvasive support (see Box 17-1). Specific pulmonary disorders that may lead to ventilatory support are shown in Table 17-2.

Table 17-2 Common Situations in Which Mechanical Ventilation Is Used and Key Considerations in Choosing Initial Support

SITUATION	EXAMPLE	PREDOMINANT PATHOPHYSIOLOGIC DISTURBANCE	SUGGESTED PEEP	V_T RANGE	CONSIDERATIONS REGARDING VENTILATOR MODE AND SETTINGS
Apnea	Preterm infant with apnea of prematurity Respiratory depression for any reason (e.g., medications, central nervous system)	Poor respiratory drive, relatively normal lung function	4-5 cm H_2O	4-6 mL/kg for neonate 6-8 mL/kg for pediatric	Should need only minimal ventilator support. Lungs often relatively compliant; care must be taken to avoid lung injury, excessive V_T.
Lung Disease					
Diffuse alveolar disease	Preterm infant with respiratory distress syndrome Pediatric acute respiratory distress syndrome	Low lung compliance, compliant chest wall, microatelectasis, ventilation/perfusion mismatch, very prone to ventilator-associated lung injury	6-8 cm H_2O, to start, may be higher	4-6 mL/kg	Recruitment using positive end-expiratory pressure (PEEP) with conventional ventilation (CV) or mean airway pressure increments with high-frequency oscillatory ventilation (HFOV). Short T_I and fast rate are well tolerated. Optimizing lung inflation and avoiding volutrauma are key considerations.
	Term or preterm infant with hemorrhagic pulmonary edema	Poor lung compliance, surfactant inactivation, pulmonary edema, fluid in the airways	8-10 cm H_2O during acute event	4-6 mL/kg	Acutely increase PEEP and peak inspiratory pressure (PIP) to tamponade edema fluid. Recruitment using PEEP increments and fixed V_T may be helpful. Longer T_I needed to help recruitment.

Continued

Table 17-2 Common Situations in Which Mechanical Ventilation Is Used and Key Considerations in Choosing Initial Support—cont'd

SITUATION	EXAMPLE	PREDOMINANT PATHOPHYSIOLOGIC DISTURBANCE	SUGGESTED PEEP	V_T RANGE	CONSIDERATIONS REGARDING VENTILATOR MODE AND SETTINGS
Obstructive and/or heterogeneous disease	Term infant with meconium aspiration syndrome Cystic fibrosis (CF) and bronchopulmonary dysplasia (BPD)	High airway resistance, low compliance, heterogeneous inflation, prolonged time constants	4-6 cm H_2O	5-8 mL/kg	Potential for overdistention of relatively normal lung regions. Need for lower ventilator rate to avoid air trapping. Higher V_T/kg is needed owing to increased alveolar dead space.
Pulmonary hypoplasia	Preterm infant born after prolonged oligohydramnios Term infant with congenital diaphragmatic hernia	Low lung compliance related to small total lung volume. Prone; prone to overdistention, air leak, and pulmonary hypertension	4-6 cm H_2O	4-5 mL/kg	Avoid high V_T and PIP, avoid overexpansion. Consider high-frequency ventilation if PIP >25 cm H_2O or if there is refractory hypoxic respiratory failure.
Air leak	Preterm infant with pulmonary interstitial emphysema	Compression of normal airspaces by interstitial gas, poor compliance, high airway resistance	4-6 cm H_2O	3-5 mL/kg	Accept higher P_{CO_2}, avoid large V_T, maintain lung volume with moderate PEEP. Low PEEP leads to atelectasis, resulting in a need for higher PIP. Selective single bronchus intubation if unilateral. High-frequency ventilation (especially high-frequency jet ventilation [HFJV]) is preferable.
	Pneumothorax	Continued leak of gas into the pleural space			
Pulmonary arterial hypertension	Pulmonary hypertension with parenchymal lung disease	Reduced pulmonary blood flow secondary to increased pulmonary vascular resistance superimposed on underlying lung disease	6-8 cm H_2O	4-6 mL/kg	V_T and PEEP requirements depend on associated parenchymal disease. Optimize lung inflation, correct acidosis, avoid overexpansion, avoid lung injury.
Pulmonary arterial hypertension	Persistent pulmonary hypertension of the neonate with normal lung parenchyma	Reduced pulmonary blood flow secondary to increased pulmonary vascular resistance; pulmonary vascular remodeling	4-5 cm H_2O	5-8 mL/kg	Avoid overexpansion, excessive V_T. Avoid increasing airway pressure to improve oxygenation. Early use of inhaled nitric oxide may be beneficial.
	Severe chronic lung disease (e.g., BPD, CF)	Reduced pulmonary vascular bed, pulmonary vascular remodeling, increased pulmonary vasoreactivity	6-8 cm H_2O	6-8 mL/kg	Optimize treatment of chronic lung disease, maintain higher SpO_2 of 94%-98%. Consider long-term pulmonary vasodilator therapy.

Table 17-2 Common Situations in Which Mechanical Ventilation Is Used and Key Considerations in Choosing Initial Support—cont'd

SITUATION	EXAMPLE	PREDOMINANT PATHOPHYSIOLOGIC DISTURBANCE	SUGGESTED PEEP	V_T RANGE	CONSIDERATIONS REGARDING VENTILATOR MODE AND SETTINGS
Severe chronic lung disease (e.g., BPD)	Former preterm infant with established chronic lung disease	Multicompartmental lung with regions of low compliance and increased resistance, poorly supported airways prone to collapse; decreased alveolarization with less gas-exchanging surface and fewer pulmonary capillaries; increased pulmonary vascular resistance	6-10 cm H_2O, sometimes higher	6-8 mL/kg, sometimes higher	Slow rate, longer T_I and T_E to allow ventilation of the diseased lung regions with long time constants. Sufficient PEEP is needed to prevent expiratory flow limitation at low lung volumes. Larger V_T is needed because of increased alveolar and anatomic dead space.
Cardiac Disease					
Left to right shunts	Preterm infant with patent ductus arteriosus Term infant with large ventricular septal defect	Pulmonary overcirculation with decreased lung compliance from pulmonary engorgement and edema	5-8 cm H_2O	5-6 mL/kg	High PEEP mitigates left to right shunt. Increasing CO_2 can help limit blood flow to some degree.
Vulnerable pulmonary circulation	Pulmonary atresia with duct-dependent pulmonary circulation Hypoplastic left heart syndrome	Pulmonary blood flow highly variable and under the influence of intraalveolar pressure	3-5 cm H_2O	5-7 mL/kg	Lung overdistention with high pressure settings will impede pulmonary blood flow. Manipulation of P_{CO_2} can help to control pulmonary blood flow: lower CO_2 to encourage blood flow, increase CO_2 to restrict blood flow.
Neuromuscular disease	Term infant with myopathy Muscular dystrophy Muscle weakness from chronic illness	Poor muscle strength, low functional residual capacity (FRC) and V_T secondary to compromised respiratory muscle function	3-5 cm H_2O	5-7 mL/kg	Support for each spontaneous breath is optimal for those diseases that will progress. Managing ventilation to an F_{IO_2} of 0.21 is optimal. Sprint weaning may be required for those with recoverable muscle function.
Airway Obstruction					
Large airway obstruction	Tracheobronchomalacia	Increased airway obstruction with crying or increased respiratory effort related to airway collapse	6-10 cm H_2O	5-8 mL/kg	Titrate PEEP upward until obstruction is relieved by splinting airway open.

Continued

Table 17-2 Common Situations in Which Mechanical Ventilation Is Used and Key Considerations in Choosing Initial Support—cont'd

SITUATION	EXAMPLE	PREDOMINANT PATHOPHYSIOLOGIC DISTURBANCE	SUGGESTED PEEP	V_T RANGE	CONSIDERATIONS REGARDING VENTILATOR MODE AND SETTINGS
Small airway obstruction	Former preterm infant with BPD Severe asthmatic requiring mechanical ventilation	Inflammation, secretions, smooth muscle hypertrophy lead to mostly fixed airway obstruction; there may be a variable bronchospastic component; prolongation of T_E and gas trapping; expiratory flow limitation at low lung volumes	6-8 cm H_2O, sometimes higher	4-6 mL/kg	Slower rate, longer T_I and T_E to accommodate long time constants. Titrate PEEP upward until obstruction is relieved by splinting airway open. Antiinflammatory agents and bronchodilators may be of value in BPD. Antiinflammatory agents and bronchodilators are the standard of care in asthma.
Postoperative Support					
General aspects	Painful surgical incision that may prevent deep breathing and coughing	Suppression of respiratory drive because of sedation; limitation of respiratory excursion because of pain	4-6 cm H_2O	5-7 mL/kg	Heavy sedation may predispose to atelectasis by suppressing sighs. Adequate PEEP and set rate needed, as they may not breathe above set rate or trigger adequately.
Abdominal surgery	Term infant with gastroschisis repair Preterm infant s/p laparotomy for necrotizing enterocolitis Abdominal trauma Congenital diaphragmatic hernia	Raised intra-abdominal pressure and diaphragmatic splinting	6-8 cm H_2O	5-7 mL/kg for term and older 4-6 mL/kg for preterm	High PEEP needed to maintain EELV and recruitment but may compromise venous return if lung compliance is normal. Adequate V_T may be difficult to achieve without very high PIP. HFOV or HFJV preferred.

Initial Mode

Although seldom used in its entirety, there is a specific rational approach to selecting the initial mode of ventilation.[9] The basic idea is as follows:

1. Assess the patient and identify the general goal of ventilation (e.g., safety).
2. Clarify the specific objective(s), such as to optimize the ventilation/perfusion relationship of the lungs (as opposed to, for example, optimizing the pressure/volume curve).
3. Formulate a clinical aim, such as to maintain a stable $Paco_2$ in the face of changing respiratory system mechanics.
4. Review your ventilator mode inventory and identify any technical capabilities that might serve the goal, within the scope of the objective and clinical aim. Some modes have only one capability and others have many, serving all three goals. The idea is to select the mode that has the most capabilities to serve the patient's needs. For this example, the clinician might choose the pressure-regulated volume control (PRVC) mode on a Maquet Servo-U (Getinge Group, Wayne, NJ) ventilator.

Of course, to implement this approach, several prerequisites must be met:

1. The individual selecting the mode must be familiar with the taxonomy of modes to recognize and distinguish modes on available ventilators. For example, if the clinician is familiar with PRVC on one ventilator but does not recognize that this is the same as a mode called *VC+* on another ventilator, an important patient care opportunity may be missed. The taxonomy helps by classifying both modes as PC-CMVa. At a bare minimum for

ventilation in children, one must understand and recognize the modes classified as simple volume control (VC-CMVs, VC-IMVs,s, and), simple pressure control (PC-CMVs, PC-IMVs,s, and PC-CSVs), pressure-targeted volume control, and volume guarantee (PC-CMVa and PC-IMVa,s or PC-CSVa). A complete review of all modes on all ventilators used in the United States using the taxonomy is available.[20]

2. All personnel responsible for managing the ventilator (e.g., respiratory therapists) must be familiar with using the mode. Otherwise, the ordering clinician will eventually be presented with the complaint that "the mode did not work for the patient."
3. The patient must be continually reassessed and goals changed as appropriate, possibly requiring a change in modes.

All that said, the most popular mode for neonates is PC-IMVs,s, just as it was more than 35 years ago (recognizing that mandatory breaths can now be easily synchronized with inspiratory efforts, SIMV), despite evidence that more technologically capable modes may be associated with lower mortality.[7] To be fair, however, PC-CMVa has been studied in children much more than in adults and has been shown to reduce death and chronic lung disease compared with ventilation of infants using conventional pressure control modes.[21] Similarly, NAVA seems to have been used and studied more in infants than adults.[22] This is perhaps easier to understand knowing that triggering and cycling with the electrical signal from the diaphragm is immune to leaks that often cripple pressure- and flow-triggered modes.

Table 17-3 shows commonly used initial conventional ventilator settings suggested for different patient sizes; however, certain conditions or severity of disease may require a different initial approach.

HIGH-FREQUENCY VENTILATION

Until recently, HFV use was limited to patients in whom CMV was failing. The literature and experience with neonates through adults are changing this impression, so that HFV is increasingly being used before rescue situations develop. These developments are changing current protocols for moving patients from CMV to HFV. Because of this, it is necessary to focus on the concepts that need to be considered when applying HFV to patients, rather than describing specific ventilator settings. The evolving literature and device-specific manufacturers' recommendations should be consulted for more details.[23] Successful application of any HFV device requires accurate comprehension of individual patient pulmonary pathophysiology and selection of an appropriate ventilatory strategy. At present, there are two fundamentally different strategies that are designed for contrasting pulmonary pathophysiologic processes.

Each HFV device was initially developed for specific lung disease states. Because of ethical, scientific, and legal constraints, use in human infants was at first confined to rescuing patients in whom conventional methods were failing.[12] With increasing anecdotal success noted by several groups, it became apparent that strategies applied to these infants were unique to each device. Subsequently, refinements in patient management led to tailoring device design, with a resultant narrowing of the spectrum of lung diseases to which they could be applied. For example, HFJV was directed toward air leak syndromes and HFOV toward diffuse alveolar disease.[10] Studies have now shown that recruitment of the atelectasis-prone lung can be accomplished with different HFV types with similar success in gas exchange,[24] histologic evidence of uniform gas distribution, and decreased hyaline membrane formation.

Table 17-3 Initial Mechanical Ventilator Settings

	PREMATURE INFANT	INFANT	TODDLER OR CHILD	LARGE CHILD OR ADOLESCENT
Weight (ideal) (kg)	<2	2-10	10-40	>40
Respiratory rate (breaths/minute)	30-50	25-40	15-25	12-20
V_T (mL/kg) mandatory	4-6	5-6	6-8	
Peak inspiratory pressure (PIP) mandatory (cm H_2O)	18-25; adjust to achieve target V_T above			
Inspiratory time (s)	0.25-0.4	0.4-0.5	0.5-0.8	0.8-1.2
PEEP (cm H_2O)	3-5	5-7		
FiO_2	Start 10% higher than preintubation FiO_2 or 1.0 unless contraindicated			
Trigger (L/minute)	0.25-0.50		1.0-2.0	
Pressure support level (cm H_2O)	Minimum level: 6-10 cm H2O; adjust to achieve a targeted V_T of generally 5-7 mL/Kg			
Pressure support flow cycle threshold cycle	10%-25% of peak inspiratory flow rate			

Although HFOV has been used to support patients of all ages with respiratory failure for many years, data remain mixed, for both efficacy and mortality. Neonates have the longest standing use of HFOV, and data in this age group most consistently demonstrate improvements in oxygenation and long-term outcomes. In patients of all ages, the general trend has been toward lung-protective ventilation with CMV and use of HFOV primarily as rescue therapy.[25]

Management Strategies

High-volume strategy. For a patient with an atelectasis-prone lung (e.g., natural or acquired surfactant deficiency), the primary therapeutic goal is to optimize lung inflation to minimize ventilation–perfusion mismatching while reducing inflation–deflation breathing patterns that initiate a cascade of events leading to lung tissue injury. This has been termed the *high-volume strategy.* Two separate means of achieving this goal have evolved.

One method is to increase mean airway pressure (mPaw) in small increments (1 to 2 cm H_2O) while watching for improvements in oxygenation (arterial blood gas determination, transcutaneous carbon dioxide, or pulse oximetry saturation) and mean lung volume (MLV) determined by chest radiograph. Mean airway pressure is increased until oxygenation improves significantly or until MLV reaches desired levels, or both, which may be determined by the presence of a well-inflated lung on a radiograph (Figure 17-6). While using this method, care must be taken to anticipate silent lung recruitment and to reduce mPaw as appropriate to prevent serious impairment to venous return and reduction in cardiac output. Silent lung recruitment is gradual lung inflation taking place with static mPaw settings. Clinical clues heralding this include rapid improvements with subsequent unexplained decrements in oxygenation, decreasing $Paco_2$ without changes in oscillatory amplitude (improving compliance), and, finally, clinical changes in perfusion. These problems often can be avoided with diligence and anticipation. Silent recruitment, although more common during initial HFV management, can occur any time attempts are made to optimize MLV. Data confirm the pulmonary, central nervous system, and cardiovascular safety and efficacy of this technique.

The other approach to recruiting the collapsed lung is the use of sustained inflation (SI)—that is, applying plateau pressures at levels in excess of expected alveolar opening pressures for periods of 5 to 30 seconds. This technique should result in incremental improvement in oxygenation if pressure levels are adequate. Furthermore, because of lung hysteresis, mPaw can often be reduced to levels slightly less than can be achieved with the other lung inflation method. SIs are usually repeated until no change in oxygenation is noted or until oxygenation decreases. Both imply that the lung is at the upper limits of capacity. The need for repeat SI maneuvers is determined by the level of mPaw used and the amount of subsequent alveolar derecruitment. The SI method may achieve optimal MLV more rapidly and, because of the lower mPaw, avoid silent recruitment. However, potential disadvantages include the risk of using too little pressure (minimal recruitment) or too much pressure (airway injury, air leak, and reduction in cardiac output). There may be a difference in the response of surfactant-sufficient collapsed lungs and uninjured surfactant-deficient lungs (i.e., preterm neonate vs full-term neonate or pediatric patient). This method has been used successfully in infants with minimal complications. Definitive superiority of one technique over the other has not been demonstrated.

Note the difference between CMV and HFV. With CMV, lung recruitment is achieved by increasing inspiratory time and pressure, PEEP, with mean airway pressure being increased indirectly. In contrast, HFV uses direct control of $mP\overline{AW}$ alone to achieve lung recruitment. Supplying adequate oscillatory amplitude around the baseline mPaw provides ventilation during HFPV and HFOV. With HFJV, ventilation is determined by changes in jet-pulse tidal volume delivery and by the amount of background CV used. It is critical to avoid the temptation to use HFV phasic pressure to recruit underinflated lung units.

Low-volume strategy. In contrast to the lung inflation strategies described, management of infants with PIE, pneumothorax, or air trapping requires the use of alternative strategies, because attempts to achieve optimal mean lung volume (MLV) in these patients will exaggerate existing lung overinflation or further damage the injured lung. Here the primary objective should be to offer a ventilatory strategy that allows the lung to slowly deflate, or one that minimizes ongoing air leakage while providing tolerable ventilation and accepting higher Fio_2. This is accomplished with all HFV systems by using a lower mPaw than that creating the problem. (These patients are usually undergoing CV before being switched to HFV.) This allows the lung to derecruit and isolates damaged areas from inflation pressure. The consequence of this, however, is the frequent requirement for a higher Fio_2. In addition, tidal volume delivery must be decreased to further reduce tidal volume exposure while using I/E ratios and ventilatory frequencies that maximize gas egress. A $Paco_2$ between 50 and 60 mm Hg is often tolerated in these patients as long as the arterial pH exceeds

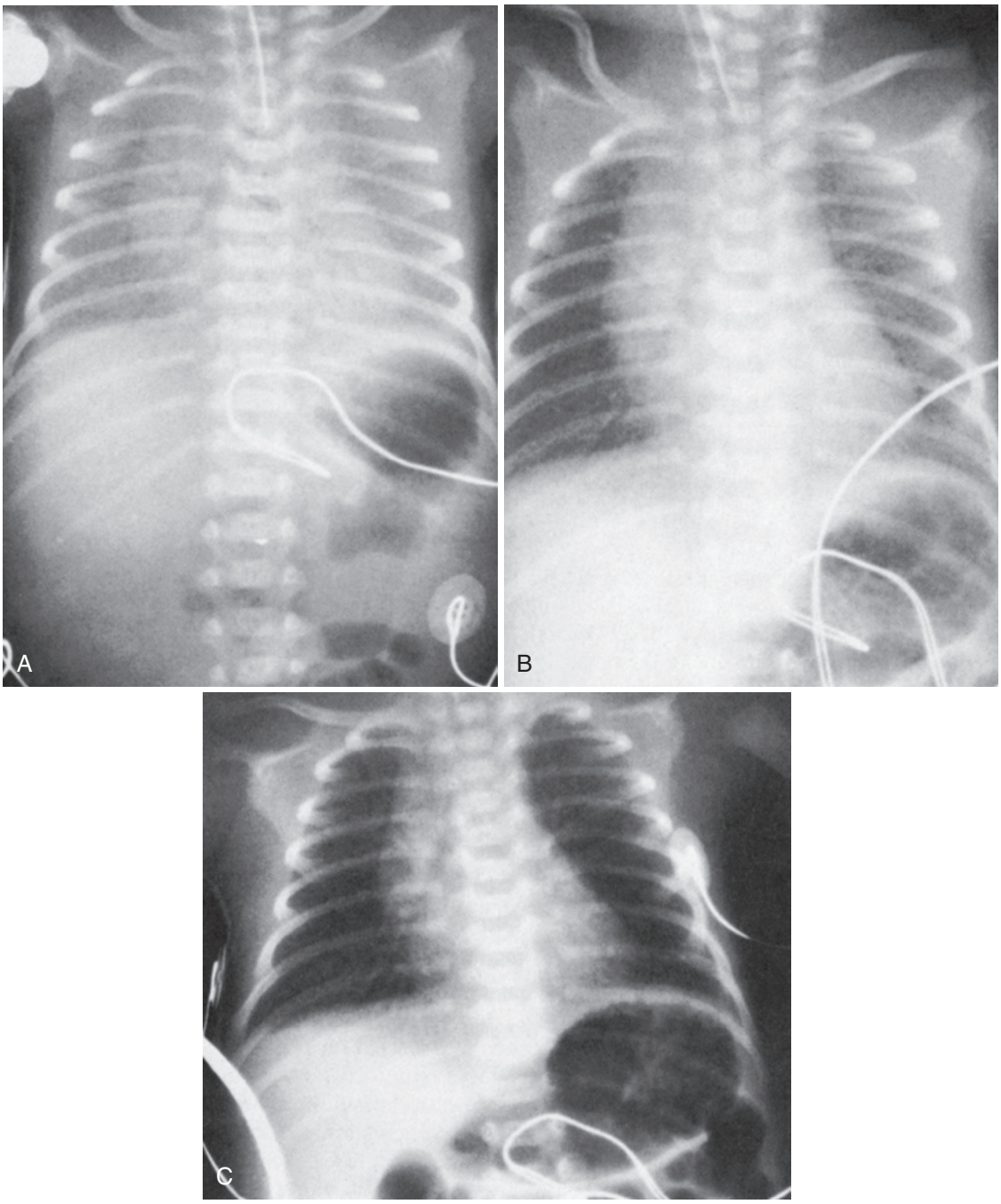


FIGURE 17-6 Radiographs during the first day of life for a 30-week premature infant with respiratory distress syndrome (RDS) managed with high-frequency oscillatory ventilation (HFOV) to achieve optimal mean lung volume (MLV). **A,** Initial $mP\overline{aw}$ equal to 10 cm H_2O, fraction of inspired oxygen (FIO_2) equal to 1. **B,** At 12 hours of age, with mPaw equal to 15 cm H_2O and FIO_2 equal to 0.45. **C,** At 24 hours of age with mPaw equal to 12 cm H_2O and FIO_2 equal to 0.28.

7.25 (these parameter limits will likely vary among institutions). Once there is radiographic evidence that the lung has adequately deflated and air leaks have resolved (for at least 12 to 24 hours), the lung is reinflated by one of the preceding lung inflation strategies. Air leak rarely recurs with this approach. This method is successful in most infants with PIE. Figure 17-7 radiographically demonstrates this practice. Those with PIE under tension and myocardial compromise are more difficult to manage and have poorer outcomes. This approach has been dubbed the *low-volume strategy.*

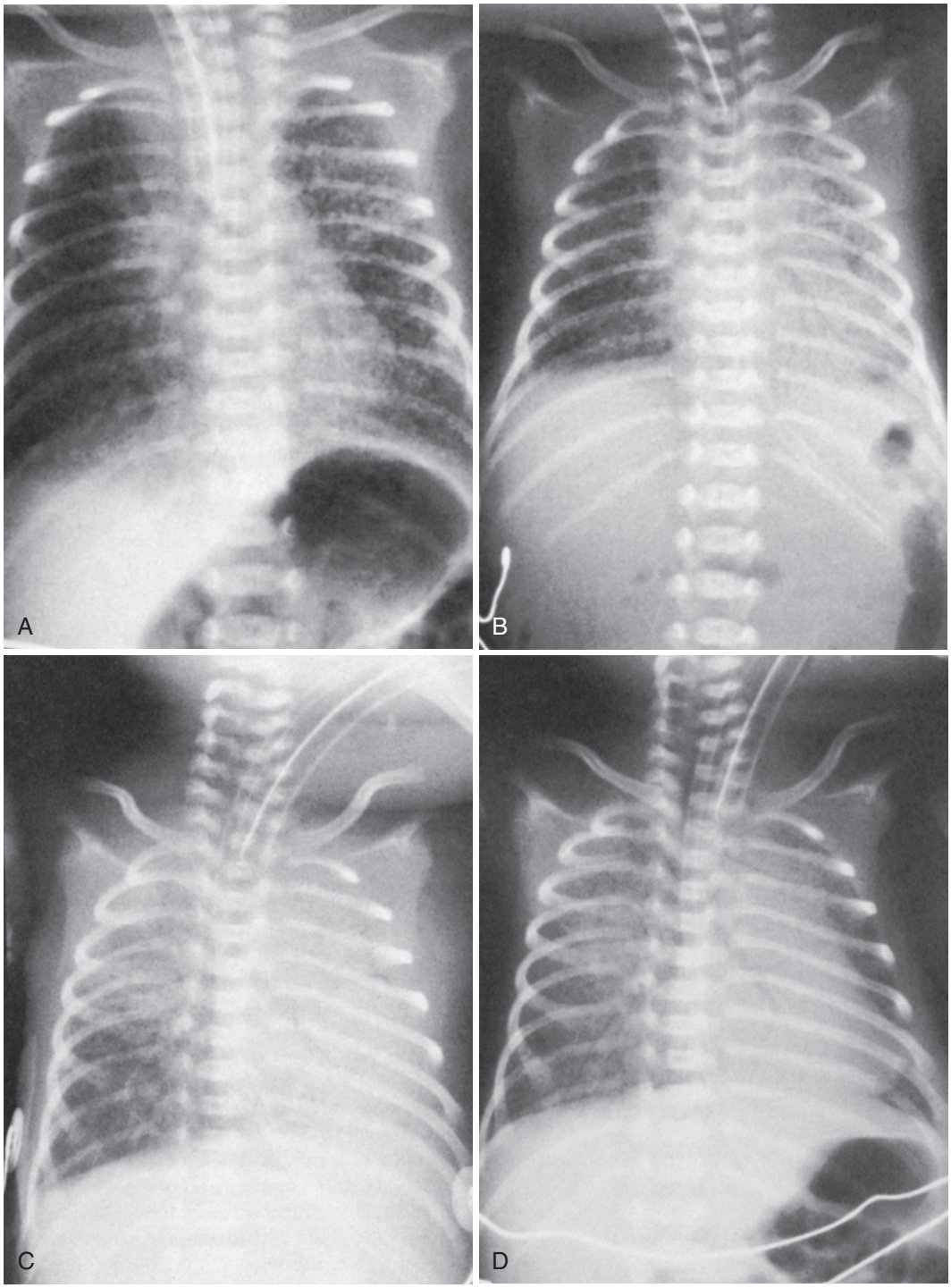


FIGURE 17-7 Radiographs of a 2-day-old preterm infant with pulmonary interstitial emphysema (PIE). **A,** mPaw equal to 16 cm H_2O and FiO_2 equal to 0.65. **B,** Six hours later, $mP\overline{aw}$ equal to 8 cm H_2O and FiO_2 equal to 1. **C,** Twelve hours later, settings were unchanged, PIE was resolved, and the lung was nearly totally deflated. **D,** Thirty-six hours later, reinflation was beginning, $mP\overline{aw}$ was equal to 12 cm H_2O, and FiO_2 was equal to 0.45.

MANIPULATING VENTILATION

CONVENTIONAL VENTILATION

One of the main goals of MV is to manipulate the arterial carbon dioxide tension ($PaCO_2$), which is affected by changing the minute ventilation. The minute ventilation is directly related to ventilation frequency and tidal volume and is inversely related to $PaCO_2$.

Frequency

Frequency or rate is generally the first method used to increase minute ventilation. At low rates and conventional I/E ratios or during weaning, adjusting

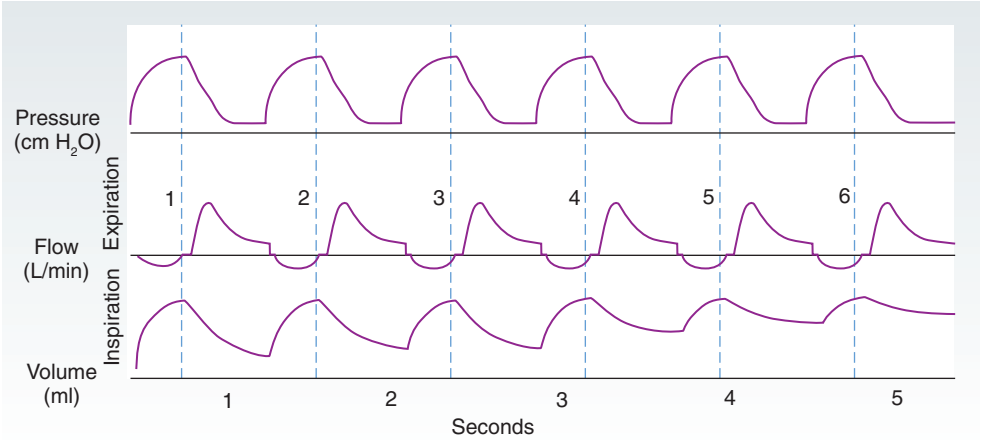


FIGURE 17-8 Air trapping illustrated in a flow (L/minute) over time scalar. Expiratory flow never returns to baseline before the ventilator cycles again.

frequency is the most desirable option. However, as frequency increases, air trapping is likely to occur because of decreasing expiratory times (but this can be minimized if I/E is held constant). Figure 17-8 illustrates this in a flow/time scalar graphic. Notice that flow does not come back to baseline. If frequency is increased with constant inspiratory pressure and PEEP, mean alveolar ventilation increases to a maximum and then decreases. The frequency at which alveolar ventilation is maximum depends on lung mechanics and the dead-space/tidal-volume ratio.[26] For premature infants with respiratory distress syndrome (and hence very short respiratory system time constants), the frequency of ventilation can possibly be increased to the maximum (150 per minute) with the purpose of using the smallest tidal volume and incurring the least risk of volutrauma.[27] However, for asthmatics or those with bronchiolitis, air trapping may more easily occur at normal-for-age respiratory rates.

Tidal Volume

An alternative to adjusting frequency is to change any variable that affects tidal volume and hence affects minute ventilation and $Paco_2$. In volume control modes, tidal volume is set directly. In pressure control modes, tidal volume is an indirect result of lung mechanics and the shape of the airway pressure waveform during inspiration, along with any inspiratory effort on the part of the patient. In pressure control modes, tidal volume is increased by (independently) increasing inspiratory pressure, decreasing pressure rise time, decreasing PEEP, or increasing inspiratory time (i.e., increasing I/E).

Research has shown that the largest contribution to ventilator-induced lung injury results from lung overdistention caused by excessive tidal volume **(volutrauma),** followed by the repetitive opening and closing of the terminal lung units **(atelectrauma).** Therefore, more emphasis is being placed on setting lower tidal volumes, improvements in tidal volume monitoring, and setting adequate PEEP levels. The tidal volume setting in neonates varies from 3 to 5 mL/kg in low-birth-weight premature infants to 5 to 6 mL/kg in term infants and to 5 to 8 mL/kg in pediatric and adolescent patients. Lower volumes have been shown to be effective for patients with restrictive lung disease such as respiratory distress syndrome (RDS) and ARDS. Tidal volume should be corrected for compressible volume loss, or a proximal flow sensor should be used. Careful monitoring of breath sounds, chest expansion, arterial blood gas values, and chest radiographs is essential in determining adequate tidal volume.

Table 17-4 shows commonly used initial HFV settings suggested for different patient sizes; however, certain conditions or severity of disease may require a different initial approach.

HIGH-FREQUENCY VENTILATION

Classic physiology teaches that level of ventilation (as indicated by $Paco_2$) is directly proportional to the metabolic production of carbon dioxide ($\dot{V}CO_2$) and indirectly proportional to alveolar ventilation ($\dot{V}_A$). However, the volume that effectively removes carbon dioxide is alveolar volume—that is, the difference between tidal and dead space volume. On the basis of this simple model, if tidal volume is less than dead space, alveolar volume is zero and $Paco_2$ should increase without bounds. Because all of the HFV methods described are effective means of ventilation, even with tidal volumes less than dead space, a new explanation is needed. Fredberg and coworkers[28] provided insight into this apparent paradox, and Chang[29] has summarized work by others describing elimination of carbon dioxide as follows:

$$(VCO_2) = (f)^x \times (V_T)^y$$

Table 17-4 Initial Settings for HFOV and HFJV

		PREMATURE INFANT	INFANT	TODDLER OR CHILD	LARGE CHILD OR ADOLESCENT
Weight (ideal) (kg)		<2	2-10	10-40	>40
Respiratory rate	HFOV	15 Hz	12-15 Hz	10-12 Hz	6-10 Hz
	HFJV	420 bpm	360-420		
	HFPV	500 bpm	500 bpm	500 bpm	500 bpm
Delta pressure	HFOV	Adjust to chest wiggle			Adjust to upper thigh wiggle
PIP	HFJV	Same as CMV PIP			
	HFPV	20-30 cm H_2O			
Inspiratory time	HFOV	33%	33%	33%	33%
	HFJV	0.02 sec	0.02 sec		
	HFPV	2 sec	2 sec	2 sec	2 sec
mPaw (cm H_2O)	HFOV	2-4 above	2-4 above	4-6 above	4-6 above
PEEP (cm H_2O)	HFJV	5-7	5-7		
	HFPV	8	8	8-10	8-12
FiO_2		Start 25-50% higher than pre-transition FiO_2 or 1.0 unless contraindicated			

CMV, conventional ventilation; *Fio_2,* fraction of inspired oxygen; *HFJV,* high-frequency jet ventilation; *HFPV,* high-frequency percussive ventilation; *HFOV,* high-frequency oscillatory ventilation; *mPaw,* mean airway pressure; *PEEP,* positive end-expiratory pressure; *PIP,* peak inspiratory pressure.
Note: Initial setting may be different according to disease or institutional practice.

where x is 0.5 to 1 and y is 1.5 to 2.2 (depending on the device). From this relationship, tidal volume shown to be more critical to ventilation than rate during HFV, and HFV appears to reduce the impact of dead space volume on ventilation.

Unlike oxygenation, in which the relationship of mPaw to MLV and subsequent optimization of gas exchange is similar between CMV and HFV, the elimination of carbon dioxide by CMV and HFV is drastically different. This difference lies not only in the alterations to the minute ventilation equation just described, but also in the nature of HFV devices themselves. In this regard, Fredberg and colleagues[28] made several interesting observations during an evaluation of multiple neonatal HFV devices. They noted that not only is carbon dioxide elimination during HFV more sensitive to changes in tidal volume than in rate, but also the tidal volume output of HFV devices is sensitive to changes in ETT diameter and lung compliance. As ETT dimensions and compliance decreased, so did tidal volume output from the HFV tested. This occurred in the presence of stable ventilator settings. Therefore, any clinical change causing a decrease in ETT diameter, such as reintubation with a different size ETT or partial ETT obstruction with tracheal secretions, alters the delivered tidal volume. Furthermore, improvements in lung compliance (e.g., volume recruitment) and decrements in lung compliance (e.g., patent ductus arteriosus or alveolar derecruitment) have a direct effect on tidal volume.

In addition, the relationship between ventilator frequency and carbon dioxide elimination is nonintuitive. Changes in ventilator rate at a given pressure amplitude cause an inverse change in tidal volume. Thus, when ventilation must be improved, a reduction in breathing frequency improves ventilation, because the increased volume output per stroke has a greater impact on ventilation than does the decrease in stroke frequency. The converse is also true. When less ventilation is needed and pressure amplitude is already minimized, increasing breathing frequency will further decrease tidal volume and allow weaning from ventilation.

Frequency

Ventilator frequency ranges between 2 and 20 Hz, depending on the device. Frequencies lower than 4 Hz and greater than 15 Hz are rarely used. The impact of frequency on ventilation during HFV is less than the impact of tidal volume. Frequency is therefore not usually changed, and management of ventilation occurs with changes in delivered volume. Changes in frequency are made when operating at machine limits of tidal volume (both low and high limits). Choice of frequency depends on understanding the optimal functional characteristics of each device and the nature of the patient and the disease treated. For example, with a similar disease such as acute RDS, neonatal and pediatric patients are managed with different frequencies during HFOV. A smaller child requires a lower tidal volume and therefore a higher frequency.

Oscillatory Amplitude or Peak Pressure

Changes in delivered pressure amplitude have a direct influence on tidal volume delivery. The purpose of measuring peak inspiratory pressure is to offer both patient safety and ease of adjustment of delivered tidal volume. Although HFJV provides

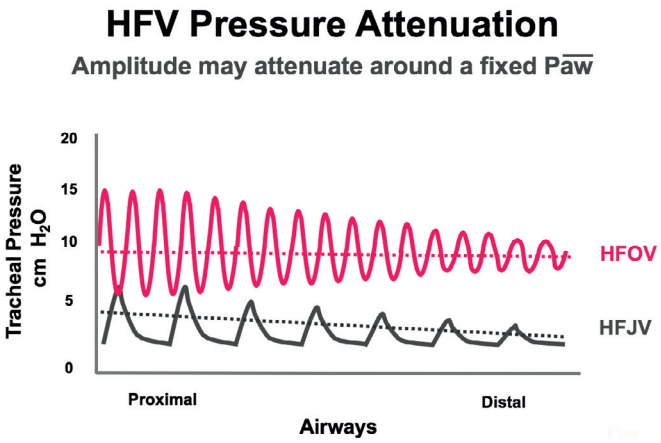


FIGURE 17-9 Graphic representation of pressure attenuation during high-frequency ventilation (HFV).

separate control and displays an estimate of distal ETT peak pressure, HFOV does not. Pressure amplitude drops significantly along the flow path. Transducers, amplifiers, and measurement of circuit fidelity must be adequate and properly to accurately measure peak-to-peak pressures at high frequencies.[30]

During HFOV, peak and trough pressures are measured, although they are not usually displayed. The difference between peak and trough pressures is known as *oscillatory amplitude* or *delta P*. The resistance and compliance of the respiratory system act like a low-pass filter to greatly dampen (decrease) the amplitude of the oscillations that reach the lungs.[31,32] Figure 17-9 demonstrates the pressure attenuation often seen with HFV. Delivered volume is directly proportional to this peak–trough difference, and adjustments result in changes in tidal volume. During HFOV, changes in downstream compliance and impingement on the ETT lumen cause tidal volumes to vary without changes in displayed pressure amplitudes. Control over tidal volume during HFJV occurs by modifications in distally measured peak pressures. Although this measurement is less vulnerable to variations in the ETT lumen, total volume delivery during HFJV is a combination of jet pulse and gas entrained with each breath from the proximal ETT connection. This entrainment volume is vulnerable to reductions in the ETT lumen.

MECHANISMS OF GAS EXCHANGE

The MV techniques previously described represent different options along the ventilation spectrum. On this spectrum, CMV is at one extreme, with relatively large tidal volumes and low breathing rates, and HFOV is at the other extreme, with very small tidal volumes and high breathing rates. The techniques of CMV breath rates up to 150, HFPV, and HFJV lie in between. As one traverses this ventilatory spectrum, the classic roles of convection to deliver bulk gas to small airways and diffusion to distribute the gas among the gas-exchanging surfaces become blurred. Most of the research attempting to refine the understanding of gas transport and exchange during CMV and HFV has been accomplished in adult or animal models with normal or injured lungs. At best, the injured states mimic secondary (not natural) surfactant deficiency, and adult pulmonary time constants and airway rigidity differ significantly from those of the neonatal lung.

Enhanced diffusion is found in large and medium airways in which alterations in gas flow velocity profiles occur. This is believed to be responsible for delivery of gas farther into the lung than can be explained by pure convection.[29] There is significant interdependence between adjacent alveolar units, because the walls of any alveolar unit are shared with juxtaposed alveoli, each providing stability to the other. Once inflated, these units, which may have different time constants, can equilibrate gases by swinging ventilation between them. This phenomenon, called *pendelluft*, tends to equilibrate gas concentrations in conducting airways and serves to improve gas exchange from distal pulmonary units. In addition, the impact of enhanced diffusion, the product of tidal volume and rate, and the relationship between pulmonary units may all vary depending on the HFV technique used, the settings chosen, the patient's lung size, and pathologic conditions. Obviously, our understanding of this complex set of gas exchange dynamics remains incomplete.

MANIPULATING OXYGENATION

FRACTION OF INSPIRED OXYGEN

The most obvious way to improve oxygen delivery is to increase the alveolar oxygen tension by increasing the Fio_2. A simple method to estimate the Fio_2 required for an arterial partial pressure of oxygen (Pao_2) is derived from the atrial/alveolar oxygen tension ratio [$P(a/A)O_2$]. Assuming constant barometric pressure and $Paco_2$ and stable lung conditions, the equation simplifies to:

$$Fio_2 \text{ desired} = Pao_2 \text{ desired} \times (Fio_2 \text{ currently}/Pao_2 \text{currently})$$

Because prolonged exposure to high levels of oxygen may be toxic, the lowest acceptable Fio_2 should be used. However, high levels of oxygen may be necessary to correct hypoxemia when treating severe lung disease or pulmonary hypertension. To prevent these complications, other variables that relate to improving oxygenation must also be considered, such as nitric oxide and PEEP.

CONVENTIONAL VENTILATION

Mean Airway Pressure

Improvement in Pao_2 is directly related to an increase in mPaw. (It may have an inverse relationship in right-to-left cardiac shunts or in pulmonary volutrauma.) This improvement is believed to be caused by recruitment of collapsed alveoli or redistribution of lung fluid, or both. *Mean airway pressure* is defined as the area under the pressure-time waveform for one ventilatory cycle divided by the total cycle time. Almost all ventilators display mean airway pressure, but there was a time when they did not, and one had to roughly estimate it using an equation:[33]

$$\overline{P}_{aw} = k(PIP - PEEP) \times \left(\frac{T_I}{TCT}\right) + PEEP$$

where *PIP* is peak inspiratory pressure above atmospheric pressure, T_I is inspiratory time, *TCT* is total cycle time (1/f), and *k* is the waveform constant (k ≈ 1.0 for pressure control with zero pressure rise time and k ≈ 0.5 for volume control with constant inspiratory flow). Note that because f = 1/TCT, if T_I is held constant, then mPaw increases as frequency increases. On the other hand, if I/E is held constant and inspiratory resistance equals expiratory resistance, then mPaw is independent of frequency.[34]

The desired mPaw is one at which both oxygenation and ventilation are optimized and the risks of pulmonary volutrauma, impaired hemodynamics, and fluid retention are minimized.

Positive End-Expiratory Pressure

PEEP improves gas exchange by improving Pao_2, maintaining recruitment of alveoli, increasing functional lung volume, decreasing intrapulmonary shunting, and improving lung compliance. Simply stated, the goal of PEEP therapy is to improve oxygenation by increasing FRC through maintenance of airway patency and alveolar recruitment. Many use an Fio_2/PEEP chart to guide the use of moderate PEEP in those with pediatric acute respiratory distress syndrome (PARDS).[35] Table 17-5 shows a titration table as a guide.

An adequate PEEP level is the amount necessary to attain an acceptable Pao_2 at the lowest Fio_2, although avoiding high PEEP levels is desirable. It is determined by many physiologic factors, which may or may not be monitored in any given clinical situation. A conservative but acceptable Pao_2 is 45 to 65 mm Hg for neonates younger than 33 weeks of gestation and 60 to 80 mm Hg for pediatric patients at an Fio_2 of 0.4 to 0.5. PEEP usually begins at 3 to 5 cm H_2O, with increases made in increments of 2 cm H_2O. A method of judging adequate PEEP levels is to monitor static lung compliance or to calculate it by dividing the tidal volume by the end-inspiratory pause pressure minus PEEP. When the functional residual capacity is low, static compliance increases as PEEP increases because of shifting of the ventilating volume to the optimal point on the compliance curve. When optimal distention is reached, lung compliance is (hopefully) maximal. If PEEP is increased further, overdistention, reduced compliance, and decreased oxygen transport may result. A static compliance measurement can be impossible to obtain in patients with cuffless ETTs that have a leak.

Monitoring the $Paco_2$ to end-tidal carbon dioxide gradient may also be useful in judging PEEP levels (see Chapter 8). Overdistention and reduced cardiac output resulting from excessive PEEP may cause the gradient to widen. Caution must be exercised with this method, because other abnormalities causing low cardiac output may also increase this gradient. Because excessive levels of PEEP can affect cardiac function, monitoring mean blood pressure, central venous pressure, mean pulmonary artery pressure, and other hemodynamic variables is also important while monitoring PEEP levels. When pulmonary artery catheters are used, cardiac output and the pulmonary shunt fraction are useful measures. A reduction of the shunt fraction, normally to less than 15%, is the goal when applying PEEP in patients with PARDS. When using this variable to adjust PEEP where the shunt fraction is reduced to less than 15%, levels of PEEP in excess of 25 cm H_2O are usually required.[36]

Not only can PEEP be applied as a ventilating variable, but it also can be present in the form of auto-PEEP (intrinsic, occult, or inadvertent PEEP). Auto-PEEP is the difference between alveolar pressure and external airway pressure at end expiration. Causes include impedance to exhalation related to airway resistance, expiratory muscle activity, imposed resistance caused by ETTs and exhalation valves, water obstructing the exhalation circuit, rapid breathing frequency, and inverse I/E ratio. The use of moderate PEEP in obstructive lung disease such as asthma is controversial; some investigators have reported improved gas exchange and decreased airway resistance, whereas others found increased air trapping and hemodynamic compromise. More recent research has shown that higher set PEEP levels can be helpful in decreasing the work of breathing in mechanically ventilated, spontaneously breathing pediatric patients with obstructive airway disease. In theory, if flow limitation is present due to collapsible airways, then external PEEP may hold the airways open and reduces expiratory resistance, thus reducing the time constant and decreasing auto-PEEP. Multiple variables affect ventilation and oxygenation. It must be

Table 17-5 Guidelines for Setting PEEP According to Set Fio_2

FiO_2	.30	.40	.40	.40	.50	.50	.60
PEEP	5	5	8	10	10	12	12
FiO_2	.60	.70	.70	.80	.80		
PEEP	14	14	16	16	16*-18		

Fio_2, Fraction of inspired oxygen; *PEEP*, positive end-expiratory pressure.
*PEEP of 16 cm H_2O in patients younger than 1 year of age.

understood that manipulating a ventilator setting with the objective of improving one condition may result in undesirable effects on another. Balancing these variables allows the clinician to meet the goals of MV, as well as to optimize oxygen delivery, recruit lung volume, improve gas distribution, and alter minute ventilation.

HIGH-FREQUENCY VENTILATION

Although from a mechanistic perspective gas exchange remains complex, the clinical management of oxygenation is more straightforward than CMV. Excluding adjustments of Fio_2, oxygenation is improved during CMV and HFV by recruiting or maintaining lung volume. In fact, there is a direct and linear relationship between lung volume and oxygenation. The exception to this is when the lung is either underinflated or overinflated. In each circumstance, the relationship between ventilation and perfusion is disturbed and oxygenation is impaired. Achieving an optimal MLV, then, optimizes ventilation–perfusion matching while avoiding impaired cardiac output. As discussed earlier, adjusting several CMV settings, such as tidal volume, peak pressure, inspiratory time, and end-expiratory pressure, accomplishes this. The resulting mPaw is an indirect expression of the pressure effort required to achieve and sustain the desired MLV. Phasic pressures delivered with CMV during attempts to recruit lung volumes can damage the fragile, yet noncompliant, infant airways and lung parenchyma. Sometimes this is referred to as tidal recruitment. Thus conventional tidal volume breathing applied to lungs with nonuniform compliance, as in the premature surfactant-deficient lung, results in nonhomogeneous gas distribution, with overinflation of compliant areas and underinflation of noncompliant regions. During spontaneous or conventional mechanical breathing, the lung swings past the MLV and mean mPaw during the cycles of inspiration and expiration, residing at the MLV (and mPaw) for only brief periods. With normal lung mechanics, a stable FRC is maintained and oxygenation is not impaired. In a lung prone to atelectasis, however, residual lung volumes are dynamic. Although volume may seem adequate at peak inflation, stable lung volumes may not exist and oxygenation will be significantly impaired (even in the presence of PEEPs).

The methods used to create and maintain mPaw therefore have a profound effect on the consequences of reaching the MLV. Conventional methods require the use of relatively high peak pressures to recruit collapsed noncompliant pulmonary units. The potential negative impact has already been described. The approach taken during HFV strategies, in contrast, is the application of a continuous distending pressure without the use of high amplitude pressure oscillations. In fact, direct control over mPaw is possible, with ventilation occurring around a relatively fixed intrapulmonary pressure and therefore relatively stable MLV. The danger of this technique, as mentioned earlier, is lung overdistention and resultant decreases in venous return and cardiac output. This can occur without changes in ventilation pressures during CMV and HFOV when lung volume is silently recruited as compliance improves.

The optimal MLV during high-volume strategies is reached when distending pressure exceeds alveolar opening pressures and, as a result, the $P(a/A)O_2$ is maximized. This measure of oxygenation is useful because it normalizes measured Pao_2 for delivered Fio_2.[37] The safe application of pressures adequate to achieve a stable MLV during management of an uninjured, atelectasis-prone lung is the goal of MV. Data from both animal and human infant studies suggest that improved oxygenation, with acceptable ventilation, does occur safely with HFV techniques when using distending pressures that are initially higher than in CMV controls. Attempts to achieve improved oxygenation using mean pressures lower than those used in CMV, although attractive in theory, have not proved fruitful except in short-term studies and in patients with pulmonary interstitial emphysema in whom low-volume strategies are desired and intentional. Experiments performed by McCulloch and coworkers[38] using the surfactant-deficient rabbit model elegantly demonstrated the relationship between lung inflation strategy and resultant lung volume and gas exchange. In this work, animals with similar pressure–volume relationships after lavage were managed for a 7-hour study period with conventional MV, HFOV with a low lung volume strategy, or HFOV with a high lung volume strategy. Figure 17-10 graphically demonstrates

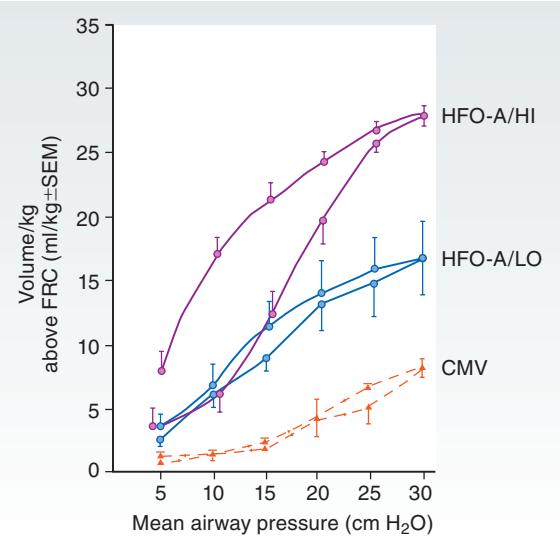


FIGURE 17-10 Respiratory system pressure–volume curves obtained after 7 hours of ventilation in surfactant-depleted rabbits. Note the intergroup differences in total respiratory system compliance and lung volumes. The differences in hysteresis (inflation–deflation limb separation) are also significant between groups. *CV,* conventional ventilation; *FRC,* functional residual capacity; *HFO-A,* high-frequency oscillatory ventilation with an active expiratory phase; *HFO-A/HI,* HFO-A at a high lung volume; *HFO-A/LO,* HFO-A at a low lung volume. (Modified from McCulloch PR, Forkert PG, Froese AB: Lung volume maintenance prevents lung injury during high-frequency oscillatory ventilation in surfactant deficient rabbits. *Am Rev Respir Dis*137:1185, 1988.)

the effects of these approaches on lung volumes. Note the significantly higher volumes obtained in the animals receiving HFOV and a high lung volume at an equivalent mPaw. As anticipated, this group also had a fivefold higher Pao_2 and less evidence of significant bronchiolar epithelial injury.

As patient compliance changes, so does the mPaw required to maintain optimal MLV. Obviously, a direct measure of MLV or compliance during HFV would be extremely useful; however, neither is currently available for routine bedside use. Clinical measures to properly wean patients and avoid inadvertent overdistention are discussed later in this chapter.

Positive End-Expiratory Pressure

As with peak pressure, the attempt to apply a conventional setting to an HFV technique can lead to confusion. One can easily measure trough pressures during HFV, but the meaning and value are unclear. With CMV, we relate oxygenation to levels of end-expiratory pressure because this pressure, measured at the airway opening, is nearly identical to that at the alveolar level (assuming no auto-PEEP). With HFJV, this remains approximately true because end-expiratory pressure is set by adding it from the CMV. During HFOV, PEEP at the airway opening is generally much lower than in the lung and the relationship between the two is dynamic and uncertain.

Mean Airway Pressure

As mPaw increases, so does mean lung volume, up to the point of overdistention. At the lung volume at which oxygenation is optimized, compliance may be as well. mPaw facilitates oxygenation and supports optimal ventilation (Figure 17-11). Therefore, using mPaw to maintain the correct lung volume is doubly critical.

Flow

The use of flow to control ventilator settings varies among the devices described. During HFJV, jet pulses are delivered by means of a timing circuit with minimal control of flow. Pressures, and therefore volumes, are determined by variations of jet on time and frequency. HFPV incorporates multiple-solenoid technology to determine rate of pressure rise and end-expiratory pressures during CMV, which has little impact on HFV functions. HFOV mPaw is determined by the combination of circuit bias flow and the back pressure created by the expiratory valve opening. Even though desired mPaw may be achieved with complete valve closure, care should be taken to avoid this, because rapid rebreathing followed by circuit (and patient) overpressurization will occur.

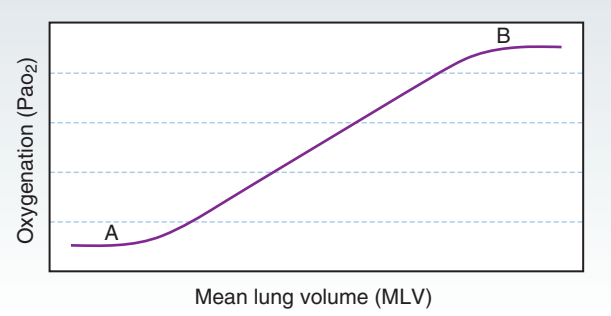


FIGURE 17-11 Relationship between mean lung volume and oxygenation (by inference between mPaw mean airway pressure and mean lung volume). **A,** Unopened lung. **B,** Overinflated lung.

Inspiratory Time

Inspiratory time adjustments result in alterations in ventilator rate, I/E ratio, and tidal volume, all of which are significant to differing degrees for each type of HFV. Inspiratory time during HFJV is adjusted by changing jet on-time. Depending on ventilator frequency, this alters the I/E ratio and influences tidal volume output. Jet on times of 20 to 34 msec are common. With HFOV, inspiratory time varies with ventilator rate, but the I/E ratio is singularly meaningful. The recommendation is a 33% inspiratory time for the HFOV devices approved in the United States. The result is that for each completed respiratory cycle, one-third is inspiratory and two-thirds is expiratory. The importance of this lies in the enhancement of gas egress during exhalation, because the 1:2 ratio favors the expiratory phase, thereby reducing inadvertent air trapping. This becomes a more significant factor as ventilator frequencies increase. Increases in inspiratory time at any given rate may increase tidal volume, but there is an obligatory reduction in I/E ratio that may offset any desirable effects. Changes in ventilator rate are made with changes in expiratory time, and the I/E ratio varies with frequency. Compared with the other ventilators, adjustments in tidal volume cannot be made by increasing inspiratory time, and the I/E ratio varies with frequency.

PATIENT–VENTILATOR INTERFACE

Understanding the ventilator circuit is an integral aspect of ventilator management. The *circuit* is the interface between the ventilator and the patient system. There are five major factors to consider when assessing the impact of the circuit on ventilation:

- Compressible volume
- Air leak
- Dead space
- Resistance
- Humidification

COMPRESSIBLE VOLUME

The influence of compressible volume on effective tidal volume during **volume control ventilation** was discussed earlier (see Adaptive Ventilation). When the

ventilator delivers a breath, pressure inside the circuit increases and compresses the gas volume within the circuit. This compressed volume never reaches the patient, and the inspired volume is less than the set volume. During expiration, however, the compressed volume passes through the exhalation valve and may be (depending on ventilator design) measured as part of the patient's exhaled volume. This may result in the patient's actual inflation volume being less than that recorded as exhaled volume. If the actual volume delivered to the lungs of a critically ill infant or young child is not accurately known, the patient may be at risk for atelectasis, hypoxia, and hypercapnia. All mechanical ventilators that do not measure tidal volume at the proximal airway calculate the compressible volume during the preuse check. The humidifier also represents a source for gas compression and is included in calculating compressible volume. It is best practice to perform the calculation with the circuit and humidifier that will be used for that patient. Using a constant-level self-feeding humidifier is necessary to minimize variations in compressible volume in all pediatric ventilation situations. When tidal volumes are measured with a proximal flow sensor placed at the ETT, ventilator circuit compliance and the confounding circuit variables are no longer pertinent factors.

AIR LEAK

In the pediatric clinical setting, it is important not to confuse compressible volume loss with air leak. Air leaks are most notable around a cuffless ETT or tracheostomy tube. Accurately monitoring tidal volume is difficult in the presence of an air leak. An excessive air leak compromises tidal volume delivery, reduces lung-distending pressure, and may adversely affect the ventilator triggering mechanism. In general, air leaks are monitored by the difference between the inhaled and exhaled volumes. Another way to identify an air leak is by examining the volume-time curve graphics. Figure 17-12 illustrates an air leak on a volume waveform. In most clinical situations, an air leak greater than 15% of the delivered tidal volume makes volume ventilation difficult. Usually reintubation is necessary to maintain consistent volume ventilation and adequate triggering of the ventilator.

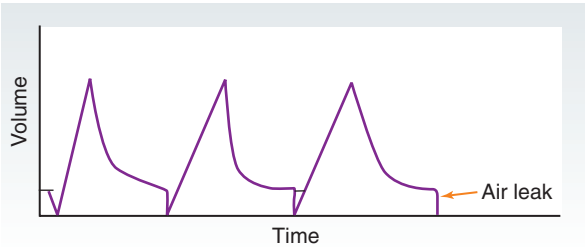


FIGURE 17-12 Air leak shown on a volume/time scale. Volume never returns to baseline before the ventilator cycles again.

DEAD SPACE AND RESISTANCE

Dead space (of the ventilator circuit) is the portion of the circuit distal to the main bias flow or circuit where gas can be rebreathed. This includes the volume of the circuit wye connector, the elbow, any monitoring device attached to the ETT connector, the ETT, and the conducting airways. The conducting airways are known as *anatomical dead space* and are not influenced by the circuit. However, the dead space added to the circuit is *mechanical dead space.* With smaller pediatric volumes, mechanical dead space may result in undesired rebreathing of carbon dioxide. Specially designed pediatric or infant monitoring devices and circuits help minimize this. Overzealous application of low dead space monitoring devices may result in increased resistance at the airway if the proper size is not used. Another component to evaluate as a choke point for gas flow is the adaptor connecting the tubing to the elbow or the ETT. A rule of thumb is that the ETT should be the point of highest circuit resistance, and mechanical dead space of 0.5 to 1.0 mL is acceptable. Although the absolute dead space may be 0.5 to 1.0 mL, often fresh gas will penetrate through the mechanical dead space.[39] If a circuit component is smaller in cross-sectional area than the ETT, another circuit or component should be used.

HIGH-FREQUENCY CIRCUIT CONSIDERATIONS

To achieve adequate gas exchange for both oxygenation and ventilation, high-frequency ventilators have unique design requirements. With the exception of MFV, all HFV devices have special patient circuit considerations. Each of them must do the following:

- Use very low circuit compliance to reduce compressible volume and increase the precision of control over the small volumes delivered
- Provide control over inspiratory times and circuit design to allow sufficient time for gas egress during exhalation
- Adequately humidify gases
- Include alarms and fail-safe devices for patient safety

As a consequence of these considerations, circuit configurations cannot be altered without careful investigation, because function and safety are extremely sensitive to small changes in engineering. The manufacturers' manuals and clinical user websites provide more details specific to individual HFVs.

HUMIDIFICATION

The humidification system is an integral part of the patient–ventilator system. When the normal heating and humidification systems of the body are bypassed or are inadequate, it is necessary to artificially heat

and humidify inhaled gases. Optimal humidity and temperature are dependent on the clinical situation. Usually a temperature of 37° C and a water content of 44 mg/L are adequate.[40-42] Servo-controlled heated humidifiers with a small compressible volume are used most often in neonatal and pediatric patients who require MV.

Complications associated with these humidifiers include overheating and nosocomial infection. Water condensation in the ventilator circuit may also lead to nosocomial infection as well as to the accidental drainage of water into the patient's lungs. With the use of a servo-controlled heated wire circuit, complications are not as common as they once were. However, awareness of the operational characteristics of the humidifier and its controlling mechanisms is important in ventilator management.

CARE OF THE PATIENT

POSITIONING

As mentioned earlier, patient positioning is constrained with the use of invasive ventilation. The unique nature of the patient circuit challenges caregivers in ensuring ETT stability. Positioning the patient appropriately by rotating among supine, prone, and left and right lateral decubitus positions remains as important during MV.

Patient positioning is believed to play a role in reducing ventilator-associated complications (VAC). For example, semirecumbent body positioning in adult intensive care unit (ICU) patients was associated with a reduction of common risk factors for VAC, such as gastroesophageal reflux and subsequent aspiration. In addition, semirecumbent positioning (30 to 45 degrees) was associated with a decrease in VAC. However, the evidence on this topic is mixed.

Although evidence on head of bed (HOB) elevation for pediatric patients is very limited, HOB elevation of 30 to 45 degrees for intubated infants and children is encouraged. In neonates, a similar effect may be achieved by positioning the incubator or radiant warmer mattress in the reverse Trendelenburg position at an angle of 15 to 30 degrees rather than 30 to 45 degrees, because the greater angle is difficult to maintain in very small patients. To facilitate HOB elevation for pediatric patients, beds and cribs with adequate positioning features should be used. Furthermore, the degree of elevation should be measured using validated instruments or bed markings and documented. Because patient positioning is believed to play an important role in VAC prevention and can be achieved with little or no negative implications, unless contraindications exist, elevating the HOB as outlined in Table 17-6 is recommended.

Note: Airway management, intubation, extubation, and suctioning are covered in Chapter 13.

Table 17-6 Patient Positioning

AGE OF PATIENT	POSITION OF BED
Neonate (<44 weeks GA)	15-30 degrees
Pediatric (≥44 weeks GA)	30-45 degrees

GA, Gestational age.

VENTILATOR CIRCUIT

Ventilator circuits only need to be changed when they are visibly soiled or malfunctioning.[43] Condensate should be removed routinely, taking care to drain away from the patient to avoid contaminating any inline nebulizers. When performing ventilator care, proper hand hygiene should be performed before and after each intervention and gloves should be worn.

AIRWAY MAINTENANCE

The mere presence of an ETT impairs the cough reflex and may increase mucus production. The *suctioning smarter* philosophy consists of suctioning only when a clinical indication arises, not on a scheduled basis. Standards for tracheal suctioning should address catheter size, length of time suction is applied, suction pressure, deep versus shallow techniques, open versus closed techniques, saline instillation, lung pathology, and ventilatory mode.

Suctioning

Suctioning should only be considered when secretions are present *or* clinical assessment is consistent with inspissation of secretions. In preparation for suctioning, selecting an appropriate catheter size is important. It is recommended that the hypopharynx is suctioned before ETT suctioning. Some patients may require limited preoxygenation. In the neonatal population, limiting preoxygenation to 10% to 20% above baseline Fio_2 is recommended.

SUCTION EQUIPMENT

Open Versus Closed System Suctioning

Research supports the use of closed system suctioning.[44] The potential benefits of using closed system suctioning include continued delivery of oxygen, supportive positive pressure, reduced risk of nosocomial infection, and reduced staff exposure. Inline suction catheters have been shown to be just as effective without breaking the ventilator circuit while allowing quicker resumption of ventilation and Fio_2.[45,46]

To prevent volume loss, health care providers should limit overall procedure time, not just actual suction time. A study of 200 neonates who weighed less than 1000 g found that twice the recovery time was necessary with the use of open suctioning versus closed suctioning.[47] In a smaller pediatric-based study, results were similar, supporting the benefit of using closed suctioning. In

neonates receiving high-frequency oscillatory ventilation, open versus closed suctioning techniques produced essentially equal decreases in saturation and heart rate. Recovery time, from these decreases, however, was significantly longer in the open suction group. Not surprisingly, open suctioning produced a greater lung volume loss.[47]

COMPLICATIONS OF MECHANICAL VENTILATION

Each of the physiologic effects of MV has an associated risk. Box 17-4 lists the complications associated with MV and is designed to be comprehensive to emphasize the point that MV, though lifesaving, can be a risky practice if not monitored and managed appropriately.

VOLUTRAUMA/ATELECTRAUMA/BAROTRAUMA

Alveolar overdistention is a primary cause of complications encountered during MV and is a result of high ventilating pressures (**barotrauma**), large tidal volumes (volutrauma), and repetitive opening and closing of the terminal lung units at low lung volumes (atelectrauma). Extrapulmonary air leaks, in the form of pneumothorax, pneumomediastinum, pneumoperitoneum, and subcutaneous emphysema, are the most notable complications and are the result of overdistention of alveolar and peribronchial tissues. Treatment consists of detecting the leak, decreasing tidal volume, and decreasing PEEP, relieving the leak with a chest tube if necessary. Permissive hypercapnia could also be a useful tool in the treatment of an air leak. Rescue modes such as HFJV, HFOV, and extracorporeal membrane oxygenation are implemented for excessive air leakage that does not respond during CMV.

Overdistention also causes a decrease in static compliance, an increase in the work of breathing, an increase in anatomic dead space, an increase in the air leak around the ETT, and possible difficulties in weaning. As compliance diminishes, the $Paco_2$ may rise or fail to improve. To counter this, ventilation is increased, which may lead to further distention.

Because volumes are smaller in neonatal and pediatric patients than in adults, avoiding and detecting overdistention are critical in ventilator management. Alarms that may help detect this are indirect and can be activated by other problems. These alarms may include high mPaw; exhaled minute ventilation and tidal volume; high peak pressure; high PEEP; high respiratory frequency; and inverse I/E ratio. Measures such as using an end-expiratory pause to look for incomplete exhalation and an increase in PEEP or to detect auto-PEEP, measuring optimal static compliance, inspecting pressure–volume loops to determine overdistention or exhaled resistance, monitoring changes in mPaw, and obtaining a chest radiograph all help to detect overdistention.

Box 17-4 Complications of Mechanical Ventilation

- Barotrauma
- Volutrauma
- Atelectrauma
- Biotrauma
- Pulmonary interstitial emphysema
- Subcutaneous emphysema
- Pneumothorax
- Pneumomediastinum
- Pneumopericardium
- Pneumoperitoneum
- Bronchopulmonary dysplasia
- Nosocomial infection
  - Acute respiratory distress syndrome
  - Pneumonia
- Patient–ventilator asynchrony
  - Auto–positive end-expiratory pressure (PEEP)
  - Hyperventilation
  - Respiratory alkalosis
  - Increased work of breathing
- Noncardiopulmonary complications
  - Psychologic distress
  - Renal dysfunction
  - Fluid retention
- Gastrointestinal dysfunction
  - Vomiting
  - Ulceration and bleeding
  - Increased intracranial pressure
  - Interventricular hemorrhage
  - Periventricular leukomalacia
- Airway complications
  - Sinusitis
  - Vocal cord injury
  - Inadvertent extubation
  - Retention of secretions
  - Glottic injury
  - Glottic edema
  - Glottic stenosis
  - Glottic erosion
- Tracheal injury
- Tracheal erosion
- Tracheomalacia
- Tracheal dilation
- Tracheal–innominate artery fistula
- Airway obstruction
  - Mainstem intubation
  - Kinking of endotracheal tube
- Plugging of endotracheal tracheostomy tube
- Cardiovascular compromise
  - Decreased venous return
  - Decreased cardiac output
- Oxygen toxicity
- Retinopathy of prematurity
- PEEP

The formation of a bronchopleural fistula presents an especially challenging clinical situation. Because the volume of gas delivered by the ventilator will follow the path of least resistance, a substantial part of the tidal volume will move into the pleural space during inspiration and escape through the chest tube. This volume is seen as air bubbles through the water seal chamber of the chest tube drainage system, and the amount may be determined by noting the difference between the inspiratory and expiratory volumes. Conventional treatment consisting of maintaining low pressures and volumes to allow permissive hypercapnia and allowing the patient to breathe spontaneously as much as possible may aid in decreasing flow through the fistula and facilitate its closure. When this is not possible in patients with severe ventilation problems, nonconventional modes of treatment may be needed. Independent lung ventilation or high-frequency ventilation may be considered, as may the use of valves to occlude the chest tube during inspiration.

CARDIOVASCULAR COMPLICATIONS

Reduced cardiac output from cardiac septal deviation, increased pulmonary vascular resistance, reduced venous return, and reduced myocardial blood flow is a complication of MV. In most cases, it is a result of increased intrathoracic pressure. In neonatal and pediatric patients, it can usually be prevented by increasing the circulating fluid volume. Vasopressor drugs may also be used to maintain cardiac output during ventilation regimens that include high distending volumes. An increase in intrathoracic pressure may be applied in some clinical situations to reduce left-to-right shunting, raise pulmonary vascular resistance, and impede pulmonary blood flow.

OXYGEN TOXICITY

Oxygen toxicity is another concern during MV. High Fio_2 levels that have been applied for an extended period may result in tissue injury that alters lung function and gas distribution. High Fio_2 levels have also been associated with an increase in chronic lung disease and retinopathy of prematurity among low-birthweight infants. Incorporating a high Fio_2 alarm and minimizing the Fio_2 to the level necessary to attain adequate tissue oxygenation, as well as using pulse oximetry and blood gas monitoring, are essential in attempting to prevent tissue damage. Most clinicians use an Fio_2 algorithm to help them determine the need to make MV interventions. See Chapter 10 for more on oxygen toxicities.

HYPOVENTILATION AND HYPERVENTILATION

The primary cause of hypoventilation during MV is disconnection from the ventilator and unplanned extubation. Care must be used when moving a patient connected to a ventilator, especially during transport and patient care procedures. ETT movement of just a few centimeters can mean the difference between intubation and extubation. An end tidal CO_2 low alarm or low-pressure/disconnect alarm is essential to alert the clinician when this occurs. Hypoventilation may also result from high impedance to inflation, which can be related to high resistance (resulting from anatomic, pathologic, or circuit design) or loss of pulmonary compliance. A low-volume monitor will detect these changes. Hypoventilation can be avoided by measuring V_T, V_D/V_T, and minute ventilation.

Hypoventilation may also be related to "operator error" in establishing ventilation. Hypoventilation caused by minute ventilation, frequency, volume, or flow rate that is insufficient to meet inspiratory demand results in increased work of breathing and muscle fatigue. These conditions may also be present when weaning from the ventilator and may cause weaning failure. An alert patient may communicate feelings of respiratory distress. Retractions, use of accessory muscles, head bobbing, and a 10% to 20% increase in heart rate and spontaneous respiratory frequency are clinical signs of insufficient ventilation. In a sedated, paralyzed, or critically ill patient, however, this problem may not be as evident. Using pressure–volume and flow–volume loops, monitoring carbon dioxide production and oxygen consumption, and obtaining other measurements such as a diaphragm electromyogram may help detect this problem. Ensuring that the initial inspiratory flow rate meets the patient's inspiratory demand is usually the best method of avoidance. An example of a pressure–volume loop demonstrating insufficient flow caused by insufficient driving pressure during ventilation with Pressure Support is shown in Figure 17-13. Figure 17-14 shows the effect of a faulty flow transducer on a diaphragm electromyogram tracing during Pressure Support, leading to increased work of breathing.

Hyperventilation can also be a problem if the patient's lung compliance improves (i.e., through surfactant administration or prone/supine positioning)

FIGURE 17-13 Inadequate flow support on flow–volume loop. A normal loop should look like a football at a 45-degree angle. The inspiratory phase of this loop is concave, a result of inadequate flow.

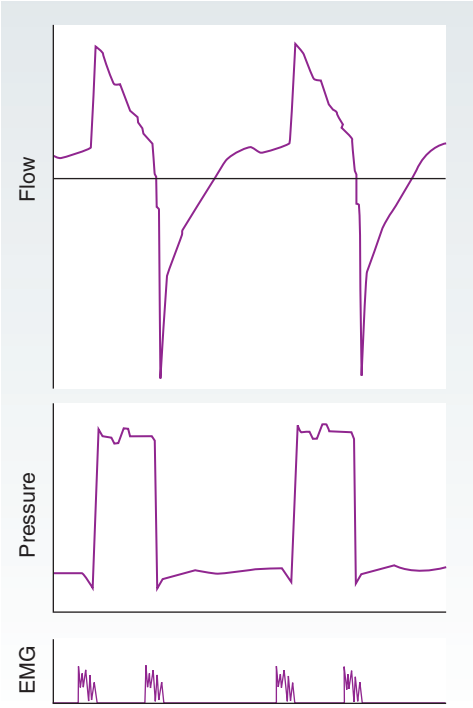


FIGURE 17-14 A recording of the electromyographic signal shows muscle activity initiating inflation during pressure-support ventilation. The flow transducer on this ventilator is defective, and the electromyogram *(EMG)* shows abnormal muscle activity, not seen by clinical observation, at the end of inflation to stop the breath. Transdiaphragmatic pressure measurements would also help detect this situation.

in a pressure control or **pressure support ventilation** mode. Autotriggering of the ventilator as a result of ETT leak, secretions in the circuit or flow sensor, or an inappropriate sensitivity setting can lead to hyperventilation. Hyperventilation and low carbon dioxide in low-birth-weight infants can result in cerebral vasoconstriction, which can cause a cystic brain lesion called *periventricular leukomalacia.* Close monitoring of end tidal or transcutaneous CO_2 levels sensitivity setting, tidal volume, and minute ventilation with alarms has proved to be useful in reducing this problem.

MONITORING DURING LOW-FREQUENCY MECHANICAL VENTILATION

Monitoring effective ventilation is accomplished by using the techniques discussed previously. Box 17-5 lists monitoring applications as they apply to pediatric MV. Most ventilators monitor airway pressure, flow, ventilatory frequency, tidal volume, and minute volume. Essential aspects of monitoring include the following:

- Determination of effective tidal volume by ensuring a properly calibrated ventilator or flow sensor at the proximal airway
- Close observation of the patient for clinical signs of adequate ventilation as well as respiratory distress, such as chest expansion and retractions
- Noninvasive methods of determining oxygenation and ventilation status, such as pulse oximetry, transcutaneous monitoring, and end-tidal carbon dioxide monitoring
- Direct measurement of blood gas values

Figure 17-15 shows possible problems detected with an end-tidal carbon dioxide monitor.

Box 17-5 Monitoring Applications in Neonatal and Pediatric Mechanical Ventilation

MEASURED VENTILATOR VARIABLES

- Effective tidal volume (calculated, CMV only)
- Minute ventilation (calculated, CMV only)
- Mean airway pressure ($\bar{P}_{aw}$) (directly measured, all)
- Low–high positive end-expiratory pressure (PEEP) (directly measured, CMV, HFPV, and HFJV only)
- High peak pressure (directly measured, CMV, HFPV, and HFJV only)
- Fraction of inspired oxygen (FiO_2) (directly measured, all)
- Pause pressure (directly measured, CMV only)
- Inspiratory-to-expiratory ratio (directly measured, all)
- Pressure waveform (directly measured and displayed, CMV and HFPV only)
- Flow waveform (directly measured and displayed, CMV only)
- Static compliance (calculated, CMV only)
- Dynamic compliance (calculated, CMV only)
- Airway resistance (calculated, CMV only)
- Maximal inspiratory occlusion pressure (measured, CMV only)
- Maximal expiratory occlusion pressure (measured, CMV only)
- Maximal minute ventilation (measured, CMV only)
- Vital capacity (measured, CMV only)
- Oscillatory/amplitude/jet peak inspiratory pressure (measured, HFV only)

SUPPLEMENTAL MONITORS

- Pulse oximetry
- End-tidal carbon dioxide with or without volumetric
- End-tidal carbon dioxide to $PaCO_2$ gradient
- Transcutaneous carbon dioxide
- Pressure–volume loop
- Esophageal pressure
- Transpulmonary pressure
- Dead space/tidal volume ratio
- Ineffective-to-effective tidal volume ratio
- Work of breathing
- Pressure–time product
- Pressure–time index

CV, conventional ventilation; *HFJV,* high-frequency jet ventilation; *HFPV,* high frequency; *HFV,* .

ESOPHAGEAL PRESSURE MONITORING

Some ventilators have the ability to monitor esophageal pressure. Esophageal pressure monitoring uses

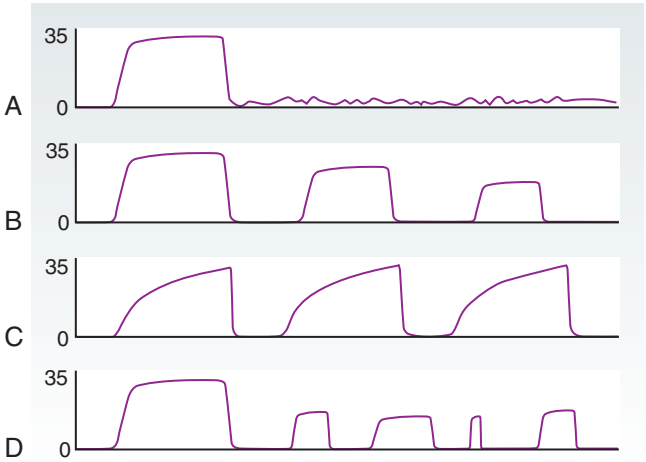


FIGURE 17-15 End-tidal carbon dioxide recordings. **A,** Abrupt disconnection from the ventilator. **B,** Falling partial pressure of end-tidal carbon dioxide possibly from an increase in tidal volume or, if $Paco_2$ is unchanged, a reduction in pulmonary blood flow from overdistention or low cardiac output. **C,** Dampened waveform from severe air flow obstruction or side stream sampling tube obstruction. **D,** System leak or secretions in the sampling chamber. (Modified from *Advanced Concepts in Capnography.* Image used by permission from Nellcor Puritan Bennett, LCC, Boulder, CO, part of Covidien.)

an air-filled, balloon-tipped catheter placed in the midsection of the esophagus, where pleural pressure measurements can be closely estimated. Esophageal pressure measurements can be extremely helpful in understanding the physiology of the respiratory system during MV. It is essential that proper placement of the balloon catheter be confirmed to accurately measure esophageal pressure. These pressure measurements can be displayed graphically or incorporated into a number of pulmonary mechanics calculations. Calculations that require esophageal pressure include chest wall compliance, lung compliance, transpulmonary pressure, work of breathing, change in esophageal pressure, and auto-PEEP.

Evaluation of the esophageal pressure waveform can be compared graphically with other ventilator graphics and provides important clinical information regarding interactions between the patient and the ventilator. Esophageal balloon technology can also guide the clinician during difficult weaning from MV without increased patient intolerance.

ESTIMATING LUNG VOLUMES

At present, the ability to determine whether ventilator breaths are delivered at, below, or above their ideal functional residual capacity is deduced from surrogate measurements, including lung appearance on the chest radiograph, vital sign trends (particularly oxygenation), and dynamic pressure–volume (P–V) curves generated by modern ventilators.

Automated Quasi-static Pressure-Volume Curves

P–V curves can provide important information about the compliance of the respiratory system when supporting mechanically ventilated patients with restrictive lung diseases. Ventilators have incorporated automated slow-flow or "quasistatic" P–V curves that use a slow inspiratory flow or pressure[48] rate delivered during a single breath. This method reduces the pressure increase caused by the resistive elements (ETT, high flow rates) to more closely approximate the alveolar pressure.

The slope of the line is measured to determine compliance of the respiratory system (line C, Figure 17-16).

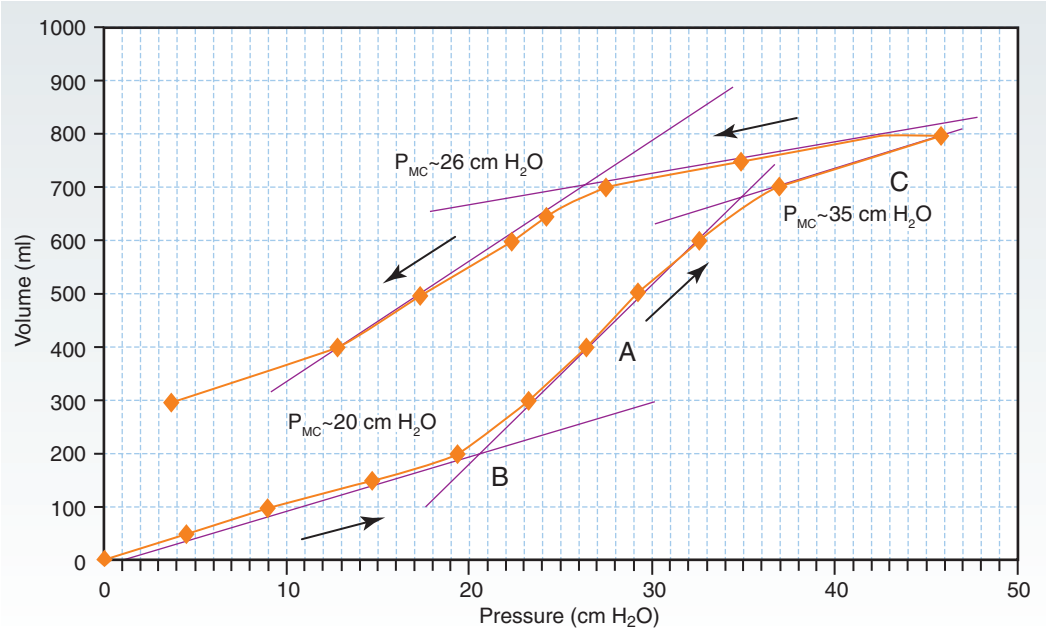


FIGURE 17-16 Pressure–volume curves as determined by the super-syringe method. PMC = pressure of maximum curvature in the pressure-volume curve.

These technologies also provide algorithms that measure the upper and lower inflection points of a nonlinear respiratory system compliance curve. These points represent areas on the P–V loop during lung inflation and deflation, where there is a substantial decrease in compliance. Figure 17-16 shows three lines that comprise the inflation limb (lower curve) of a static P–V curve. Line B represents an area of low compliance related to the opening of atelectatic lung units early during inflation of the lung. The point at which the slope of the line changes (where line A intersects line B) reflects an area where there is an acute improvement in compliance; this is the point of maximum curvature, but sometimes called the *lower inflection point* as the *lower inflection point.* Mechanical ventilator practices that adopt an "open lung approach" set PEEP to a pressure just above the lower inflection point. In theory, as long as PEEP is set above the lower inflection point on the inflation or deflation limb, oxygenation improves by resolving atelectasis and increasing the functional residual capacity. Lung injury can also be reduced, because the patient is ventilated above the closing pressure of the lung, and thus repetitive cycling of the lung at low volumes decreases atelectrauma. Figure 17-16 also distinguishes a second point where compliance decreases (where line A intersects line C); this is another point of maximum curvature, often called the *upper inflection point.* This point represents the start of overdistention of the respiratory system. Ventilator pressures or tidal volume settings can be set below this point to avoid lung overdistention or volutrauma.

MONITORING DURING HIGH-FREQUENCY VENTILATION

As during CV, the frequency of blood gas sampling is related to the patient's clinical status and noninvasive monitoring capability. Blood gas measurements should be obtained frequently during the early course of ventilatory management and in patients in extremis (e.g., every 1 to 4 hours). Intervals between samples should be increased as clinical conditions improve. For trending purposes, pulse oximetry and transcutaneous Pco_2 monitoring should be used. Because of rapid changes in $Paco_2$ noted especially during initial HFV management, transcutaneous monitoring is strongly recommended. There is no alteration in performance of these noninvasive gas exchange methods for patients receiving HFV.

Note: For more information on invasive blood gas analysis, see Chapter 8. For more details on noninvasive monitoring, see Chapter 9.

WEANING FROM MECHANICAL VENTILATION

LOW FREQUENCY

Initiation

Weaning is the gradual process by which MV is discontinued and the patient resumes spontaneous breathing. The process may be rapid or slow, depending on the individual clinical situation. It is difficult to define at exactly what point during MV the weaning process should begin; however, most would agree that ideally it is after significant resolution or reversal of the pathologic condition for which it was initiated. Before weaning begins, the patient's condition should be stable and the patient should be receiving adequate nourishment and be able to breathe spontaneously and maintain a clinically acceptable $Paco_2$. The ventilator should be on acceptable settings—usually PEEP less than 8 cm H_2O; peak pressure less than 25 cm H_2O; mandatory rate less than 20 breaths per minute for a neonate, 15 breaths per minute for an infant or toddler, and 10 breaths per minute for a child or adolescent; and Fio_2 less than 0.4 to 0.5.

Various methods exist for measuring respiratory muscle endurance and predicting successful weaning. Simple observations such as accessory or paradoxical muscle activity, respiratory rate, tidal volume, and minute ventilation are the first indicators of weaning readiness. An increase in respiratory frequency of 15% to 20% or a reduction in tidal volume is associated with impending fatigue. Maintaining normal or clinically acceptable $Paco_2$ with normal minute ventilation (estimated to be 100-120 mL/kg for infants and toddlers or 4-9 L/minute for adolescents and adults) would indicate that the patient might tolerate weaning. Normal carbon dioxide production in an infant is 6 mL/kg/minute, and it is 3 mL/kg/minute in an adult. Excessive carbon dioxide production indicates a hypermetabolic state and may be corrected by adjusting nutritional elements to lower the respiratory quotient. Another helpful determinant of the ability to wean is the V_D/V_T ratio. The normal value is 0.3; however, intubation and MV may alter this. A value of less than 0.6 to 0.7 may predict successful weaning. Another clinically measurable variable that roughly approximates the V_D/V_T ratio is the ineffective/effective tidal volume ratio. Abnormal values may indicate continued pulmonary or cardiac dysfunction. Measurement of the end-tidal carbon dioxide to $Paco_2$ gradient may also help detect continued pulmonary or cardiac dysfunction. In this case, cautious weaning may be indicated, although resolution of the clinical condition is most likely indicated.

Other predicting factors may also be considered. A flow–volume loop may help discover impedance to inspiratory or expiratory flow that will precipitate fatigue. A pressure–volume loop may help determine work of breathing and evaluate various weaning modes. Measurements of dynamic and static compliance, resistance, transpulmonary pressure tracing, work of breathing, the respiratory time fraction, the pressure time product (PTP), and the pressure time index (PTI) are useful in monitoring the course of weaning. The PTP reflects the metabolic work of the respiratory system and is an electronically integrated value derived from tidal volume, compliance, esophageal pressure, and duration of the breath. The PTI

combines the PTP and the respiratory time fraction and correlates directly with muscle fatigue and oxygen consumption. Spontaneous maximal inspiratory and expiratory occlusion pressures may also be of value. These measurements are routine weaning values in many adult units, along with maximal spontaneous minute ventilation and vital capacity measurements. Unlike these measurements, however, occlusion pressure measurements do not require that a patient understand the breathing techniques necessary to effectively determine the values.

Concepts of Weaning

The basic weaning techniques used in neonates and pediatric patients include CPAP, PC-SIMV, and PSV. Using during weaning is not very common among pediatric patients. The positive airway pressure is used to provide the physiologic PEEP, which is bypassed when the patient is intubated. Two techniques for using CPAP are practiced. The first is applied when there is sufficient respiratory drive and endurance but the physiologic effects of PEEP are still required. In this case, CPAP is gradually reduced during the weaning process. The second technique is a postoperative weaning technique. The usefulness of this technique in pediatrics may be limited, however, because of the high resistance of the small-diameter airways. It may occasionally be used to build respiratory muscle endurance by using a bias flow during short-duration exercises alternating with long periods of complete rest. The exercise periods are slowly increased as the resting periods are decreased. The process continues until the patient can breathe without support for a specified time. This technique is typically used only when the goal is to wean the patient to intermittent periods off the ventilator, such as with certain neuromuscular diseases or quadriplegia or in preparation for phrenic nerve pacing.

Intermittent mandatory ventilation, IMV, (with volume control or pressure control) involves a gradual decrease in the ventilator frequency, usually in increments of 2 to 5 breaths per minute. As the set frequency is reduced, the patient is required to contribute more spontaneous breaths to the total ventilatory frequency. How quickly the set frequency is decreased depends on an assessment of the patient's clinical status and blood gas values. The more slowly the process is performed, the more time the patient has to acclimate to less ventilator support. Factors such as ventilator system resistance, a sluggish demand valve, an inappropriate size endotracheal tube, or insufficient inspiratory flow may affect the success of weaning with IMV. Weaning with IMV is generally uncomplicated and is usually successful.

Weaning with PSV provides sufficient positive pressure to overcome ETT resistance and minimize the metabolic requirement for ventilation during weaning. Keep in mind that PSV supports both the resistive and the elastic work of breathing, and therefore may lead to over-estimation of the patient's ability to sustain the full work of breathing once extubated. Once weaning is indicated and PSV is selected, the pressure support level should be adjusted to deliver a tidal volume of 3 to 4 mL/kg in neonates and 5 to 7 mL/kg in pediatric patients. Frequency should be monitored and the pressure support level adjusted to attain appropriate V_T. Once satisfactory volume, flow, and spontaneous respiratory frequency are attained, the pressure support level can be reduced in increments of 2 to 5 cm H_2O. Although at a higher pressure level, the patient contributes only the muscle work required to trigger the inflation. As the pressure is reduced, the patient progressively shares more of the work of breathing. The pressure support should be weaned at a rate that is reasonable for each clinical situation. ETT or tracheostomy tube leaks can hinder this progress. For those with large ETT leaks, modalities like NAVA may be beneficial. The patient who has been mechanically ventilated for only a short time, such as a stable postoperative patient, can be weaned at a rapid pace. A patient who has undergone long-term MV requires patience and persistence on the part of clinicians in reducing the support level by only 1 or 2 cm H_2O over a longer period, such as a day or even a week. In these patients, weaning can be slowed by clinical events such as a viral illness or fluid and electrolyte imbalance. Once these clinical conditions are resolved, usually weaning can be continued with a successful outcome.

HIGH FREQUENCY

Initiation

At this stage of HFV development, weaning remains a challenge. Weaning from ventilation is, for the most part, simple. Weaning from minute ventilation can be accomplished by reducing oscillatory amplitude or increasing the frequency during HFOV and by decreasing peak pressure and on time with HFJV. Changes in ventilation rarely have an impact on oxygenation, because lung volume is preserved. Conversely, weaning from mPaw with improving compliance and increasing lung inflation is less straightforward. Radiographic assessment of lung volume and Fio_2 may provide empirical information guiding management sufficiency. A well-inflated lung requires a reduction in mean pressure to avoid the negative consequences of excessive lung volume. However, a too rapid reduction in distending pressure can cause alveolar derecruitment in the unstable lung, and reinflation will be necessary. In general, mPaw should be reduced slowly (1 to 2 cm H_2O) every 2 to 3 hours as long as there are no signs of overdistention (suggesting a much more rapid decreases are necessary) or alveolar derecruitment (decrements in oxygenation). By taking advantage of lung hysteresis, gradual reductions in mean pressure generally do not cause significant changes in oxygenation or, by inference, lung volume (Figure 17-17). Simple and reproducible bedside measures of lung volume are on the horizon. The application of these techniques to weaning may be useful in the future.

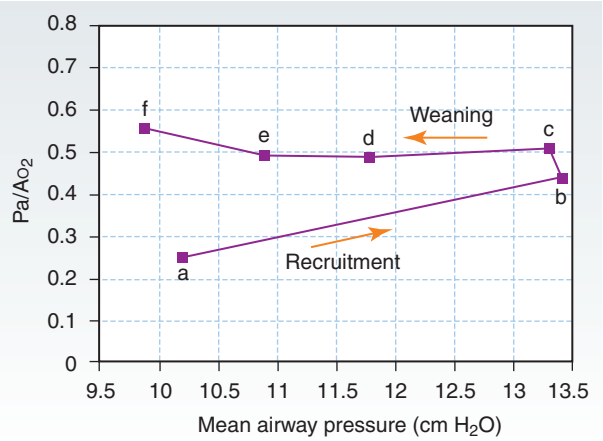


FIGURE 17-17 Mean arterial/alveolar oxygen tension ratio [$P(a/A)O_2$] and mPaw of 21 premature infants managed with high-frequency oscillatory ventilation (HFOV) immediately after surfactant replacement. Note that increasing mPaw initially results in increased $P(a/A)O_2$ (alveolar recruitment); subsequent mPaw weaning does not reduce oxygenation but is associated with gradual improvement in $P(a/A)O_2$. The line between points b and c represents silent lung recruitment as assessed by improving $P(a/A)O_2$ mPaw with essentially constant. *a*, Surfactant replacement; *b*, 12 hours later; *c*, 12 to 24 hours later; *d*, 24 to 48 hours later; *e*, 48 to 72 hours later; and *f*, 72 to 96 hours later.

Radiographic assessment of lung volume takes considerable practice. The novice is cautioned that although, in general, lung volume can be assessed by counting the number of posterior ribs seen above the diaphragm, radiographs of neonates are usually AP views, and counting ribs requires the juxtaposition of an anterior structure (the diaphragm) against a posterior structure (the rib interfacing with the diaphragm). This method assesses a three-dimensional object (the lung) with a two-dimensional picture (the radiograph) and is vulnerable to technician-selected focus angles. It is possible, then, to underestimate or overestimate inflation.

The inability to routinely measure lung volume or compliance at the bedside and the ease with which acceptable oxygenation is achieved with relatively high mPaw can confuse the clinician about the speed at which weaning should occur. Experience seems to be the best teacher in this situation. The consequences of failing to wean the patient quickly enough are significant pulmonary overdistention and impairment of cardiac output. In neonates, this complication can increase the risk of intracranial hemorrhage, because venous return from vessels draining the head is impeded and venous hypertension and vessel rupture can ensue. Conversely, rapid weaning of mPaw can result in alveolar derecruitment, requiring reinitiation of lung recruitment procedures.

TROUBLESHOOTING

The approach to troubleshooting does not differ from that of CMV or HFV. Either deterioration of the patient's vital signs or a ventilator alarm may alert the clinician. In either circumstance, it is necessary to ensure that the patient is in no further jeopardy before proceeding with a detailed troubleshooting procedure. High-frequency ventilators are dependent on patient airway caliber for adequate volume delivery. A change in airway diameter (e.g., by accumulation of secretions or by migration of the tip of the ETT against the tracheal wall) may significantly reduce delivered volumes. The first step should be a quick assessment of chest wall movement. If chest wall motion is substantially decreased, brief manual ventilation while troubleshooting the airway and ventilator may dramatically improve the situation. Steps should be taken to correct any problems with the ETT lumen or position (e.g., suctioning, chest radiograph).

As with CMV, there are conditions for which HFV techniques are not uniformly successful. HFV seems especially vulnerable to the state of myocardial performance. In patients with poor cardiac output (e.g., decreased intravascular volume or reduced contractility), lung inflation with high mPaw can result in abrupt and serious cardiac output impairment. Ensuring the adequacy of cardiac output before initiating HFV can mitigate this. Low-volume strategies will have less impact on cardiac output. For this reason, HFJV is successful during cardiac surgery and in circumstances in which lung compliance is normal and cardiac output is reduced.

Because a relatively high MLV is necessary for HFOV, this technique is not optimal for use in normal lungs. Furthermore, in conditions in which airway resistance is increased, such as fresh particulate meconium aspiration, bronchopulmonary dysplasia, and reactive airway disease, HFOV may not be optimal. Because of the tremendous impedance to flow created by reductions in airway lumen with these disorders (thus increasing pulmonary time constants), decreases in delivered tidal volume or gas trapping, or both, cause derangement in gas exchange. In contrast, HFJV or HFPV using larger tidal volumes and lower breathing frequencies may be more efficacious for conditions in which airway time constants are pathologically prolonged. These impressions are based on theoretical considerations and anecdotal experience. Extensive controlled data supporting these contentions are not currently available.

Each ventilator manufacturer has developed detailed approaches to troubleshooting the mechanical problems of its own device, and these recommendations should be followed, tempered by actual clinical experience. A regular preventive maintenance program will help reduce mechanical failures.

ADVANCING CONCEPTS

CONVENTIONAL VENTILATION

Advances and improvements in technologies and practices such as high-frequency ventilation, nitric oxide, corticosteroids, prone positioning, permissive

hypercapnia, extracorporeal membrane oxygenation, and surfactant replacement all influence future design of and approaches to conventionally ventilating neonates and pediatric patients.

Automated regulation of inspired oxygen (closed-loop Fio_2) is a novel concept that is likely to be on the horizon for use in the near future. This feature requires the clinician to set a patient saturation range (e.g., 85% to 92%) on the ventilator. A pulse oximeter is attached to the patient, and signal extraction software within the ventilator obtains the measurements from the oximeter probe. If the saturation measurement increases above or decreases below the target range, the ventilator will adjust the Fio_2 to keep oxygen saturation within the prescribed range. This can potentially reduce the frequency of hypoxic or hyperoxic episodes in very-low-birth-weight infants receiving MV. It has been speculated that long-term closed-loop Fio_2 control may reduce clinician time maintaining adequate oxygenation and reduce the risk of morbidity (retinopathy of prematurity and bronchopulmonary dysplasia) associated with supplemental oxygen and frequent episodes of hypoxemia and hyperoxemia.

Ventilators are increasingly becoming "partial support" in that they must work dynamically with the patient. Proportional assist ventilation is an innovative new mode that is currently being investigated for neonatal and pediatric MV. This mode uses an algorithm that varies pressure support or pressure control levels on the basis of patient effort and changes in patient elastic and resistive loads during inhalation and exhalation. Preliminary work suggests that this mode may result in improvements in patient synchrony, oxygenation index, and overall cardiovascular stability. Newer ventilator companies are incorporating many modes, triggers, and graphics to help clinicians pick and choose what is best for an individual patient's needs. This fosters a dynamic relationship between the ventilator and the patient. Negative-pressure ventilation is also finding its way back into the critical care setting. Cardiopulmonary interactions are being investigated in children after simple cardiac surgery.

HIGH-FREQUENCY VENTILATION

The learning curve for these techniques continues to progress. Clinicians using HFV early in patients with respiratory distress syndrome believe that hospital courses are reduced and significant pulmonary morbidity is decreased. The impact of HFJV on patients with PIE has been clearly demonstrated.[49] The precise role of HFV with respect to long-term outcome and cost of care continues to be defined. The availability of exogenous surfactant replacement, newer modes of CV for primary management, and ECMO and inhalation nitric oxide for patients with intractable respiratory failure continue to affect HFV use. Ongoing investigations into the field of liquid ventilation, particularly partial liquid ventilation, are likely to stimulate new applications and enhance patient outcomes.

Key Points

- The mechanical ventilator is a lifesaving piece of equipment and should be maintained as if lives depend on it. Remember that ventilators require calibration, preventive maintenance, and proper cleaning to ensure the best respiratory support.
- An ounce of prevention is worth a pound of a cure. MV should only be provided for as long as it is needed. All steps should be taken by the respiratory care practitioner to minimize ventilator-associated lung injury or adverse events.
- No one mode of ventilation has been shown to be superior to another. It is vitally important that no matter what mode of ventilation the clinician chooses, he or she knows all the management strategies associated with good outcomes.
- The HFV choice of strategy (high or low lung volumes) is lung disease–specific. Although simplistic, it is reasonable to try to inflate an underinflated lung and deflate an overinflated or air-trapped one.
- Auto-PEEP is the difference between alveolar pressure and external airway pressure at end expiration.
- Simply stated, the goal of PEEP therapy is to improve oxygenation by increasing FRC through maintenance of airway patency and alveolar recruitment.
- Lowering the HFV frequency may improve ventilation.

Assessment Questions

1. Which of the following issues would most likely explain why a newborn infant's measured respiratory rate would rise from 40 to 100 breaths/minute on a ventilator after the patient was turned and an audible endotracheal tube leak was heard?
   A. Pneumothorax
   B. Auto-triggering
   C. Secretions
   D. Bradypnea
2. A 10-year-old child is intubated and receiving mechanical ventilation. The tidal volume is set at 280 mL, peak airway pressure is 38 cm H_2O, plateau pressure is 20 cm H_2O, and PEEP is 5 cm H_2O. The tubing compliance factor is 1.5 mL/cm H_2O. What is the actual delivered V_T to this patient if the ventilator does not compensate for compressible volume loss?
   A. 255 mL
   B. 157 mL
   C. 230 mL
   D. 330 mL

3. A term infant is being invasively ventilated in the pressure-targeted SIMV mode of ventilation; set rate is 16, PIP is 18, PEEP is 4, inspiratory time is 0.4, and Fio_2 is >30, and the physician would like to wean the infant from the ventilator. The clinician has tried turning the patient's set rate on SIMV down to 10 breaths/minute, but the infant immediately becomes tachypneic and desaturates to 85%. Which of the following should be done at this time?
   A. Increase PEEP
   B. Initiate pressure support ventilation
   C. Increase inspiratory time
   D. Extubate to nasal CPAP
4. A 600-g neonate is being mechanically ventilated in pressure control ventilation with the following settings: PIP, 24 cm H_2O; PEEP, 4 cm H_2O; Fio_2, 0.45; respiratory rate, 40 breaths/minute. Which inspiratory time should the clinician recommend?
   A. 0.6 second
   B. 0.3 second
   C. 0.8 second
   D. 1.0 second
5. The physician would like to begin dual-control ventilation of a 500-g infant. What would be the initial corrected volume target?
   A. 5 mL/kg
   B. 7 mL/kg
   C. 8 mL/kg
   D. 10 mL/kg
6. While observing a ventilator flow graphic for a 12-year-old patient with asthma on a rate of 10 breaths per minute, the clinician notices that expiratory flow does not return to baseline and the patient's auto-PEEP level is 6 cm H_2O. Which ventilator manipulation might help this patient the most?
   A. Increase respiratory rate by 8 breaths/minute
   B. Decrease inspiratory time
   C. Decrease peak inspiratory flow
   D. Increase PEEP
7. A neonatal patient with respiratory syncytial virus (RSV) is receiving mechanical ventilation in the pressure control mode with the following current settings: PIP, 14 cm H_2O; PEEP, 5 cm H_2O; Fio_2, 0.50; respiratory rate, 28 breaths/minute. The patient has poor chest rise bilaterally, and breath sounds are underaerated with faint wheezes bilaterally. You notice that the measured tidal volume is 3 mL/kg and the respiratory rate is 80 breaths/minute. The patient has nasal flaring, retractions, and head bobbing. What should be suggested at this time?
   A. Placing the patient on a high-frequency oscillator
   B. Suctioning and then increasing PIP
   C. Decreasing the respiratory rate
   D. Using a neuromuscular blocking agent
8. Which ventilator approach would be good for a 10-year-old with severe ARDS who is spontaneously breathing while undergoing ventilation?
   A. PCV
   B. APRV
   C. CPAP
   D. IRV
9. Which of the following factors does not affect mean airway pressure?
   A. PEEP
   B. I-time
   C. Time constant
   D. PIP
10. High-frequency ventilation is defined by the FDA as delivering more than:
   A. 150 breaths/minute
   B. 120 breaths/minute
   C. 100 breaths/minute
   D. 60 breaths/minute
11. HFJV delivers gas by:
   A. Intermittently occluding a high flow of gas with a rotating vane
   B. Pulsing gas down the ETT at a high velocity
   C. Passing gas past the ETT and agitating it with a piston
   D. The same method as conventional ventilation, just at a higher frequency
12. HFOV delivers gas by:
   A. The same method as conventional ventilation, just at a higher frequency
   B. Pulsing gas down the ETT at a high velocity
   C. Alternating gas in and out via a rotating vane
   D. Passing gas past the endotracheal tube and agitating it with a piston
13. The exhalation phase of HFOV differs from other forms of high-frequency ventilation because:
   A. Exhaled gas is actively pulled out via the patient as the piston moves back.
   B. Exhalation is passive, whereas on the HFJV gas is pulled out via a Venturi effect.
   C. Exhalation is active during HFOV because of a separate vacuum-assist device.
   D. Exhaled gas passively exits the patient because of passive chest recoil.
14. Which of the following most accurately describes the relationship of lung volume in a restrictive disease and $\bar{P}_{aw}$:
   I. Increasing $\bar{P}_{aw}$ increases lung volume and improves ventilation–perfusion matching.
   II. Increasing $\bar{P}_{aw}$ increases the pressure gradient, allowing more oxygen to cross the alveolar capillary membrane.
   III. Increasing $\bar{P}_{aw}$ improves the efficiency of the jet or piston.
   IV. At very high and very low lung volumes, ventilation–perfusion matching is impaired.
      A. I
      B. II
      C. I, III, IV
      D. I and IV
15. The goal in treating atelectatic-prone lung is:
   A. High lung volume to recruit alveolar lung units
   B. Low lung volume to reduce the chance of barotrauma
   C. High tidal volumes during convention ventilation to assist in carbon dioxide removal
   D. High lung volume to recruit the lung and large tidal volumes to aid ventilation

16. The goal in treating infants with pulmonary interstitial emphysema or active air leak is:
    - **A.** High lung volume to recruit alveolar lung units
    - **B.** Low lung volume to reduce the chance of creating or worsening an air leak
    - **C.** High lung volume to recruit the lung and large tidal volumes to aid ventilation
    - **D.** Low tidal volumes combined with high lung volumes
17. A neonate is progressing satisfactorily on HFOV, with a mean airway pressure of 15 cm H_2O. The physician consults the respiratory clinician to determine in what increment the $\bar{P}_{aw}$ should be reduced for weaning. What should the respiratory therapist recommend?
    - **A.** 4-6 cm H_2O
    - **B.** 3-4 cm H_2O
    - **C.** 1-2 cm H_2O
    - **D.** No increment; simply extubate
18. A clinician prepares to suction a patient undergoing HFV. What is the most likely consequence of suctioning?
    - **A.** Hypoxia, requiring a temporary increase in $\bar{P}_{aw}$ to resolve
    - **B.** Pulmonary hemorrhage, requiring ETT epinephrine
    - **C.** Negative-pressure pulmonary edema, requiring a temporary increase in $\bar{P}_{aw}$ to resolve
    - **D.** None of the above
19. An infant has just been placed on HFJV. What trending monitor(s) should be recommended?
    - **A.** In-line blood gas analyzer
    - **B.** Pulse oximetry
    - **C.** Transcutaneous monitoring
    - **D.** B and C

REFERENCES

1. Cheifetz IM. Pediatric ARDS. *Respir Care*. 2017;62(6):718-731.
2. Amini R, Herrmann J, Kaczka DW. Intratidal overdistention and derecruitment in the injured lung: a simulation study. *IEEE Trans Biomed Eng*. 2017;64(3):681-689.
3. Nash G, Blennerhassett J, Pontoppidan H. Pulmonary lesions associated with oxygen therapy and artificial ventilation. *Laval Med*. 1968;39(1):59-64.
4. Northway Jr WH, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. *N Engl J Med*. 1967;276(7):357-368.
5. Taghizadeh A, Reynolds EO. Pathogenesis of bronchopulmonary dysplasia following hyaline membrane disease. *Am J Pathol*. 1976;82(2):241-264.
6. Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342(18):1301-1308.
7. Wang C, Guo L, Chi C, et al. Mechanical ventilation modes for respiratory distress syndrome in infants: a systematic review and network meta-analysis. *Crit Care*. 2015;19:108.
8. Shetty S, Greenough A. Neonatal ventilation strategies and long-term respiratory outcomes. *Early Hum Dev*. 2014;90(11):735-739.
9. Mireles-Cabodevila E, Hatipoğlu U, Chatburn RL. A rational framework for selecting modes of ventilation. *Respir Care*. 2013;58(2):348-366.
10. Courtney SE, Asselin JM. High-frequency jet and oscillatory ventilation for neonates: which strategy and when? *Respir Care Clin N Am*. 2006;12(3):453-467.
11. Musk GC, Polglase GR, Bunnell JB, Nitsos I, Tingay D, Pillow JJ. A comparison of high-frequency jet ventilation and synchronised intermittent mandatory ventilation in preterm lambs. *Pediatr Pulmonol*. 2015;50(12):1286-1293.
12. Ethawi YH, Abou Mehrem A, Minski J, Ruth CA, Davis PG. High frequency jet ventilation versus high frequency oscillatory ventilation for pulmonary dysfunction in preterm infants. *Cochrane Database Syst Rev*. 2016;5:CD010548.
13. Chatburn RL, Primiano Jr FP. Decision analysis for large capital purchases: how to buy a ventilator. *Respir Care*. 2001;46(10):1038-1053.
14. Sinderby C, Beck JC. Neurally adjusted ventilatory assist. In: Tobin MJ, ed. *Principles and Practice of Mechanical Ventilation*. 2013.
15. Sinderby C, Liu S, Colombo D, et al. An automated and standardized neural index to quantify patient-ventilator interaction. *Crit Care*. 2013;17(5):R239.
16. Greenough A, Dimitriou G, Prendergast M, Milner AD. Synchronized mechanical ventilation for respiratory support in newborn infants. *Cochrane Database Syst Rev*. 2008(1):CD000456.
17. Chatburn RL, Mireles-Cabodevila E. Closed-loop control of mechanical ventilation: description and classification of targeting schemes. *Respir Care*. 2011;56(1):85-102.
18. Schulze A. Respiratory gas conditioning and humidification. *Clin Perinatol*. 2007;34(1):19-33, v.
19. Heinze H, Eichler W. Measurements of functional residual capacity during intensive care treatment: the technical aspects and its possible clinical applications. *Acta Anaesthesiol Scand*. 2009;53(9):1121-1130.
20. Volsko TA, Chatburn RL, El-Khatib MF. *Equipment for Respiratory Care*. Burlington: State abbreviation needed. Jones & Bartlett Learning; 2016.
21. Wheeler KI, Klingenberg C, Morley CJ, Davis PG. Volume-targeted versus pressure-limited ventilation for preterm infants: a systematic review and meta-analysis. *Neonatology*. 2011;100(3):219-227.
22. Beck J, Emeriaud G, Liu Y, Sinderby C. Neurally adjusted ventilatory assist (NAVA) in children: a systematic review. *Minerva Anestesiol*. 2016;82(8):874-883.
23. Grazioli S, Karam O, Rimensberger PC. New generation neonatal high frequency ventilators: effect of oscillatory frequency and working principles on performance. *Respir Care*. 2015;60(3):363-370.
24. Wheeler CR, Smallwood CD, O'Donnell I, Gagner D, Sola-Visner MC. Assessing initial response to high-frequency jet ventilation in premature infants with hypercapnic respiratory failure. *Respir Care*. 2017;62(7):867-872.
25. Hupp SR, Turner DA, Rehder KJ. Is there still a role for high-frequency oscillatory ventilation in neonates, children and adults? *Expert Rev Respir Med*. 2015;9(5):603-618.
26. Mireles-Cabodevila E, Chatburn RL. Mid-frequency ventilation: unconventional use of conventional ventilation as a lung-protection strategy. *Respir Care*. 2008;53(12):1669-1677.

27. Bhat R, Kelleher J, Ambalavanan N, Chatburn RL, Mireles-Cabodevila E, Carlo WA. Feasibility of mid-frequency ventilation among infants with respiratory distress syndrome. *Respir Care*. 2017;62(4):481-488.
28. Fredberg JJ, Glass GM, Boynton BR, Frantz ID. Factors influencing mechanical performance of neonatal high-frequency ventilators. *J Appl Physiol (1985)*. 1987;62(6):2485-2490.
29. Chang HK. Mechanisms of gas transport during ventilation by high-frequency oscillation. *J Appl Physiol Respir Environ Exerc Physiol*. 1984;56(3):553-563.
30. Jackson AC, Vinegar A. A technique for measuring frequency response of pressure, volume, and flow transducers. *J Appl Physiol Respir Environ Exerc Physiol*. 1979;47(2):462-467.
31. Chatburn RL, Lough M, Primiano Jr FP. Modification of a ventilator pressure monitoring circuit to permit display of mean airway pressure. *Respir Care*. 1982;27(3):276-281.
32. Weisberger SA, Carlo WA, Chatburn RL, Fouke JM, Martin RJ. Effect of varying inspiratory and expiratory times during high-frequency jet ventilation. *J Pediatr*. 1986;108(4):596-600.
33. Primiano Jr FP, Chatburn RL, Lough MD. Mean airway pressure: theoretical considerations. *Crit Care Med*. 1982;10(6):378-383.
34. Marini JJ, Crooke PS, Truwit JD. Determinants and limits of pressure-preset ventilation: a mathematical model of pressure control. *J Appl Physiol (1985)*. 1989;67(3):1081-1092.
35. Rimensberger PC, Cheifetz IM. Ventilatory support in children with pediatric acute respiratory distress syndrome: proceedings from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Criti Care Med*. 2015;16(5 suppl 1):S51-S60.
36. Kheir JN, Walsh BK, Smallwood CD, et al. Comparison of 2 lung recruitment strategies in children with acute lung injury. *Respir Care*. 2013;58(8):1280-1290.
37. Gilbert R, Keighley JF. The arterial-alveolar oxygen tension ratio. An index of gas exchange applicable to varying inspired oxygen concentrations. *Am Rev Respir Dis*. 1974;109(1):142-145.
38. McCulloch PR, Forkert PG, Froese AB. Lung volume maintenance prevents lung injury during high frequency oscillatory ventilation in surfactant-deficient rabbits. *Am Rev Respir Dis*. 1988;137(5):1185-1192.
39. Keszler M, Montaner MB, Abubakar K. Effective ventilation at conventional rates with tidal volume below instrumental dead space: a bench study. *Arch Dis Child Fetal Neonatal Ed*. 2012;97(3):F188-F192.
40. Williams R, Rankin N, Smith T, Galler D, Seakins P. Relationship between the humidity and temperature of inspired gas and the function of the airway mucosa. *Crit Care Med*. 1996;24(11):1920-1929.
41. Cerpa F, Cáceres D, Romero-Dapueto C, et al. Humidification on ventilated patients: heated humidifications or heat and moisture exchangers? *Open Respir Med J*. 2015;9:104-111.
42. Restrepo RD, Walsh BK. Humidification during invasive and noninvasive mechanical ventilation: 2012. *Respir Care*. 2012;57(5):782-788.
43. Guidelines for preventing health-care-associated pneumonia, 2003 recommendations of the CDC and the Healthcare Infection Control Practices Advisory Committee. *Respir Care*. 2004;49(8):926-939.
44. Morrow BM, Mowzer R, Pitcher R, Argent AC. Investigation into the effect of closed-system suctioning on the frequency of pediatric ventilator-associated pneumonia in a developing country. *Pediatr Crit Care Med*. 2012;13(1):e25-e32.
45. Tume LN, Baines PB, Guerrero R, et al. Pilot study comparing closed versus open tracheal suctioning in postoperative neonates and infants with complex congenital heart disease. *Pediatr Crit Care Med*. 2017;18(7):647-654.
46. Pirr SM, Lange M, Hartmann C, Bohnhorst B, Peter C. Closed versus open endotracheal suctioning in extremely low-birth-weight neonates: a randomized, crossover trial. *Neonatology*. 2013;103(2):124-130.
47. Kalyn A, Blatz S, Sandra F, Paes B, Bautista C. Closed suctioning of intubated neonates maintains better physiologic stability: a randomized trial. *J Perinatol*. 2003;23(3):218-222.
48. Grooms DA, Sibole SH, Tomlinson JR, Marik PE, Chatburn RL. Customization of an open-lung ventilation strategy to treat a case of life-threatening acute respiratory distress syndrome. *Respir Care*. 2011;56(4):514-519.
49. Keszler M, Donn SM, Bucciarelli RL, et al. Multicenter controlled trial comparing high-frequency jet ventilation and conventional ventilation in newborn infants with pulmonary interstitial emphysema. *J Pediatr*. 1991;119(1 Pt 1):85-93.

18 Administration of Gas Mixtures

Brian K. Walsh

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. Identify the basic chemical properties of nitric oxide.
2. Describe the process of smooth muscle contraction and relaxation.
3. Differentiate between intravenous vasodilators (such as nitroprusside or prostaglandin E) and inhaled nitric oxide regarding ventilation-perfusion matching and shunt.
4. Identify the potential side effects of inhaled nitric oxide.
5. Describe the beneficial properties of helium when used medically.
6. Describe how heliox affects nebulizers, flow meters, and mechanical ventilators.
7. List the inhaled anesthetic agents commonly used to treat status asthmaticus.
8. List the physiologic effects of inhaled anesthetic agents.

Key Terms

anesthetic mixtures
helium–oxygen mixture
inhaled nitric oxide
isoflurane
pulmonary vasodilation
sevoflurane
therapeutic gas mixtures

One of the primary goals of critical care is to optimize oxygen delivery to the tissues. Often this entails the delivery of supplemental oxygen. However, other gases may be used to improve oxygen delivery, based on the patient's clinical diagnosis. The gases discussed in this chapter dilate the pulmonary vasculature and reduce airway resistance by relaxing bronchial smooth muscle tone.

NITRIC OXIDE

Nitric oxide is an endogenous free radical synthesized in the endothelial cells and plays a major role in the regulation of vascular tone. Inhaled nitric oxide (iNO) is an odorless, colorless, sweet-smelling, nonflammable gas that, when delivered to the pulmonary system, has emerged as a reliable and effective treatment for term or near-term infants with hypoxemic respiratory failure associated with pulmonary hypertension. Nitric oxide is also an unstable, highly reactive, lipophilic, diatomic free radical. Because of its high reactivity, nitric oxide is often combined with nitrogen in various concentrations and stored in aluminum alloy cylinders. The most common concentration available commercially is 800 ppm.

PHYSIOLOGIC BASIS OF ACTION

Nitric oxide is a ubiquitous substance produced by nearly every cell and organ in the human body (Box 18-1). Directly or indirectly, nitric oxide performs numerous functions, including vasodilation, platelet inhibition, immune regulation, enzyme regulation, and neurotransmission.[1]

Pulmonary Smooth Muscle Relaxation and Contraction

An understanding of the mechanism of smooth muscle relaxation in the pulmonary vascular bed is based on the regulation of smooth muscle tone. In general, smooth muscle tone is regulated by chemical, hormonal, nervous, and physical interactions.[2] Current understanding suggests that vascular smooth muscle is largely dependent on intracellular calcium ion (Ca^{21}) concentration. Smooth muscle tissue comprises bundles of myofibrils, threadlike contractile fibers encased by the sarcoplasmic reticulum, a network of tubes or

Box 18-1 Organs and Cells Involved in the Endogenous Production of Nitric Oxide

- Brain
- Peripheral nerves
- Skeletal muscle
- Liver
- Myocytes
- Epithelium
- Platelets
- Adrenals
- Macrophages
- Lungs

channels that store calcium ion. Muscle contraction begins with the release of calcium ion from the sarcoplasmic reticulum. Calcium ion binds with the protein calmodulin. The calcium–calmodulin complex activates the enzyme myosin light-chain kinase, enabling phosphorylation of the myosin, resulting in contraction of the cell. Contraction continues until calcium ion is reabsorbed into the sarcoplasmic reticulum. Therefore, any process that inhibits the release of calcium ion will interrupt smooth muscle contraction.

In the body, the process of smooth muscle relaxation uses cyclic guanosine monophosphate (cGMP) to reduce calcium ion levels. In smooth muscle cells, cGMP activates cGMP-dependent kinase, preventing the release of calcium ion from the sarcoplasmic reticulum, resulting in smooth muscle relaxation. In the early 1980s, researchers reported a potent smooth muscle–relaxing agent, endothelium-derived relaxing factor (EDRF),[3] now understood to be endogenous nitric oxide. Formation of EDRF results in increased levels of cGMP in smooth muscle cells. EDRF and cGMP are conceivably the two most important substances in regulating smooth muscle tone.[24]

Nitric Oxide Synthase and Endogenous Nitric Oxide Production

In the body, nitric oxide is produced by the combination of nitric oxide synthase (NOS) enzymes with the amino acid L-arginine and molecular oxygen. This combination results in the formation of the amino acid L-citrulline and nitric oxide (Figure 18-1). The two types of NOS enzymes are constitutive and inducible. The constitutive NOS (cNOS) enzymes are normally expressed in tissues and consist of two isoforms: eNOS (endothelial in origin) and nNOS (neuronal in origin).[1] The one inducible NOS (iNOS) enzyme results from enzyme induction.[5] The cNOS enzymes, which are calmodulin dependent, produce relatively small amounts of nitric oxide (picomoles). The iNOS enzyme functions independently of calmodulin and produces relatively large amounts of nitric oxide (nanomoles). Nitric oxide resulting from iNOS is most often produced in sepsis and is probably responsible for the pathologic decrease in systemic vascular resistance observed in septic shock.

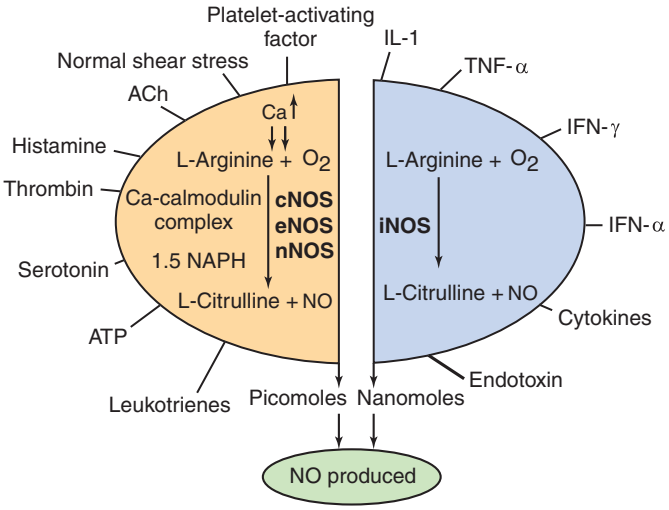


FIGURE 18-1 Endogenous nitric oxide *(NO)* production. Under normal conditions, picomoles of NO are produced. When inducible nitric acid synthase is activated in conditions of sepsis or inflammation, nanomoles of NO are produced. *ACh,* Acetylcholine; *ATP,* adenosine triphosphate; *cNOS,* constitutive nitric oxide synthase; *eNOS,* endogenous nitric oxide synthase; *IFN,* interferon; *IL,* interleukin; *iNOS,* induced nitric oxide synthase; *nNOS,* neuronal nitric oxide synthase; *TNF,* tumor necrosis factor. (From Aranda A, Pearl RG: The biology of nitric oxide, *Respir Care* 44:157, 1999.)

Once nitric oxide is formed and bound to hemoglobin, guanylyl cyclase is activated, which converts cyclic guanidine triphosphate to cGMP. This increased cGMP results in reduced calcium ion and smooth muscle relaxation.

Inhaled Nitric Oxide

The underlying principle of inhaled nitric oxide (iNO) is its selectivity as a pulmonary vasodilator. iNO will relax only pulmonary smooth muscle adjacent to functioning alveoli. Atelectatic or fluid-filled lung units will not participate in iNO uptake. Therefore if the pulmonary vasculature is constricted in atelectatic regions of the lung, pulmonary blood flow will remain minimal in these regions, reducing intrapulmonary shunt (Figure 18-2). This is in contrast to intravenous vasodilators such as nitroprusside or prostacyclin. These drugs relax pulmonary vasculature globally, reducing pulmonary vascular resistance but also increasing blood flow past nonfunctioning alveoli and intrapulmonary right-to-left shunt.

Newborn hypoxic respiratory failure. The concept of treating pulmonary hypertension of term or near-term infants with iNO has been advocated in many early reports and randomized controlled trials. These studies confirmed that iNO improved oxygenation and reduced the need for extracorporeal membrane oxygenation. In 2000 the first US Food and Drug Administration (FDA) approval of iNO for the treatment of primary pulmonary hypertension of term

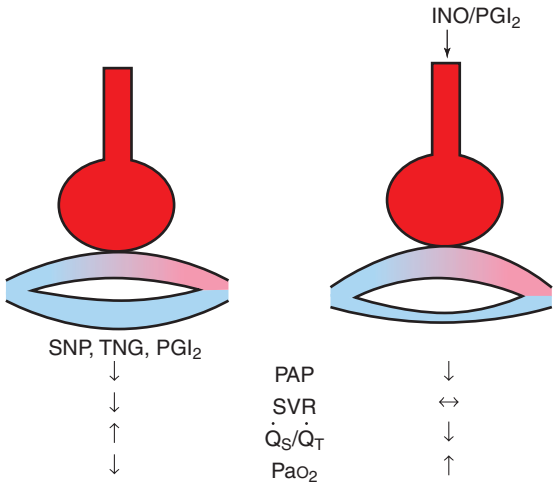


FIGURE 18-2 Comparison of the vasodilator effects from systemic drugs and nitric oxide. Both reduce pulmonary artery pressure, but the systemic vasodilators also dilate the blood vessels not participating in gas exchange, thereby increasing the intrapulmonary shunt. Pa_{O_2}, Arterial partial pressure of oxygen; *PAP*, pulmonary artery pressure; PGI_2, prostacyclin; *S/T*, intrapulmonary shunt; *SNP*, sodium nitroprusside; *SVR*, systemic vascular resistance; *TNG*, nitroglycerin. (Redrawn from Hess D et al: Use of inhaled nitric oxide in patients with acute respiratory distress syndrome, *Respir Care* 41:428, 1996.)

and near-term (more than 34 weeks of gestational age) neonates with hypoxic respiratory failure associated with evidence of pulmonary hypertension. Hypoxic respiratory failure may be primary or a secondary effect of another disorder (meconium aspiration, congenital diaphragmatic hernia, pneumonia, etc.).

Dosing strategies should be focused on physiologic end points. This involves titrating the delivered NO in increments until a positive response is achieved. Many use an increase in oxygen saturation of 20% over baseline as an indication that the infant is responsive with optimal dosing of 20 ppm. Some infants will not respond. The Neonatal Inhaled Nitric Oxide Study (NINOS) trial indicated that only 6% of nonresponders will demonstrate a positive response when given NO at 80 ppm.[6] Typically, a response would be seen almost immediately; however, it is recommended that determining an infant's response last no longer than 30 minutes to 1 hour to limit the exposure to nitric oxide. Endogenous nitric oxide is downregulated when the patient receives iNO. This may result in a worsening of pulmonary hypertension and hypoxemia.

Although there is strong evidence for the use of iNO in term or near-term infants,[8] its efficacy in premature babies is less clear. Nitric oxide has been shown to improve oxygenation and outcomes in a few studies. Despite some initial promise in preterm infants showing improved pulmonary and neurologic outcome, subsequent trials have shown no benefit and may increase the risk of intracranial hemorrhage.[7] The preterm population at baseline is at an increased risk for intraventricular hemorrhage and chronic lung disease. These larger, more recent trials did not show any increase in these comorbidities. Therefore, although its usefulness is still in question, nitric oxide does appear to be safe for premature infants. Box 18-2 describes the recommendation from the Evidence-Based Clinical Practice Guidelines for iNO.[9]

Pediatric acute respiratory distress syndrome. Current research is investigating the use of nitric oxide in pediatric acute respiratory distress syndrome (PARDS) and acute lung injury. PARDS is a complex syndrome characterized by noncardiogenic pulmonary edema, diminished lung compliance, and pulmonary hypertension. Current therapy for PARDS is primarily supportive, allowing time for the lung to heal. Although no definitive studies show improved outcomes, iNO has been suggested to improve oxygenation and ventilation–perfusion (V/Q) matching, consequently lowering airway pressure and oxygen concentration. However, studies investigating the use of iNO for the treatment of PARDS or acute lung injury have failed to demonstrate improved outcomes, and therefore it is not recommended for routine use.[10] Nitric oxide will reach more capillary endothelium by opening collapsed alveoli. In turn, a greater degree of vasorelaxation should occur. Studies have shown that responsiveness to iNO may be enhanced by the application of positive end-expiratory pressure, and perhaps turn nonresponders into responders (to iNO therapy).[11-14] Kinsella and colleagues[15] reported improved outcomes when using high-frequency oscillatory ventilation (HFOV) combined with iNO compared with HFOV or iNO alone. Mehta and colleagues[16] also studied the combined effects of iNO and HFOV, the rationale being that if lung volume were optimized they could further enhance the effects of iNO. They demonstrated that the use of HFOV did improve oxygenation response to iNO. Further studies are warranted to determine whether this combination is clinically useful.

APPLICATION

Multiple methods have been advocated for the delivery of iNO. Early systems were custom-built in-house and comprised two basic subsystems: delivery and monitoring. In these systems, nitric oxide is bled into the breathing circuit through a flow meter or blender. Nitric oxide and nitrogen dioxide levels are monitored with an analyzer. These systems were cumbersome and were often difficult to assemble. Now that the use of iNO has increased, a few vendors have developed systems incorporating nitric oxide delivery with nitric oxide and nitrogen dioxide monitoring. These devices come in a variety of designs. Some are larger and designed for in-hospital

Box 18-2 Practice Guidelines on Inhaled Nitric Oxide

Recommendation from the AARC Evidence-Based Clinical Practice Guidelines on Inhaled Nitric Oxide for Neonates with Acute Hypoxic Respiratory Failure.

1. A trial of INO is recommended in newborns (34 wk gestation, 14 d of age) with PaO2 100 mm Hg on FIO2 1.0 and/or an oxygenation index (OI) 25 (Grade 1A).
2. It is recommended that INO therapy be instituted early in the disease course, which potentially reduces the length of mechanical ventilation, oxygen requirement, and stay within the intensive care unit (Grade 1A).
3. It is recommended that INO should not be used routinely in newborns with congenital diaphragmatic hernia (Grade 1A).
4. It is suggested that INO therapy should not be used routinely in newborns with cardiac anomalies dependent on right-to-left shunts, congestive heart failure, and those with lethal congenital anomalies (Grade 2C).
5. It is suggested that there are insufficient data to support the routine use of INO therapy in postoperative management of hypoxic term or near-term infants with congenital heart disease (grade 2C).
6. The recommended starting dose for INO is 20 ppm (Grade 1A).
7. It is recommended that response to a short trial (30–60 min) of INO should be judged by an improvement in PaO2 or oxygenation index (OI); if there is no response, INO should be discontinued (Grade 1A).
8. For the newborn with parenchymal lung disease, it is recommended that optimal alveolar recruitment be established prior to initiation of INO therapy (Grade 1A).
9. For newborns with a response to INO therapy, it is recommended that the dose should be weaned to the lowest dose that maintains that response (Grade 1A).
10. It is recommended that INO should not be discontinued until there is an appreciable clinical improvement; that the INO dose should be weaned to 1 ppm before an attempt is made to discontinue; and that the FIO2 should be increased prior to discontinuation of INO therapy (Grade 1A).
11. It is recommended that FDA-approved INO delivery systems should be used to assure consistent and safe gas delivery during therapy (Grade 1C).
12. During conventional mechanical ventilation, it is suggested that the INO gas injector module should be placed on the dry side of the humidifier (Grade 2C).
13. During conventional ventilation, it is suggested that the sampling port be placed in the inspiratory limb of the ventilator, downstream from the site of injection, no greater than 15 cm proximal the patient connection/interface (Grade 2C).
14. It is suggested that the FIO2 be measured downstream from the injection of INO into the circuit (Grade 2C).
15. It is suggested that the patient/ventilator system be continuously monitored for changes in ventilation parameters, with adjustments to maintain desired settings during INO therapy (Grade 2C).
16. It is suggested that the lowest effective doses of INO and O2 be used, to avoid excessive exposure to NO, NO2, and methemoglobinemia (Grade 2C).
17. It is suggested that the INO delivery system be properly purged before use to minimize inadvertent exposure to NO2 (Grade 2C).
18. It is suggested that the high NO2 alarm be set at 2 ppm on the delivery system to prevent toxic gas exposure to the lungs (Grade 2C).
19. It is suggested that methemoglobin be monitored approximately 8 hours and 24 hours after therapy initiation and daily thereafter.
20. It is suggested that the INO dose be weaned or discontinued if methemoglobin rises above 5% (Grade 2C).
21. It is suggested that continuous pulse oximetry and hemodynamic monitoring be used to assess patient response to INO therapy (Grade 2C).
22. It is suggested that scavenging of exhaled and unused gases during INO therapy is not necessary (Grade 2C).

DiBlasi RM, Myers TR, Hess DR. Evidence-Based Clinical Practice Guideline. Inhaled Nitric Oxide for Neonates with Acute Hypoxic Respiratory Failure. *Resp Care*. 2010;55(12): 1717–1745.

use (Figure 18-3). Currently available systems can be battery operated, include a manual system, and may be used for transport.

In general, nitric oxide is bled into the breathing circuit before the humidifier. To analyze inspired nitric oxide and nitrogen dioxide concentrations, gas is sampled before the patient–circuit interface. These devices provide alarms to monitor these values and oxygen. The Mallinckrodt Pharmaceuticals INOMAX DSIR (Clinton, NJ) is the only commercially available device in the United States. These flow measurements allow the device to modulate nitric oxide output to provide a stable concentration throughout the breath.

Nitrogen Dioxide

As discussed earlier, when combined with oxygen, nitric oxide produces nitrogen dioxide, a toxic gas. Although rare, the patient and health care providers can be adversely affected. Factors influencing nitrogen dioxide production are oxygen concentration, nitric oxide concentration, and time of contact between nitric oxide and oxygen. Therefore the patients most at risk of nitrogen dioxide delivery include those receiving high oxygen concentrations and low ventilator flow rates.

Decreasing the nitric oxide or oxygen concentration is usually not an option; therefore, to reduce nitrogen dioxide delivery to the patient, reduce the duration of contact between nitric oxide and oxygen. Two methods accomplish this: (1) increase the inspiratory flow or (2) add the nitric oxide as close to the patient as possible. Each of these methods has practical limitations. Increasing the ventilator flow will reduce the time of contact between nitric oxide and oxygen before reaching the patient, but it may also

FIGURE 18-3 The INOMAX DSIR drug-delivery system that is approved by the US Food and Drug Administration for administration and monitoring of pharmaceutical-grade inhaled nitric oxide. (Used with permission of IKARIA, Hampton, NJ.)

affect inspiratory time, tidal volume, mean airway pressure, and so on. Adding nitric oxide into the inspiratory limb of the ventilator circuit close to the patient will reduce contact time, but it also creates monitoring difficulties. The practitioner must allow an adequate distance for proper mixing to ensure accurate nitric oxide measurement.

Methemoglobin

The half-life of iNO is extremely short, about 5 seconds. Once nitric oxide crosses the vascular endothelium, it is rapidly bound by hemoglobin, forming nitrosyl hemoglobin (methemoglobin). Methemoglobin production results from the oxidation of the iron in the hemoglobin.[17] The quantity of methemoglobin depends on iNO concentration and concurrent nitrate-based drug therapy (e.g., nitroprusside, nitroglycerin). If the methemoglobin level is excessive, a reduction in iNO or other nitro-based vasodilators is warranted. Ultimately, nitric oxide metabolites are excreted, primarily by the kidneys, as nitrates and nitrites.[18]

HELIUM-OXYGEN MIXTURES

Helium was discovered in 1895 by Sir William Ramsay and independently by Langley and Cleve. Helium is one of the lightest elements, second only to hydrogen. It is a colorless, odorless, tasteless, and physiologically inert noble gas. Helium is present in dry air at a concentration of 0.0005%. At present, most helium comes from natural gas mines in the United States. The supply is limited, and until the Helium Privatization Act of 1996, production was under the control of the US government.

Helium is remarkable for its low density and high viscosity (Table 18-1). Pure helium gas has a density of 0.179 g/L, one seventh the density of air. A common misconception is that because of its low density, helium has low viscosity. Actually, helium is slightly more viscous than air. However, its kinematic viscosity (the ratio of absolute viscosity to density) is almost seven times greater than that of air. Therefore, from the standpoint of fluid dynamics, helium is much more viscous than air.[19]

PHYSIOLOGIC BASIS OF ACTION

The use of helium-oxygen mixtures in treating airway obstruction was first described in 1934 by Barach. Barach's studies reported a decrease in work of breathing in patients with both upper and lower airway obstruction.[20] Helium is an inert gas, has no pharmacologic properties of its own, and does not participate in or interfere with any biochemical activity in the body. Its sole purpose is to lower the total density of any gas mixture.

It is important to note that helium is not used to treat the underlying cause of increased airway resistance but rather to decrease the work of breathing until more definitive therapies are effective. When helium is combined with oxygen, the resulting gas mixture density is one third that of air. Poiseuille's law states that if the diameter of a tube is reduced by half, the pressure gradient to achieve the same flow increases 16 times. Graham's law states that the flow

Table 18-1 Comparison of Inhaled Gas Densities and Viscosities

	DENSITY (g/L)	VISCOSITY (μP)
Helium	0.179	188.7
Nitrogen	1.25	167.4
Air	1.29	170.8
Oxygen	1.42	192.6

Box 18-3 Reynold's Equation for Turbulent Flow

$$\text{Reynold's Number} = \frac{\text{Flow} \times \text{Diameter Density}}{\text{Viscosity}}$$

Laminar ≤ 2000 ≥ Turbulent

of gas through an orifice is inversely proportional to the square root of its density.[21] In other words, if the driving pressure remains constant, a gas with lower density will have higher flow than a gas with higher density. Alternatively, less pressure is required to maintain a given flow through a fixed orifice. This physical property of helium may be useful in overcoming airway resistance and obstruction.

In normal human anatomy, inspired gas is turbulent between the glottis and the tenth-generation airways, primarily because of the high gas flow and larger radii of the airways. Physics dictates that greater pressure is required to move gas through a tube (or airway) under turbulent conditions compared with the same volume of gas during laminar flow. A quick review of Reynold's equation shows that decreasing density and increasing viscosity will reduce turbulent flow, decreasing the pressure and work required to move the gas (Box 18-3). Likewise, gas flow through a large, partially obstructed airway will create the same turbulent flow. Decreasing turbulent flow reduces the amount of pressure required to move the gas through the airways, decreasing the work required to breathe.

APPLICATION

Helium must be combined with oxygen when used clinically—thus the term *heliox.* Several concentrations of medical-grade helium are available commercially: 80% helium–20% oxygen heliox mixture (80:20), 70% helium–30% oxygen (70:30), and 100% helium–0% oxygen (100%). The 80:20 mixture has essentially the same concentration of oxygen as air; the nitrogen and trace gases are replaced with helium. The 70:30 mixture is useful for patients with airway obstruction who require increased oxygen concentration. The 100% helium concentration is rarely used, and it must be used with oxygen to be compatible with life. Clinicians who use 100% helium do so to reduce the number of tanks required to maintain a patient on heliox. Extreme caution and close monitoring are crucial when using this concentration, because it is possible to deliver a hypoxic gas mixture to the patient, possibly resulting in asphyxiation and death.

For the purposes of this chapter, only the use of nonhypoxic gas mixtures is discussed. Heliox cylinders containing at least 20% oxygen are brown and white (or brown and green) and use a CGA-280 fitting.

Aerosol Delivery

Multiple studies have investigated the use of helium-oxygen mixtures and the deposition of aerosolized particles.[22-27] Anderson and colleagues[22] studied patients with stable asthma. Ten patients inhaled radiolabeled particles of Teflon suspended in air or a helium-oxygen mixture. The study concluded there was more aerosol deposition in the lung and less deposition in the upper airways when breathing helium-oxygen mixtures. In a similar study, 42 patients were randomly assigned to receive β-agonists with helium-oxygen mixtures or air.[26] Patients who used the helium-oxygen mixtures showed more improvement in expiratory peak flows than the group using air. These studies support the concept that aerosol has deeper and prolonged deposition in the lung when it is delivered with heliox as the carrier gas.

Heliox mixtures cause pneumatic nebulizers to perform differently than if air or oxygen is used. When driving a pneumatic nebulizer with helium, the nebulizer will produce smaller particles, nebulize more slowly, and have reduced output compared with similar devices driven with air. When using a conventional pneumatic nebulizer driven with heliox, it is advisable to increase gas flow.[27] This will increase drug output by producing denser aerosol and larger particles. Newer generations of vibrating-mesh nebulizers (Aerogen Micropump) may provide an alternative to gas-driven nebulizers. If vibrating-mesh nebulizers are used, heliox can be the carrier gas.

Oxygen Flow Meters

Helium is less dense and therefore more diffusible than oxygen. As a consequence, standard oxygen flow meters will indicate an incorrect flow when used with helium-containing mixtures. This error will cause the indicated flow to be erroneously low. An 80:20 heliox mixture is 1.8 times more diffusible than oxygen. To correct for the difference in gas density, the indicated flow on the flow meter is multiplied by 1.8. A 70:30 heliox mixture is 1.6 times more diffusible than oxygen. To obtain the accurate flow rate for this mixture, the indicated flow is multiplied by 1.6. This error is present in most gas-measuring devices (see discussion later in this section).

Spontaneously Breathing Patients

Spontaneously breathing patients with upper or lower airway obstruction can be given heliox via mask. Because the goal of heliox therapy is to reduce the density of the inspired gas, it is important to deliver the greatest concentration of helium. Therefore the patient must be able to tolerate the lowest possible fractional concentration of inspired oxygen (Fio_2), and room air entrainment must be minimized, resulting in a higher fractional concentration of inspired helium (Fi_{He}). Nasal cannulas (with the exception of high-flow nasal

cannulas) and simple masks allow far too much room air entrainment, thereby diluting the helium concentration. Therefore a close-fitting nonrebreathing mask should be used. This limitation makes the treatment of young patients difficult. Children in distress may not tolerate the tightly fitting mask required to minimize air entrainment. Stillwell and colleagues[28] investigated the use of heliox mixtures delivered through an infant hood. Not surprisingly, they found a greater concentration of helium at the top of the hood (because of its lower gas density), away from the infant's nose and mouth. This resulted in a lower Fi_{He} and therefore a denser gas being delivered to the infant.

High-Flow Nasal Cannula

Heliox has been shown to reduce turbulence and improve aerosol delivery in a range of clinical settings. Ari and colleagues assessed the effects of heliox on medication delivery by comparing with 100% oxygen while testing infant and pediatric cannulas running at flows of 3 and 6 L/minute and adult cannulas running at 10 and 30 L/minute. At higher flows, they found that heliox increased aerosol deposition compared with oxygen. At lower flows, there was less benefit from the use of heliox compared with oxygen in the pediatric and adult cannulas and no benefit for the infant cannulas. Aerosol delivery was significantly greater at lower flows with both heliox and oxygen in adults and pediatric ($p < 0.05$) cannulas; the use of heliox at 6 L/minute increased albuterol delivery by 40% compared with heliox at 3 L/minute ($p = 0.049$) and oxygen at 6 L/minute ($p = 0.043$) in infants. They surmised the use of heliox with high-flow nasal cannulas increased aerosol delivery more than oxygen at most flow rates.[29]

Mechanically Ventilated Patients

If the intent of heliox use is to prevent respiratory fatigue or failure, then it should be discontinued when mechanical ventilation is initiated. In this scenario, the ventilator assumes the work of breathing. When mechanical ventilation is initiated, the patient will be in impending respiratory failure, hypoxic and requiring high levels of oxygen, making heliox less effective. Once the patient is mechanically ventilated and continues to suffer from severe lower airway obstruction (as seen in status asthmaticus [SA]) and continues to have reduced expiratory flows and gas trapping. The use of heliox mixtures has been advocated to minimize air trapping, hemodynamic compromise, and reduce peak inspiratory pressures.

The primary obstacle to heliox delivery via a mechanical ventilator is error in volume and flow measurement if compensation measures have not been taken. Many mechanical ventilators rely on gas density to measure flows and volumes but offer heliox delivery modes that assume concentrations and apply corrective calculations to improve accuracy of tidal volume measurements. If compensation was not taken for the helium gas mixture, most ventilators would underestimate flow because of the low-density characteristics of helium. Volume is typically a mathematical integration of flow and time; therefore volumes will be equally affected. This error in flow and volume is also seen in external monitors.

The safest method to deliver helium-oxygen mixtures via mechanical ventilation is to connect an 80:20 heliox mixture to the heliox-approved inlet of the mechanical ventilator. The practitioner then uses the ventilator's oxygen concentration control to adjust helium and oxygen to the desired mixture. This allows the practitioner to deliver a helium concentration up to the 80% helium. It is important to note that ventilators may not function properly with helium as a source gas. Clinicians should refer to the manufacturer's manual before attempting to add helium to the air inlet of any ventilator. It is never advisable to provide 100% helium through any ventilator.

The anomaly in volume calculations appears to be related to the heated-wire flow anemometer. The high thermal conductivity of helium rapidly cools the wires, simulating a high-flow condition. The microprocessor responds by closing the gas valves to such a degree that the ventilator will not function.

Gas Mixtures in Extracorporeal Membrane Oxygenation

Some patients require extracorporeal membrane oxygenation to achieve adequate gas exchange (see Chapter 19). Gas from a blender passes through the oxygenator cartridge (artificial lung), and gas exchange occurs. The oxygen in this gas oxygenates the blood. Carbon dioxide diffuses from the blood into the sweep gas. The membrane oxygenator in the extracorporeal membrane oxygenation circuit is efficient, and sometimes too efficient, in exchanging gases with the blood. When the sweep gas (blended gas flow through the membrane lung; usually free of carbon dioxide) through the oxygenator removes too much carbon dioxide from the blood, carbogen may be substituted as the sweep gas to inhibit excessive carbon dioxide removal. Carbogen is a mixture of carbon dioxide and oxygen, typically 95% oxygen and 5% carbon dioxide.

ANESTHETIC MIXTURES

Patients in SA can be placed on helium-oxygen therapy as a temporizing measure to reduce the work of breathing until other therapy (β-agonists, methylxanthines, and corticosteroids) is effective. However, these patients often have bronchospasm that is refractory to conventional therapy. Certain volatile inhaled anesthetics are known for their bronchodilatory properties.

Table 18-2 Comparison of Two Commonly Used Inhaled Anesthetic Agents

	ISOFLURANE	SEVOFLURANE
Mean arterial pressure	↓↓↓	↓
Pulmonary vascular resistance	↓↓	↓
Heart rate	↑	↑
Cardiac output	—	—
Airway irritant	↑↑	—
Respiratory depression	↑	↑
Myocardial sensitization to catecholamines	—	—
Risk of explosion	—	—

Although no clinical trials have investigated the use of inhaled anesthetics (IAs) in the routine treatment of SA, several case reports exist.[30-32]

Of the several IAs used clinically for anesthesia, only isoflurane and sevoflurane appear to be widely reported as potential treatments for SA. Sevoflurane, a methyl ethyl ether, has been shown to be as effective as halothane in reducing lung resistance; however, safety studies for its use in children with asthma are needed[33,34] (Table 18-2).

PHYSIOLOGIC BASIS OF ACTION

Volatile IAs reduce bronchospasm through a number of pathways: β-adrenergic receptor stimulation, direct smooth muscle relaxation, antagonism of acetylcholine and histamine, and inhibition of hypocapneic bronchoconstriction. In essence, they reduce central afferent parasympathetic activity. Therefore, a patient receiving standard bronchodilators may see an additional response with the addition of an IA.[35]

APPLICATION

Qualified individuals must perform the setup and delivery of IAs. Respiratory care practitioners can be properly trained in the setup and operation of closed-loop (rebreathing circuit) anesthetic ventilators for the primary purpose of bronchodilation. In general, the anesthesiologist or specialty-trained intensivist performs the initial setup and troubleshooting. Adjustments are usually done by protocol or RCP under the direct supervision of the intensive care physician or anesthesiologist. The bedside caregiver handles routine monitoring procedures. All caregivers must understand the pharmacology of the IA being delivered and its side effect profile.

The two ways to deliver IAs are by face mask for spontaneously breathing patients and through a mechanical ventilator. In either system, the setup is similar to that used in the operating room. Both methods require similar equipment: vaporizers for the volatile anesthetic, scavenging devices, anesthetic gas analyzers, and vital sign monitoring.

Inhaled Anesthetics via Face Mask

To avoid intubation and mechanical ventilation, treating a spontaneously breathing patient with an IA could be advantageous. The systems used for spontaneous breathing of IAs are complicated but are similar to full-face noninvasive continuous positive airway pressure circuits. The expiratory gases pass through a carbon dioxide absorber and then return to the inspiratory limb, creating a circle. A fresh gas supply (including the IA) is introduced after the carbon dioxide absorber. This design is called a *rebreathing circuit*.

The face mask must be tight fitting to prevent the leakage of the IA into the room and to ensure that the patient receives the IA. Because patients may be somewhat awake, they must be cooperative enough not to remove the mask. The IA must also be compatible with face mask administration. Isoflurane-type IAs are irritants to the upper airway and are unpleasant to breathe while conscious, especially for pediatric patients. These vapors may produce laryngospasm and fighting. Isoflurane is more suited for use with an intubated and mechanically ventilated patient. Conversely, sevofluranes are neutral-smelling vapors and may be accepted more readily via mask.

Inhaled Anesthetics via Mechanical Ventilation

Most modern anesthesia ventilator systems can be transported to the ICU and provide modern modes of ventilation such as pressure support ventilation. Waste anesthetic agent may pose a risk for staff and visitors. Therefore exhaled and waste gases need to be scavenged from the circuit. These waste gases are typically collected via waste anesthetic gas (WAG) outlets connected to the hospital vacuum system. Most ICUs are not outfitted with WAG suction outlets.

Case Study

A 12-year-old boy with known persistent severe asthma has been admitted to the intensive care unit for further management of a severe exacerbation. He has received an appropriate dose of steroids and has been given continuous albuterol, 15 mg/hour for the last 4 hours, in the emergency department. There is a concern for respiratory fatigue. S_{PO_2} is 96% on 0.21 F_{IO_2}.

What would you recommend at this point?

1. Heliox 80/20
2. Noninvasive ventilation
3. Intravenous β agonist
4. Volatile inhaled anesthetics

See Evolve Resources for answers.

Key Points

- Nitric oxide can improve oxygenation and reduce the need for extracorporeal membrane oxygenation in the clinically indicated patient population.
- Inhaled endothelium relaxing factor (nitric oxide) can vasodilate the pulmonary capillary bed ventilated lung units and improve gas exchange.
- Inhaled nitric oxide is a selective vasodilator, which improves it side effect profile.
- A helium-oxygen gas mixture can reduce the patient's work of breathing during severe obstructive airways disease such as status asthmaticus or croup. Reducing fatigue heliox enables medications such as steroids the time required to become effective without escalating to positive pressure ventilation.
- Heliox can be provided through most modern mechanical ventilators while accurately measuring tidal volumes.
- Inhaled anesthetics such as isoflurane and sevoflurane are potent bronchodilators.
- Modern anesthetic ventilators can adequately ventilate pediatric patients while safely providing, monitoring, and conserving volatile anesthetic agent.

Assessment Questions

See Evolve Resources for answers.

1. Which of the following is/are chemical properties of nitric oxide?
   - **A.** Lipophilic
   - **B.** Highly reactive
   - **C.** Unstable free radical
   - **D.** All of the above
2. Which chemical is most associated with smooth muscle contractility?
   - **A.** Iron
   - **B.** Calcium
   - **C.** Citric acid
   - **D.** L-Arginine
3. Inhaled nitric oxide reduces shunt by:
   - **A.** Vasodilating only pulmonary capillaries adjacent to atelectatic lung units
   - **B.** Decreasing pulmonary vascular resistance
   - **C.** Increasing systemic oxygenation
   - **D.** Vasodilating only pulmonary capillaries adjacent to functioning lung units
4. Which of the following are potential side effects of iNO administration?
   - **A.** Nitrous oxide formation in the ventilator circuit
   - **B.** Fetal hemoglobin formation
   - **C.** Decrease in guanylyl cyclase in the sarcoplasmic reticulum
   - **D.** Methemoglobin formation
5. Which of the following are useful properties of helium when used to treat patients in status asthmaticus?
   - **I.** Lower density
   - **II.** Lower viscosity
   - **III.** Higher viscosity
   - **IV.** Low thermal conductivity
     - **A.** I and II
     - **B.** I and III
     - **C.** I, II, and IV
     - **D.** I, III, and IV
6. All of the following are effects of heliox on mechanical ventilation *except:*
   - **A.** Measured flow is falsely low when using a differential pneumotachometer.
   - **B.** Nebulizer output is decreased.
   - **C.** Actual flow from the flow meter is lower than indicated.
   - **D.** Measured flow is falsely high when using a hot-wire anemometer.
7. Which of the following is *not* an inhaled anesthetic agent used to treat status asthmaticus?
   - **A.** Halothane
   - **B.** Sevoflurane
   - **C.** Isoflurane
   - **D.** Nitrous oxide

REFERENCES

1. Hurford WE. The biological basis of inhaled nitric oxide. *Respir Care Clin North Am*. 1997;3:357.
2. Dagby RM, Corey-Kreyling MD. Structural aspects of the contractile machinery of smooth muscle: is the organization of contractile elements compatible with a sliding filament mechanism? In: Stephens NL, ed. *Smooth muscle contraction*. New York: Marcel Dekker; 1984:47-74.
3. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature*. 1980;288:373.
4. Miller CC, Miller J. Pulmonary vascular smooth muscle regulation: the role of inhaled nitric oxide gas. *Respir Care*. 1992; 37:1175.
5. Aranda A, Pearl RG. The biology of nitric oxide. *Respir Care*. 1999;44:156.
6. Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. *N Engl J Med*. 1997;336:597.
7. Barrington KJ. Inhaled nitric oxide for respiratory failure in preterm infants. Cochrane Database of Systematic Reviews 2017, Issue 1. Art. No.: CD000509. DOI: 10.1002/14651858.CD000509.pub5, January 2017.
8. Clark RH, Kueser TJ, Walker MW, et al. Clinical Inhaled Nitric Oxide Research Group: Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. *N Engl J Med*. 2000;342:469.
9. DiBlasi RM, Myers TR, Hess DR. Evidence-Based Clinical Practice Guideline. Inhaled Nitric Oxide for Neonates with Acute Hypoxic Respiratory Failure. *Resp Care*. 2010;55(12): 1717-1745.
10. Pediatric Acute Respiratory Distress Syndrome. Consensus Recommendations From the Pediatric Acute Lung Injury

Consensus Conference. *Pediatr Crit Care Med*. 2015;16: 428-439.
11. Barrington KJ, Finer NN. Inhaled nitric oxide for respiratory failure in preterm infants. *Cochrane Database Syst Rev*. 2006;1:CD000509.
12. Puybasset L, Rouby JJ, Mourgeon E, et al. Factors influencing cardiopulmonary effects of inhaled nitric oxide in acute respiratory failure. *Am J Respir Crit Care Med*. 1995;152:318.
13. Okamoto K, Kukita I, Hamaguchi M, Motoyama T, Muranaka H, Harada T. Combined effects of inhaled nitric oxide and positive end-expiratory pressure during mechanical ventilation in acute respiratory distress syndrome. *Artif Organs*. 2000;24:390.
14. Johannigman JA, Davis, K, Campbell, RS, et al. Positive end-expiratory pressure and response to inhaled nitric oxide: changing nonresponders to responders. *Surgery*. 2000;127:390.
15. Kinsella JP, Truog WE, Walsh WF, et al. Randomized, multicenter trial of inhaled nitric oxide and high-frequency oscillatory ventilation in severe, persistent pulmonary hypertension of the newborn. *J Pediatr*. 1997;131:55.
16. Mehta S, MacDonald R, Hallett DC, Lapinsky SE, Aubin M, Stewart TE. Acute oxygenation response to inhaled nitric oxide when combined with high-frequency oscillatory ventilation in adults with acute respiratory distress syndrome. *Crit Care Med*. 2003;31:383.
17. Curry S. Methemoglobinemia. *Ann Emerg Med*. 1982;11:214.
18. Jacob TD, Nakayama DK, Seki I, et al. Hemodynamic effects and metabolic fate of inhaled nitric oxide in hypoxic piglets. *J Appl Physiol*. 1994;76:1794.
19. Papamoschou D. Theoretical validation of the respiratory benefits of helium–oxygen mixtures. *Respir Physiol*. 1995; 99:183.
20. Barach AL. The use of helium in the treatment of asthma and obstructive lesions of the larynx and trachea. *Ann Intern Med*. 1935;9:739.
21. Nunn JF. Diffusion and alveolar/capillary permeability. In: *Applied respiratory physiology*. London: Butterworth; 1987: 184-206.
22. Anderson M, Svartengren M, Bylin G, Philipson K, Camner P. Deposition in asthmatics of particles inhaled in air or helium–oxygen. *Am Rev Respir Dis*. 1993;147:524.
23. Svartengren M, Anderson M, Philipson K, Camner P. Human lung deposition of particles suspended in air or in helium/oxygen mixture. *Exp Lung Res*. 1989;15:575.
24. Bandi V, Velamuri S, Sirgi C, Wendt J, Wendt R, Guntupalli K. Deposition pattern of heliox-driven bronchodilator aerosol in the airways of stable asthmatics. *J Asthma*. 2005; 42:583.
25. Corcoran TE, Shortall BP, Kim IK, Meza MP, Chigier N. Aerosol drug delivery using heliox and nebulizer reservoirs: results from an MRI-based pediatric model. *J Aerosol Med*. 2003;16:263.
26. Melmed A, et al. The use of heliox as a vehicle for β-agonist nebulization in patients with severe asthma [abstract]. *Am J Respir Crit Care Med*. 1995;151:A269.
27. Hess DR, Acosta FL, Ritz RH, Kacmarek RM, Camargo Jr CA. The effect of heliox on nebulizer function using a β-agonist bronchodilator. *Chest*. 1999;115:184.
28. Stillwell PC, Quick JD, Munro PR, Mallory Jr GB. Effectiveness of open-circuit Oxyhood delivery of helium–oxygen. *Chest*. 1989;95:1222.
29. Ari A, Harwood R, Sheard M, Dailey P, Fink JB. In vitro comparison of heliox and oxygen in aerosol delivery using pediatric high flow nasal cannula. *Pediatr Pulmonol*. 2011; 46(8):795. doi:10.1002/ppul.21421.
30. Restrepo RD, Pettignano R, DeMeuse P. Halothane, an effective infrequently used drug, in the treatment of pediatric status asthmaticus: a case report. *J Asthma*. 2005;42:649.
31. Carroll, CL, Smith SR, Collins MS, Bhandari A, Schramm CM, Zucker AR. Endotracheal intubation and pediatric status asthmaticus: site of original care affects treatment. *Pediatr Crit Care Med*. 2007;8(2):91. doi:10.1097/01.PCC.0000257115.02573.FC.
32. Shankar V, Churchwell KB, Deshpande JK. Isoflurane therapy for severe refractory status asthmaticus in children. *Intensive Care Med*. 2006;32(6):927. doi:10.1007/s00134-006-0163-0.
33. Rooke GA, Choi JH, Bishop MJ. The effect of isoflurane, halothane, sevoflurane, and thiopental/nitrous oxide on respiratory system resistance after trachea intubation. *Anesthesiology*. 1997;86:1294.
34. Habre W, Wildhaber JH, Sly PD. Prevention of methacholine induced changes in respiratory mechanics in piglets with sevoflurane and halothane. *Anesthesiology*. 1997;87:585.
35. Johnson RG, Noseworthy TW, Friesen EG, Yule HA, Shustack A. Isoflurane therapy for status asthmaticus in children and adults. *Chest*. 1990;97:698.

19 Extracorporeal Membrane Oxygenation

Craig Wheeler, Michael Le

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. Describe the extracorporeal membrane oxygenation systems.
2. Explain the rationale for the use of extracorporeal membrane oxygenation in the management of respiratory and cardiac failure in newborns, infants, and children.
3. Compare and contrast the various modes of support for extracorporeal membrane oxygenation.
4. Describe the elements of monitoring the extracorporeal membrane oxygenation functions and patient response.
5. Identify complications associated with extracorporeal membrane oxygenation.

Key Terms

centrifugal pump
extracorporeal membrane oxygenation
hemofiltration
oxygenation index
roller pump
sweep gas
venoarterial
venovenous
extracorporeal carbon dioxide removal
ventricular assist devices

Extracorporeal membrane oxygenation (ECMO) is an invasive technique in which blood is drained from the venous system, mechanically pumped through an artificial lung, and reinfused to the patient through either the pulmonary or systemic system. The primary aim of ECMO is to support organ function in patients with respiratory or cardiorespiratory failure to provide time for the disease process to reverse or to further evaluate the underlying condition and determine whether medical or surgical treatment options are available.[1]

BACKGROUND

ECMO, also referred to as *extracorporeal life support (ECLS)*, was derived from a modified form of cardiopulmonary bypass used during cardiac surgery. The earliest reports of artificial gas exchange and mechanical circulatory support in humans are attributed to Gibbon in 1953.[2] His invention, the heart-lung bypass machine, substituted a **roller pump** for the heart, which distributed deoxygenated blood over a series of thin films and screens to provide an interface with oxygen.[3]

However, the duration of bypass was limited to a few hours, because the direct blood–gas interface resulted in cellular damage from the exposure of blood to gas. The interposition of a membrane oxygenator between the blood and gas interface resolved many of these limitations and paved the way for further clinical applications.[4]

The first successful use of ECMO was reported in 1972, when a 24-year-old man with multiple trauma and respiratory failure was maintained on extracorporeal support for 75 hours, during which time his lung injury resolved.[5] This prompted a multicenter randomized prospective study of ECMO in adults with acute respiratory failure, and a collaborative study was published in 1979.[6] Unfortunately, this study was terminated prematurely for lack of efficacy, with a reported 90% mortality for both ECMO and conventional management groups. Publication of this trial halted further investigation of ECMO for adult respiratory failure for the next 2 decades. However, successful application was described by Bartlett et al. in neonates with respiratory failure and congenital heart disease.[7] Their success continued, and in 1982 they reported a 55% survival rate in a series of 45 neonates treated with ECMO.[8] This generated interest in further research, clinical applications, and the development of ECMO programs.

By the mid-1980s, two prospective randomized trials comparing ECMO to conventional mechanical ventilation were published. The study by Bartlett and colleagues reported 100% survival of the 11 patients receiving ECMO and 0% survival in the control group, although only one patient constituted the control group.[9] O'Rourke and colleagues subsequently reported 100% survival for nine ECMO patients, compared with 33% for six newborns treated conventionally.[10] Both trials used unconventional designs and had too few subjects to make a definitive conclusion that ECMO was more efficacious than conventional treatment. Based on these findings, ECMO did appear to be an effective therapy in otherwise moribund subjects; however, clinical equipoise persisted in the medical community. The largest trial enrolled 185 term subjects with persistent pulmonary hypertension and severe respiratory failure randomized to receive ECMO or continued conventional management.[11] The trial was stopped early by the data monitoring committee, because a clear reduction in mortality was demonstrated with ECMO. These results confirmed the clinical effectiveness of ECMO and led the authors to conclude that ECMO should be considered in infants with severe but potentially reversible respiratory failure. A metaanalysis of the aforementioned studies concluded that ECMO in mature infants with severe respiratory failure results in significantly improved survival without the risk of severe disability.[12]

Throughout the 1980s and 1990s, numerous neonatal ECMO programs were established, and in 1989 the Extracorporeal Life Support Organization (ELSO, Ann Arbor, MI) was formed.[13] ELSO has guided the progression of ECLS through education, guidelines, clinical research, and a comprehensive registry of patient data. Currently, there are 305 ECMO centers worldwide that contribute data to this registry.[14] Although the initial applications of ECLS were focused on neonatal respiratory failure, it has become an integral therapy used in children and adults for a multitude of reasons, including perioperative management of complex congenital heart disease, cardiopulmonary resuscitation (CPR), ARDS, and sepsis. Since its inception, ECMO technology has become more efficient and reliable, which has allowed for prolonged usage in intensive care units.

USES OF EXTRACORPOREAL MEMBRANE OXYGENATION

ECMO continues to be a vital component of critical care medicine. It is used to support neonates, children, and adults with near-fatal respiratory and cardiac failure and continues to serve as the ultimate safety net while advanced therapies, medications, and surgical options are explored.[1] Box 19-1 summarizes the use of ECMO in neonates and pediatric patients.

NEONATAL HYPOXEMIC RESPIRATORY FAILURE

Nearly 30,000 newborns with respiratory failure have been reported in the ELSO registry, which represents the bulk of the neonatal ECMO experience.[14] This includes patients with the diagnosis of persistent pulmonary hypertension of the newborn, meconium aspiration syndrome, respiratory distress syndrome (RDS), sepsis, and air leak syndromes, all reversible conditions, which is a key element for positive outcomes when providing ECMO.

The classic trajectory of neonatal hypoxemic respiratory failure typically begins with evidence of respiratory distress shortly after birth, which progresses to a point

Box 19-1 ECMO Selection Criteria for Newborns with Hypoxemic Respiratory Failure

- Diagnoses
  - Persistent pulmonary hypertension of the newborn
  - Meconium aspiration syndrome
  - Respiratory distress syndrome
  - Neonatal sepsis
  - Congenital diaphragmatic hernia
  - Air leak syndromes
- Oxygen index more than 40 with CMV and more than 60 with HFOV
- Absence of fatal congenital anomalies
- Reversible lung disease
- Age more than 32 weeks of gestation
- No major intraventricular hemorrhage

CMV, Conventional mechanical ventilation; *ECMO,* extracorporeal membrane oxygenation; *HFOV,* high-frequency oscillatory ventilation.

where intubation, assisted ventilation, and supplemental oxygen are required. Conventional mechanical ventilation is used initially, and high-frequency ventilation is often deployed when near-injurious conventional ventilator settings are required or when air leaks occur.[15] Adjunct therapies, including surfactant replacement therapy and inhaled nitric oxide (iNO), are also used.[16,17] The physiology and clinical management of these conditions are well described in Chapters 14 and 18.

Many of these neonates can be managed with pharmacologic adjuncts and mechanical ventilation—conventional or high-frequency. A small percentage are unresponsive to conventional measures, manifested in varying degrees of respiratory acidosis, hypoxemia, preductal and postductal shunting, right ventricular dysfunction associated with pulmonary hypertension, and overall poor perfusion and organ function.[18] Before the availability of ECMO, many of these babies did not survive. ECMO aids in interrupting the vicious cycle of pulmonary hypertension, improves perfusion and organ function, and allows the use of lung-protective mechanical ventilation.

One particularly challenging disease, occurring in approximately 1 in 2000 to 3000 births, is congenital diaphragmatic hernia.[19] The physiology of this disease is well described in Chapter 22. Although conventional measures, including lung-protective ventilation, iNO, high-frequency ventilation, and delayed surgical repair, have improved survival, a proportion of these infants continue to be supported with ECMO. However, the role of ECMO is unclear and somewhat controversial, because the degree of lung hypoplasia and pulmonary hypertension is difficult to predict.[20] This has resulted in some centers adopting a philosophy that if conventional interventions fail, the degree of lung hypoplasia and subsequent pulmonary hypertension is considered non–life-sustaining and ECMO is felt to be futile.[21] Nevertheless, ECMO continues to be used as a perioperative rescue modality, but the survival rates have remained stagnant at around 51%.[22]

Selection Criteria

An important aspect guiding the decision to use ECMO, because it is associated with a number of risks, is the reversible nature of the neonate's underlying condition and the timing of the decision.[23] Various metrics have been proposed as objective selection criteria for ECMO. The **oxygenation index** (OI), a calculation that incorporates mean airway pressure ($\overline{P}_{aw}$), Fio_2, and arterial oxygenation (Pao_2) [$OI = \overline{P}_{aw} \times (Fio_2/Pao_2) \times 100$], has been the most widely accepted metric. Ortega and colleagues found that when the OI exceeded 40 during conventional mechanical ventilation, the risk of mortality exceeded 80%.[24] Their results have been reproduced by other institutions, and the OI remains a widely accepted predictor of mortality in neonates with respiratory failure and is part of the selection criteria for using ECMO.[25] In an analysis of 174 newborns receiving mechanical ventilation, Bayrakci et al. determined that an OI of 33.2 was a suitable threshold for ECMO use.[25] Additionally, these authors identified a greater risk of chronic lung disease when OI was 40 or more and ECMO was not used, which suggests a benefit to earlier deployment.

The introduction of high-frequency oscillatory ventilation (HFOV) decreased the need for ECMO and is a standard of care in the management of hypoxemic respiratory failure.[26] Because HFOV uses higher mean airway pressure than CMV, an OI of 60 has been considered a more realistic threshold for identifying mortality risk and the need for ECMO when this form of ventilation is used.[27, 28] ECMO use declined further in the late 1990s with the discovery of the selective pulmonary vasodilator properties of iNO and its subsequent approval by the Food and Drug Administration.[16] During the iNO clinical trials, it became apparent that HFOV combined with iNO was optimal and further reduced the need for ECMO by nearly 35%.[29] HFOV and iNO are no longer limited to specialty centers that have ECMO capability and are commonly used in most newborn intensive care units. This paradigm shift initially led to concerns that there would be increased mortality in patients who did not respond well to treatment and became too unstable to transfer to an ECMO center.[27] Thus timing is an important factor in determining the use of ECMO. The OI trend, level of support, ability to transport with iNO, and distance to an ECMO center need to be factored into the decision process. A few studies have suggested that mortality has not increased when advanced therapies have been used, and that these therapies lessen the severity of illness at the point of ECMO initiation and do not prolong the time to ECMO.[28]

Contraindications to ECMO in newborns have become less clear. In the early ECMO epoch, prolonged positive-pressure ventilation was felt to be injurious, thus creating an irreversible condition. With a greater understanding of lung-protective ventilation techniques, there is less concern that chronic lung disease will develop, assuming true lung-protective strategies have been used. Typically, the need for ECMO is identified within the first couple of days. The need for ECMO after a prolonged period of mechanical ventilation, such as 7 to 10 days, may suggest an atypical, potentially irreversible pathologic lung condition.[12]

ECMO eligibility varies significantly among centers and becomes more complicated in the presence of specific comorbidities where quality of life may be difficult to predict.[30] Another consideration for deciding not to use ECMO is the patient's size and gestational age. There are ECMO catheter size limitations for newborns less than 2 kg, and newborns younger than 32 weeks of gestation may be at greater risk of developing intracranial hemorrhage when exposed to

anticoagulants. The presence of preexisting intracranial bleeds beyond stage I or II is an added risk with ECMO, because anticoagulation may worsen bleeding and result in poor neurologic outcomes. The use of antifibrinolytic therapy may help abate the progression of bleeding.[31] Moreover, patients who have neurologic sequela or develop neurologic injury on ECMO may require long-term rehabilitation and accumulate a significant financial burden.[32] Additional relative contraindications include the presence of known fatal congenital anomalies and bleeding disorders. Box 19-1 summarizes patient selection criteria.

RESPIRATORY FAILURE IN INFANTS AND CHILDREN

More than 8000 pediatric respiratory ECMO cases have been reported in the ELSO registry.[14] This group of ECMO cases consists of a more heterogeneous assortment of diagnoses compared with the newborn experience. The broad categories include infectious or aspiration pneumonias, septic shock, and acute respiratory distress syndrome (ARDS) associated with trauma, surgery, or medical conditions. Overall survival of pediatric respiratory failure managed with ECMO consistently averages 57%, despite the rapid expansion in this population over the past decade.[33] Much of the pediatric literature consists of observational studies or has been extrapolated from the ELSO database. The role of ECMO in the treatment of severe respiratory failure in children is not well defined, because there have been no randomized control trials aimed at trying to make this determination.[34] Findings from the Conventional Ventilation or ECMO for Severe Adult Respiratory Failure (CESAR) trial demonstrated a cost-effective survival benefit with ECMO. In this study, subjects randomized to ECMO exhibited a 63% survival rate, compared with 47% in those who continued to be managed on conventional ventilation.[35] Despite the lack of "gold standard" evidence in children, ECMO use and the related body of literature have grown exponentially. ECMO has evolved from being a last resort to an accepted standard of care for pediatric patients failing lung-protective ventilation strategies.[36]

Although there is no definitive consensus on when ECMO should be initiated in pediatric respiratory failure, early implementation is increasing in attempts to minimize lung injury and multisystem organ failure.[37] The Pediatric Study Group compared ECMO and non-ECMO groups based on the Pediatric Risk of Mortality (PRISM) score, with the ECMO cohort demonstrating improved survival.[38] This multicenter review further demonstrated that OI is an independent predictor of mortality in pediatric respiratory failure. Several single-center reviews have attempted to identify pre-ECMO factors that may help predict outcome. Mehta and colleagues suggested that an OI greater than 35 or a pre-ECMO pH of less than 7.20 may result in higher mortality.[39] Additionally, the Pao_2/Fio_2 (P/F) ratio has also been validated as a metric of oxygenation deficit severity in pediatric acute respiratory distress syndrome (PARDS).[40] In a case series by Turner et al., it was suggested that there are no true contraindications to using ECMO in pediatric patients with refractory respiratory failure. They further commented that ECMO is appropriate if patients are transferred to an ECMO center early, if lung-protective ventilation is used, and if severe neurologic injury is not present.[38]

In 2015, the Pediatric Acute Lung Injury Consensus Conference expert panel made recommendations regarding indications for ECMO in PARDS.[36] This group recommended that ECMO should be considered for severe PARDS if the underlying disease process has a high likelihood of being reversed. They concluded that it is not possible to apply strict inclusion criteria for ECMO candidacy; however, it should be considered when lung-protective strategies cannot resolve deficiencies in gas exchange. Furthermore, serial structured evaluations, including case history, should be used to determine candidacy for ECMO. Clinicians should also consider the likelihood of benefit and long-term outcomes in relation to comorbidities, quality of life, and potential financial burden.

Once advanced treatments fail, ECMO is often the only remaining option. Pre-ECMO management, the reversible nature of the patient's underlying problem, and the potential to exacerbate complications with ECMO are fundamental to formulating a decision. Ideally, the patient will have been transferred to an ECMO center early, will have been managed with lung-protective ventilation, and does not have any known incurable comorbidities. Monitoring the trajectory of illness with indicators such as the OI, PRISM score, P/F ratio, and pH may aid the decision process.[43]

CARDIAC APPLICATIONS

Mechanical circulatory support is an important tool in the management of neonates and children with congenital heart disease (CHD), and its use is increasing.[14] Cardiac ECLS can be separated into two general categories, ventricular assist devices and ECMO. As ECLS technology has progressed, indications have also evolved, allowing more complex patients to be managed. The indications for cardiac ECMO can be parsed into categories based upon the presence or absence of CHD.[41] Common indications are listed in Table 19-1. More than 16,000 cases have been reported in the ELSO database for neonatal and pediatric cardiac ECMO. Additionally, nearly 5000 cases of ECMO as an adjunct to cardiopulmonary resuscitation, referred to as *extracorporeal cardiopulmonary resuscitation (ECPR)*, in this population have been documented. Collectively, survival after ECMO in neonates and pediatric patients ranges from 41% to 51%.[14] Because full replacement of heart and lung support is generally

Table 19-1 Indications for Cardiac ECMO

RELATED TO CONGENITAL HEART DISEASE	RELATED TO MEDICAL CARDIAC DISEASE
Preoperative stabilization	Myocarditis
Failure to wean from CPB	Cardiomyopathy
Low cardiac output syndrome	Cardiac arrest
Cardiac arrest	Pulmonary hypertensive crisis
Bridge to ventricular assist device	Intractable arrhythmia
Bridge to transplantation	Sepsis or other forms of shock

CPB, Cardiopulmonary bypass; *ECMO*, extracorporeal membrane oxygenation.

required in this population, **venoarterial** (VA) ECMO is used in 95% of cases.[33]

Preoperative stabilization using ECMO may be required in a subset of patients, with the aim of avoiding unfavorable outcomes by emergently operating on moribund patients. The primary objectives include the timely optimization of hemodynamics, oxygen delivery, correction of acidosis, and mitigation of any multiorgan failure preceding surgical repair.[41] Hypoxemia and cardiogenic shock in patients with transposition of the great vessels, and hypoplastic left heart syndrome (HLHS) without adequate atrial shunt or mixing have been documented as the most common neonatal indications.[42] Preoperative stabilization on ECMO allows for a period of recovery, which may potentially lead to improved outcomes. This approach has been described in various case reports involving a multitude of congenital heart defects; however, is not advised in neonates with obstructed total anomalous venous return. In this scenario, pulmonary venous pressure remains dangerously elevated despite mechanical circulatory support, and surgical repair should be expedited.[43]

The use of ECMO in the postoperative management of complex CHD is well established. ECMO is a fundamental means of circulatory support for patients failing to wean from cardiopulmonary bypass (CPB) and those with refractory low cardiac output syndrome (LCOS), and in the presence of cardiac arrest.[44] LCOS is a well-recognized complication in children after CPB and typically manifests 6 to 12 hours after surgery. In general, myocardial dysfunction associated with LCOS is anticipated and can be preemptively managed with inotropic support, afterload reduction, and pulmonary vasodilators. However, the most severe subset of LCOS patients become progressively worse and account for 36% of postoperative cannulations.[45] The incidence and timing of postoperative ECMO support vary significantly based on patient population and center. It has been reported that postoperative ECMO was used in as many as 17% of patients who underwent surgery for complex CHD, such as HLHS.[46]

Although much cardiac ECMO is used in the perioperative period, it is also deployed to support infants and children with forms of heart failure unrelated to CHD, such as myocarditis and cardiomyopathy. VA ECMO is considered for infants and children in this setting who are unresponsive to medical treatment, with the aim of averting cardiac arrest. In general, survival in this subset of patients is 70% and 62% higher, respectively, than their counterparts with CHD.[47] Furthermore, other causes of cardiac failure, including arrhythmias, infection, and cardiac arrest, may require ECMO. ECPR has been recommended by the American Heart Association for in-hospital cardiac arrest, given that ECMO is readily available, protocols are in place, and the center has expertise in ECPR application.[48] Globally, centers have developed rapid-deployment ECMO programs that train clinicians to initiate support during ongoing CPR, often in less than 30 minutes.[49] As with many ECMO applications, there is strong evidence that ECPR provides a survival benefit with relatively favorable neurologic outcomes, and many of these patients would most likely die otherwise.[50,51]

SIMULATION

Rapid deployment of ECMO requires an expeditious, coordinated response by the multidisciplinary team to establish support promptly. To improve this process, many centers are using high-fidelity simulation to increase team preparedness. This training is particularly helpful in the setting of ECPR, where minimizing the time to establishing support is imperative to improving outcomes. Simulation has been shown to improve provider comfort and ability to function during a code and has become an integral component in the maintenance of ECMO programs.[52]

MODES OF EXTRACORPOREAL MEMBRANE OXYGENATION SUPPORT

ECLS is the use of an artificial gas exchanger and associated circuity to provide cardiac support, blood oxygenation, and carbon dioxide removal to maintain normal physiologic processes for reversible cardiac or respiratory failure that is refractory to conventional measures. There are two standard modes of ECLS: VA and **venovenous** (VV). Each modality uses the same circuit components, including an outflow cannula extended by an outflow line connected to a servo-regulated pump, either an occlusive roller-head device or a **centrifugal pump.** The pump propels blood through a membrane oxygenator, where carbon dioxide is removed and oxygenation occurs. Oxygenated blood is then rewarmed or cooled to the desired temperature and returned to the patient through the inflow cannula. The difference in physiologic support is

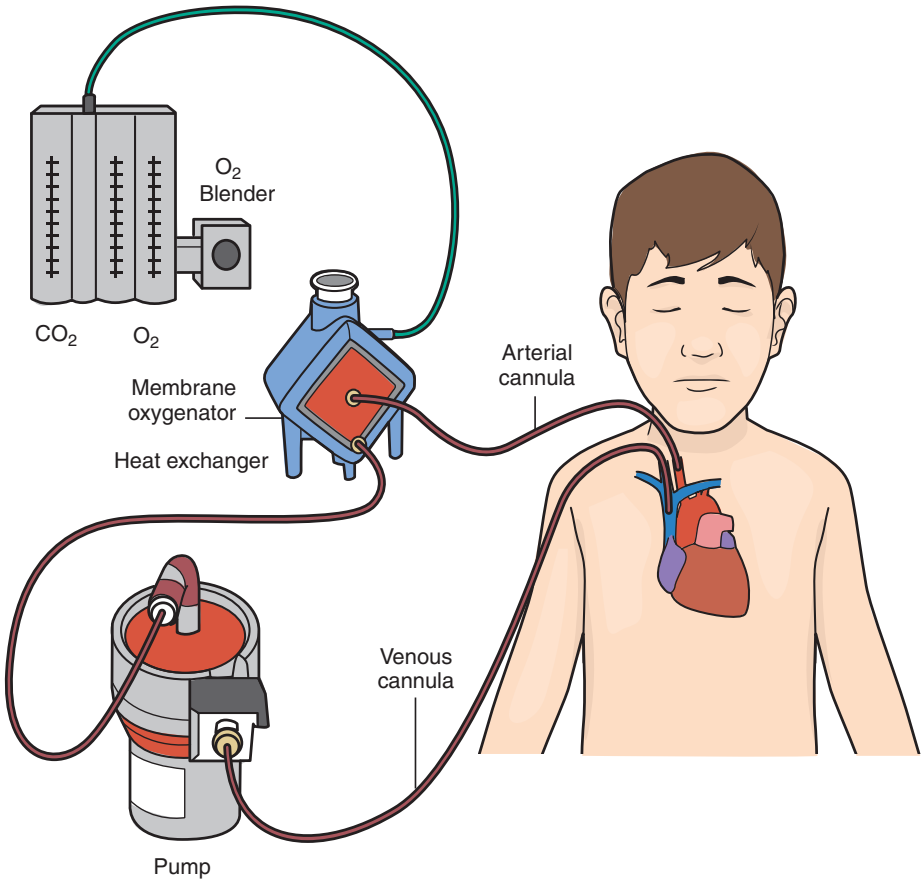


FIGURE 19-1 Basic extracorporeal membrane oxygenation (ECMO) circuit configuration and common cannulation sites. Venous drainage *(blue)* returns to the pump and is directed through a membrane oxygenator, which removes P_{CO_2} and adds oxygen to the blood. Oxygenated blood leaves the membrane and is reinfused into an artery (venoarterial) or vein (venovenous).

determined by the placement of the vascular cannulas[53] (Figure 19-1).

VENOARTERIAL

VA ECMO is indicated for patients with primary cardiac failure or patients with both respiratory and cardiac dysfunction, because it provides gas exchange and circulatory support by bypassing the lungs and heart. This is accomplished by draining from a venous source and returning to the patient's arterial circulation.[54] In newborns and infants, cannulas are surgically placed into the right common carotid artery and right internal jugular vein, with the distal tip of the venous cannula situated in the right atrium and the arterial cannula positioned at the aortic arch.[55] VA ECMO may also be established by a peripheral cannulation technique through a femoral vessel in larger pediatric patients or by central transthoracic access placed directly into the heart, a common approach for postoperative cardiac surgical patients.[56]

VENOVENOUS

VV ECMO provides an alternative means of extracorporeal support for patients with severe respiratory failure who do not require cardiac support. In VV ECMO, deoxygenated blood is drained and oxygenated decarboxylated blood is reinfused back into the venous circulation at the same rate simultaneously, thereby providing only pulmonary support. The oxygenated blood mixes with the venous blood in the right atrium, thereby raising the oxygen content. Because both the drainage and reinfusion cannulas are in the venous system, oxygenated blood from the return cannula that passes back into the drainage cannula does not contribute to arterial oxygenation. This phenomenon, known as recirculation, decreases the efficiency of gas transfer between the circuit and the patient.[57] The degree of recirculation is monitored by comparing the oxygen saturation of the venous drainage ($S\bar{v}o_2$) with the patient's arterial oxygen saturation (Sao_2).[58] If $S\bar{v}o_2$ is greater than Sao_2, the recirculation is excessive, which would require either an adjustment in cannula position or a change in blood flow rate.

VV ECMO does not provide the same level of oxygenation as VA, and the maximal Sao_2 achievable can be as low as 85% until lung function improves. VV ECMO essentially operates in series with the native circulation, so alterations in cardiac output will not

have a significant effect on oxygenation. The volume of blood removed is equal to the volume reinfused, so there is also no effect on the patient's hemodynamics.

There are a few advantages of VV over VA support, mainly that carotid artery ligation is not required and full pulsatile native blood flow is maintained.[62] A disadvantage is the lack of cardiovascular support. However, the presence of mild to moderate myocardial dysfunction should not discourage use of the VV approach, because cardiac function may improve by increasing mixed venous saturation in the pulmonary arteries, resulting in decreased pulmonary vascular resistance and right ventricular afterload.[55] If myocardial dysfunction does not improve or worsens, however, conversion to VA support generally remains an option.[59]

VV is the preferred mode of ECMO support in infants or children with respiratory failure and is accomplished through either a two-cannula approach (VV), a double-lumen cannula (VVDL), or a bicaval dual-lumen cannula. In the two-cannula method, blood is drained from a femoral vein and reinfused through the right internal jugular vein.[60] Although the femoral vein could serve as the reinfusion site, return to the right side of the heart helps to lessen recirculation and improve systemic oxygenation. In larger patients, a second drainage cannula, established through the opposite femoral vein, may be needed to improve drainage to provide increased ECMO support, hence VVV—two femoral venous drainage cannulas and one reinfusion.[58]

Another approach to establishing VVDL support is the use of a single cannula that has two channels or lumens, one for drainage and one for reinfusion, with the drainage lumen representing two-thirds of the diameter and the reinfusion one-third.[61] The cannula is placed in the right internal jugular vein and is oriented with the reinfusion lumen superiorly so that the oxygenated blood returning to the right atrium is predominantly directed toward the tricuspid valve and subsequently the pulmonary circulation, which helps to minimize recirculation. These cannulas had been limited to patients 10 kg or smaller until larger bicaval dual-lumen cannulas were developed.[62] Bicaval dual-lumen cannulas provide concurrent drainage and reinfusion similar to the infant VVDL cannulas, with the difference being the presence of two drainage areas—one situated in the superior vena cava and one in the inferior vena cava. Proper orientation of this cannula is critical so that arterialized blood is streamlined into the right atrium[63] (Figure 19-2).

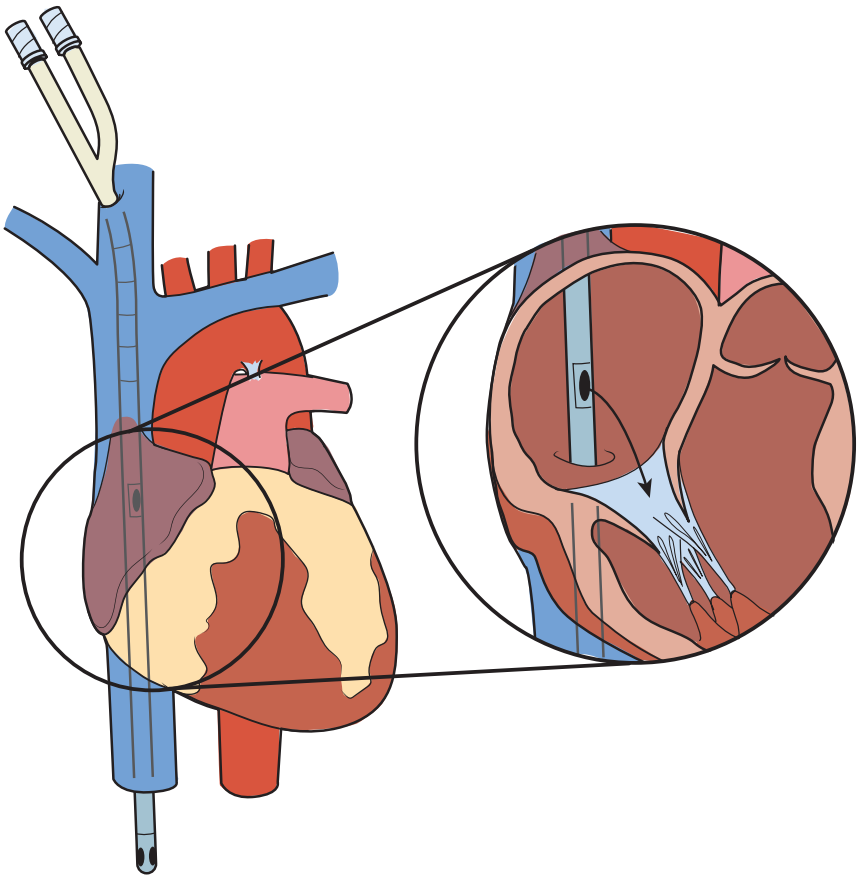


FIGURE 19-2 The bicaval dual-lumen cannula commonly used for pediatric venovenous extracorporeal membrane oxygenation (VV-ECMO). Two drainage areas—one situated in the superior vena cava and one in the inferior vena cava—return venous blood *(blue)* to the pump. The reinfusion cannula *(red)* is oriented so that arterialized blood is directed toward the right atrium and tricuspid valve.

One of the advantages of this approach, along with smaller and more compact pumps, is the ability to increase patient mobility.

Historically, the use of VV ECMO has focused on supporting patients with reversible lung injury. An increasing trend is the use of ECMO as a bridge to lung transplantation or recovery. With newer, more compact ECMO technology and advances in cannulation techniques, it is now possible to provide support for longer durations. In this subset of patients, there is a growing body of evidence suggesting that early mobilization and participation in physical therapy may provide a mortality benefit.[64] A cohort study by Abrams and associates reported 53% survival in the BTT cohort and concluded that physical therapy, including early mobilization, may be performed safely for patients receiving ECMO.[65] These authors separately analyzed patients requiring ECMO as a bridge to recovery from acute respiratory failure and found that 88% of this cohort survived to discharge. These findings suggest that early rehabilitation on ECMO may help to maintain transplant candidacy and concomitantly improve the likelihood of recovery. Moreover, further research is needed to better characterize cost-effectiveness and whether these interventions are advantageous on major clinical outcomes.

EXTRACORPOREAL MEMBRANE OXYGENATION SYSTEMS

The ECMO system has two principle components, a pump and a gas exchange device. Additional circuit components include cannulas, pressure monitoring modules, gas metering devices, a heater/cooler exchanger, and circuit tubing. Some of the newer devices have a pressure, temperature, and blood analyzer fully integrated into the system. Although the mechanical principles are fairly universal, there is a lack of standardization of the ECMO circuit, and therefore the general designs are institution-specific.

Blood is always drained from the venous system, by gravity or actively through tubing connected to the venous cannula. Blood then flows to the pump and, in many designs, passes through a venous chamber or reservoir that serves as a safety mechanism and a place to monitor venous drainage. The blood proceeds to the pump, which is either a peristaltic roller design or centrifugal. At this point the blood is still deoxygenated until it travels through the artificial lung or membrane oxygenator, where gas exchange occurs. Blood fully saturated with oxygen exits the membrane and is pumped into the reinfusion limb of the circuit, where it is warmed in a heat exchanger and then returned to the patient, thus completing the loop. Along the ECMO circuit there are ports for monitoring various pressures and for obtaining blood samples.[66] Additionally, some institutions use a separate piece of tubing or a "bridge" that spans between the drainage and reinfusion limbs of the circuit. The bridge is typically used to separate the patient from the ECMO circuit during the weaning phase.

PUMPS

Pumps used for ECMO are either occlusive roller pumps or nonocclusive centrifugal pumps. The purpose of the pump is to propel the blood through the contiguous ECMO circuit from the patient to the membrane oxygenator and back to the patient. There is some debate as to which pump is more beneficial. ECMO centers established in the earlier years used roller pumps primarily because of availability and ease of use. In the present ECMO era, centrifugal pumps are becoming predominant as pump head designs and streamlined systems have been developed.[67]

Roller Pumps

Roller pumps are positive displacement devices that operate on the principle of compression and displacement, with flow being achieved by the compression of a tubing segment between the pump's wall and two roller heads that are spaced 180 degrees apart. The second roller begins compressing the tubing as the first roller is finishing; therefore, the raceway (the tubing in the pump housing) is always being compressed. The output depends on the size of the tubing, the rotations per minute (RPMs), and the tension or occlusion of the rollers on the raceway.

Evaluating raceway occlusion is essential; too much roller tension—overoccluding—may cause tubing damage and hemolysis, and too little roller tension—underoccluding—may result in inadequate flow. Occlusion adjustments are usually made with a dial mechanism while observing the rate at which a column of fluid drops. When a column of fluid falls 1 cm/minute, occlusion is considered optimal—meaning the ideal flow rate with the least amount of raceway and blood cell damage. Occlusion may be judged less precisely by observing the peristaltic kick of the postpump tubing, by physically feeling a pulse in the tubing, or by observing changes in membrane pressures.

One drawback to roller pumps is that they are not influenced by afterload and will continue to pump to deliver preset RPMs, which determines the flow rate. If excessive pressure builds up within the ECMO circuit, the pump will continue to spin until the problem is recognized or rupture occurs. For safe operation, a roller pump should incorporate a venous servoregulation system that consists of a compliant venous reservoir or bladder. This aids gravity drainage, which is the principal mechanism by which blood is introduced into a roller pump system. When venous return is sufficient to meet the demands of the flow rate, the venous reservoir is full and the roller pump spins freely at the set speed. As venous drainage decreases, the reservoir becomes less full and may even collapse completely, and either a mechanical switch in the

bladder stand or the pressure monitor relays this change in drainage volume to the pump, which will in turn slow its speed or stop altogether. Without this servoregulation, the pump will continue to operate and eventually generate significant negative pressure, and may cause air entrainment.

Roller pumps are set to deliver a specific flow rate by adjusting RPMs. This results in the delivery of a consistent flow rate despite changes in the patient's hemodynamics. However, in the presence of an obstruction distal to the pump, such as kinking of the tubing, extremely elevated pressures can be generated, potentially causing circuit rupture. Also, there is constant wear and tear on the raceway tubing, and a raceway rupture is possible. This risk can be lessened if highly durable tubing with a larger diameter is used, allowing for fewer rotations per minute, along with periodic shifting of the raceway to distribute wear and tear across the length of the raceway.[57]

Centrifugal Pumps

Centrifugal pumps are nonocclusive devices. Energy is transferred to the blood by a rapidly rotating cone-shaped pump head that creates a constrained vortex.[67] Blood is actively pulled inward and propelled outward by the energy created by the vortex, thus drainage is considered active. Because this type of pump is nonocclusive, it is dependent on the patient's preload and afterload. As preload decreases, such as decreased venous drainage, or if afterload increases because of increased systemic vascular resistance, flow will decrease. Typically, RPMs are set and the patient's preload and afterload influence the amount of flow delivered. In contrast to roller pumps, excessive pressurization will not occur, but flow delivery to the patient will be more variable.

Centrifugal pumps have potential advantages over roller pumps where ECMO circuit lengths are reduced, because a venous reservoir is not needed. A more compact circuit with fewer connectors decreases turbulent flows, which reduces areas of clot formation, and requires less priming volume.[68] Earlier centrifugal pump head designs caused more hemolysis, because blood came in contact with the rotating parts. Modern centrifugal pump heads use a more floating head design so that blood passes over impellers that move it along with less contact.[67]

MEMBRANE OXYGENATORS

Artificial gas exchange devices, also known as membrane oxygenators or diffusion membranes, substitute the oxygen and carbon dioxide exchange mechanism of the native lung. These devices are separated into gas and blood compartments and are highly efficient. There are two general types of membranes: silicone and microporous. Most of the experience in ECMO has been with the silicone rubber membrane originally designed by Kolobow and Bowman.[4] These devices were time-consuming to prepare, because meticulous deairing by physical tapping is required to ensure that pockets of air bubbles are removed before connecting to the patient. Additionally, silicone oxygenators were characterized by higher resistance to blood flow, increased blood component consumption, and higher priming volumes.[69]

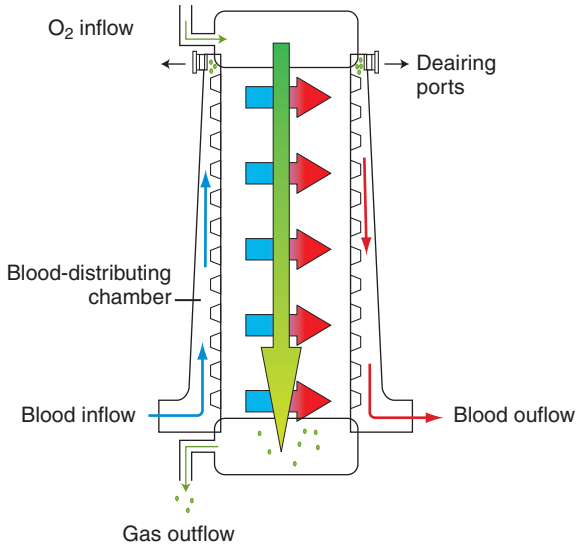


FIGURE 19-3 A microporous membrane oxygenator. (Redrawn from Meyer A, Struber M, Fischer S: Advances in extracorporeal ventilation. *Anesthesiol Clin* 26:381, 2008.)

One of the technologic advances of ECMO components is the microporous membrane. Microporous or hollow-fiber membranes are made of woven capillaries of microporous plastic. Gas passes through the capillaries, while blood flows around them[70] (Figure 19-3). The microporous membrane has excellent gas exchange capabilities, and low resistance, therefore making it easier to prime and deair. Older versions were prone to condensation or wettability, and plasma leakage occurred over long durations, which made it less desirable for long-term use.[71] However, advances have been made in microporous technology with the introduction of polymethylpentene-sealed fibers, which resist the wetting-out or leaking phenomenon. This gas exchange device has essentially replaced silicone membranes in the United States.[72]

Gas transfer across the membrane depends on the composition of the gas, the thickness of the membrane, the surface area, and the difference in partial pressure of the gases on each side of the membrane. This partial-pressure difference is referred to as the *driving pressure* or *transmembrane pressure,* and it uses the principles of Fick's Law of Diffusion.[73] Carbon dioxide elimination decreases as water accumulates in the gas compartment of the membrane because of the temperature gradient between the two sides of the membrane. The warm blood and the cooler **sweep gas** cause condensation to occur. A minimal fresh gas flow

is required for continuous flushing of these water droplets. Unfortunately, the minimal flow rate required to remove condensation usually results in excessive elimination of carbon dioxide as well. To compensate for this, sweep gas is often blended with a combination of O_2 and CO_2, commonly referred to *carbogen*, which reduces the driving pressure across the membrane and maintains normocarbia.

TEMPERATURE REGULATION

Body temperature is regulated by a circulating water bath and heat exchanger in the circuit. As blood travels through the ECMO circuit, heat is continually lost from the exposed surface of the tubing and through the oxygenator because of the cooling effects of the sweep gas and water evaporation. Therefore, the ECMO system must be capable of providing temperature regulation. This is accomplished either by the addition of a separate heat exchanger, such as the one used with a silicone membrane, or with an integral heat exchanger, common to most microporous membranes. The heat exchanger, is connected to a water pump that heats the water and regulates the temperature. The patient's temperature is monitored and the temperature of the water is adjusted to maintain a target range. Although the water pump is mainly used for warming, it can also be used for cooling, a strategy used to aid in neuroprotection of patients after resuscitation or to slowly rewarm hypothermic patients. Water pumps are also capable of monitoring blood temperature and providing servoregulated temperature control.[71]

CIRCUITS AND CIRCUIT PREPARATION

An ECMO circuit consists of a contiguous loop of polyvinyl chloride tubing arranged in a sterile package that contains all the necessary disposable components to easily and sometimes rapidly prepare the system for patient use. As previously stated, there is a lack of standardization of the design of ECMO circuits. Most institutions have designed configurations based on the type of pump used and their patient population. The ideal ECMO circuit should be as streamlined as possible, contain minimal access points, and be long enough to have a safe distance between the pump and the patient while minimizing overall circuit volume.

Another attribute that is somewhat debatable is components that are coated with biocompatible substances. These surface coatings, composed of protein-or heparin-based compounds, may potentially reduce the activation of the coagulation cascade and trigger less of an inflammatory response, because the circuit is less foreign as blood comes in contact with the tubing.[74]

CANNULAS AND ESTABLISHING SUPPORT

The ECLS circuit begins and ends with the cannulas. The appropriate cannulas are chosen to influence the maximal flow rate that the system can achieve. The ideal cannula should be thin-walled to achieve the largest internal diameter possible, kink-resistant, and radiopaque. Wire-reinforced cannulas have many of these characteristics. A standardized rating system, the M number, has been developed to score various devices on their pressure-to-blood flow characteristics.[75] A device with a low M number indicates that a higher blood flow rate is possible at a lower pressure.

The arterial cannula is the source of highest resistance in the circuit because of its small diameter. Because hemolysis can occur at system pressures exceeding 350 mm Hg, it is important to select an arterial cannula large enough to handle the anticipated flow rates for the patient.[58] The major differences between the venous and arterial cannulas are that the lower portion of the venous cannula is longer and has multiple side ports for optimal drainage, whereas the arterial cannula has a single lumen and is shorter, to reduce resistance. In addition to the diameter of the venous cannula, drainage depends on cannula position, right atrial pressure, and the height of the patient in a gravity-dependent roller pump system. Subtle manipulations of these variables may be necessary to optimize flow. The most common causes of a decrease in venous return include malpositioning of the venous cannula, kinking of the cannula, shifting of the mediastinum, and hypovolemia.

The cannulation procedure begins with the deployment of a surgical team, applicable instruments, and related equipment to the patient's bedside. While the patient is prepped, the ECMO specialist prepares the ECMO system and circuit. Establishing ECMO, although critical, is considered to be either elective, in which case the circuit is primed with blood, or emergent, such as an ECPR application, when there is generally insufficient time to complete the full blood priming step. The surgeon and ECMO specialist confer on the mode of support, type of cannula, and alternatives if cannulation becomes difficult. Once the cannulas are surgically inserted and secured, the ECMO circuit is connected to the patient, with verification that drainage and reinfusion lines are correctly aligned to the corresponding cannulas. The ECMO pump is activated, and several simultaneous observations are made, including hemodynamics, oxygen saturation, venous return, ability to achieve desired flow rates, ECMO circuit pressures, and patient temperature.

As the ECMO flow is established and the patient is stabilized, a chest radiograph is obtained to confirm cannula position, and on occasion echocardiography is used to further verify cannula position and flow patterns, particularly with VVDL.

HEMOFILTRATION

It is not uncommon for patients requiring ECMO to develop renal insufficiency from pre-ECMO fluid resuscitation, acute renal dysfunction, and blood product replacement. To augment renal function and remove

larger quantities of fluid, a semipermeable membrane or hemofilter can be added to the ECMO circuit.[76] This semipermeable membrane, similar to a hemodialysis filter, uses hydrostatic pressure to move plasma water from the high-pressurized blood across the low-pressure filter. This results in the removal of plasma water and small-sized solutes but preserves larger cellular elements and protein in the blood.

The hemofilter is commonly positioned after the ECMO pump with the return placed on the prepump side of the circuit, forming a postpump-to-prepump shunt. The removal of plasma water can be regulated by restricting the hemofilter outlet or using a secondary pump to achieve a specific output. Stand-alone renal replacement therapy systems are also used in series with ECMO systems. There are two approaches to using these filters, hemoconcentration and ultrafiltration. Hemoconcentration is the rapid removal of plasma water to reverse hemodilution associated with crystalloid priming. Ultrafiltration is a more gradual removal of fluid.[76]

EXTRACORPOREAL CARBON DIOXIDE REMOVAL

Another form of ECLS that has gained traction is pumpless **extracorporeal carbon dioxide removal,** commonly referred to as *ECCO$_2$R*. ECCO$_2$R operates very similarly to VV ECMO, in which carbon dioxide is removed and oxygenated blood is reinfused back into the venous circulation. The biggest difference between the two modes is that ECCO$_2$R does not use an external mechanical pump to circulate blood; instead, it uses the patient's native cardiac function to propel blood forward. By draining blood from a large artery and reinfusing into the inferior vena cava, adequate gas exchange may be achieved. Indications for this modality began with ARDS and lung-protective ventilation using low-tidal-volume ventilation and low-pressure mechanical ventilation. Even though this form of ventilation may decrease iatrogenic injury to the lungs, there is recent evidence that demonstrates that permissive hypercapnia, along with hypoxia, may cause other ill effects. ECCO$_2$R allows normal physiologic blood gases while minimizing ventilator-induced injury to a mechanically ventilated patient.[77]

Another variation of ECCO$_2$R that has been used to provide respiratory support in infants and children is the paracorporeal lung assist device. This configuration involves central cannulation with blood inflow from the pulmonary artery and return to the left atrium. This helps to alleviate elevated pulmonary vascular resistance and end-stage respiratory failure for patients with pulmonary hypertension. By shunting venous blood propelled by the right ventricle through the membrane and into the left atrium as oxygenated blood, right ventricular pressure is reduced and the demand for mechanical ventilation is lessened. Given that survival outcomes for patients receiving ECMO before lung transplantation are poor, alternative options such as ECCO$_2$R have been used as a bridge to lung transplantation. This therapy has demonstrated feasibility to enhance mobility, reduce sedation requirements, and facilitate liberation from mechanical ventilation in small case studies.[78]

VENTRICULAR ASSIST DEVICES

Ventricular assist devices (VADs) have been used routinely in the treatment of end-stage adult heart failure and have become a progressively emerging technology in pediatrics over the past 5 years. Before this period, there were few options to bridge these patients to heart transplantation aside from ECMO.[79] The use of ECMO as a bridge to heart transplantation is associated with higher waitlist mortality and poor survival to discharge, thus providing an impetus to develop alternative methods of prolonged mechanical circulatory support.[80] VADs are used solely for cardiac support and can be differentiated from ECMO by the lack of an oxygenator, heat exchanger, and pulmonary support.

Based on a paucity of long-term mechanical circulatory support options, larger children have previously been supported using adult VADs. In contrast, support in smaller infants was limited to the novel use of modified ECMO circuitry or traditional ECMO. In the United States, the only commercially available VAD option for infants and children is the Berlin Heart EXCOR. This system uses a pneumatic paracorporeal pump capable of providing pulsatile flow and can be used for right, left, or biventricular support. VADs have demonstrated superiority to traditional ECMO in pediatric patients awaiting heart transplantation. Dipchand et al. found that patients who were receiving ECMO at the time of listing and were weaned off or converted to VAD support had equally good outcomes to unsupported patients.[80] Thus the management of these patients often includes stabilization with ECMO in the acute phase of illness and transition to a VAD for longer-term cardiac support. Despite improvements in VADs, neurologic complications occur in approximately 30% of patients and remain the primary cause of mortality. Other factors contributing to high waitlist mortality in this population include the presence of CHD or renal failure, small patient size, and single ventricle physiology.[81]

CLINICAL MANAGEMENT

ANTICOAGULATION

The components of an ECMO circuit are artificial, and the immediate contact of blood on the circuit activates the clotting cascade. The use of anticoagulation, primarily continuous unfractionated heparin infusion, must be established and closely monitored to maintain a desired level of hemostasis.[82] Heparin has no direct anticoagulant effect on the blood by itself

but combines with a cofactor, antithrombin III (ATIII), to prevent thrombi from forming. This stops the conversion of fibrinogen to fibrin and ultimately prevents clot formation. A deficiency in ATIII can cause heparin to be ineffective, resulting in the use of excessive amounts of heparin. If excessive clotting in the circuit is noted, a deficiency in ATIII is a possible cause.[83] Patients who are sensitive to heparin may be managed with alternative anticoagulants such as bivalirudin or argatroban.[84]

The classic method for monitoring anticoagulation is measuring the activated clotting time (ACT) with a point-of-care device. The heparin dose is titrated to achieve an ACT range of typically 180 to 220 seconds. Although the ACT is a simple bedside test, it does not fully monitor the complexity of the clotting system, and other laboratory tests, including monitoring anti-factor Xa activity in conjunction with ATIII, provide a more complete assessment.[85]

Although not routinely used for the management of anticoagulation, thromboelastography (TEG) has been shown to be effective in guiding the management of bleeding. TEG graphically displays the viscoelastic properties of whole blood as it clots.[86] It is logical to believe that with more experience, this technology would provide additional aid in managing coagulation.

MONITORING CIRCUIT FUNCTION

ECMO systems are equipped with integrated safety systems and adjunct components that provide continuous monitoring of various circuit functions. The water pump previously described can be autoregulated with the use of a blood temperature probe placed within the membrane oxygenator. A temperature is targeted, and the water is cooled or warmed accordingly.

There are adjunct devices that continuously monitor blood gases, chemistry values, and hematologic parameters such as hemoglobin and hematocrit. These provide the ECMO specialist with early warning signs of physiologic changes. Additional monitored parameters include venous saturation, which is mainly used to gauge the degree of recirculation during VV ECMO.

The oxygen–carbon dioxide concentration of the sweep gas is regulated by flow meters from oxygen air blenders and stand-alone carbon dioxide cylinders. The sweep gas lines can contain an oxygen analyzer equipped with alarms that provide the user with warnings of low carbon dioxide cylinder pressure or inadvertent changes in sweep gas flow rate.

Circuit integrity is monitored by visually inspecting the circuit and components for thrombus and air, and by continuously monitoring premembrane and postmembrane pressure (Box 19-2). As the circuit or membrane resistance changes, as is common with clot formation, the pressure will change. As an example, a membrane that has been used for a prolonged duration will tend to develop clots and increased resistance, which would be identified by an increase in premembrane pressure or a widened gradient between premembrane and postmembrane pressures.

Box 19-2 Circuit Integrity and Safety

- Circuit inspection
  - Air
  - Clots
- Adjunct monitoring
  - Svo_2
  - Hemoglobin
  - Hematocrit
  - Blood flow rate
- Membrane function
  - Premembrane and postmembrane pressures
  - Premembrane and postmembrane blood gases
- Thermal regulation
  - Normothermia
  - Induced hypothermia
- Sweep gas adjustments
  - Oxygen–carbon dioxide combinations
- Safety features
  - Bubble detector
  - Drainage pressure
  - Membrane pressure alarms
  - Temperature alarms

Membrane function is also evaluated by periodically measuring premembrane and postmembrane blood gases. Gas exchange across the membrane may become less efficient over prolonged ECMO duration, which may be diagnosed by changes in the pre– and post–blood gas values. For instance, a narrower premembrane and postmembrane Pco_2 gradient is suggestive of a decrease in carbon dioxide elimination.

Another commonly used adjunct monitor measures the blood flow rate by an externally applied ultrasonic probe on the reinfusion limb of the circuit. This displays the true flow rate and is particularly important to observe when there are built-in shunts in the circuit, such as a hemofilter.

An additional commonly used safety device is an air or bubble detector, which is attached to the external aspect of the circuit and can be placed on either the drainage or reinfusion line. The purpose of the bubble detector is for blood flow to cease in the presence of an air bubble. This would prevent the delivery of an air embolism to the patient, particularly with VA ECMO. Bubble-sensing devices are programmed to directly communicate with the pump so that if a bubble or microbubble is sensed, the pump immediately stops and a warning alarm signals. In some centrifugal pumps, the air detection and flow measurement occur with the same sensing mechanism integrated into the pump drive.

HEMODYNAMICS

Hemodynamic parameters are continuously monitored during ECMO, at a minimum heart rate and blood pressure. In a patient with CHD, the pressure of additional intracardiac lines, such as central venous, left atrial, and pulmonary artery, may be also monitored. Observing changes in blood pressure is imperative during ECMO, particularly in newborns, because anticoagulation combined with hypertensive periods may result in an intracranial hemorrhage. Causes of hypertension include discomfort, increases in afterload, changes in neurological status, and sudden or inadvertent increases in ECMO pump flow rate. Hypotension is associated with increases in urine output, bleeding, decreases in afterload, cardiac tamponade, tension pneumothorax, and sudden or inadvertent decreases in pump flow rate. Additionally, any roller pump occlusion that has loosened will cause a lower actual flow delivered to the patient even though the same RPMs are being used; this would result in a decrease in blood pressure.

During VV ECMO, blood pressure support may be needed initially until the patient's condition moves from the acute phase to a more stable period. Blood pressure is supported with the use of vasoactive agents and fluid replacement. As previously noted, VA ECMO supports cardiac function, therefore blood pressure lability is not usually an issue unless the patient develops a capillary leak, in which fluid moves from the intravascular compartment to the extravascular space. The patient develops total body edema, and preload falls to a point where drainage decreases and ECMO pump flows need to be reduced. When using centrifugal pumps, changes in preload and afterload affect the pump flow rate, which in turn influences blood pressure.

In cardiac patients, particularly in the postoperative period, additional parameters, including central venous pressure and left atrial pressure—the filling pressures of the heart—provide useful information on heart function. In the failing heart, high filling pressures are a sign that the heart is not effectively ejecting. This can be remedied by increasing the mechanical support to relieve the heart's work. Moreover, volume overload in cardiac patients may lead to LA hypertension, LV dysfunction, and dilation. LA decompression may be accomplished by insertion of an LA vent or balloon atrial septostomy and has been associated with a higher probability of both weaning from ECMO and LV recovery.[87]

ORGAN PERFUSION

Preserving end-organ perfusion by providing sufficient oxygen to the tissues is the fundamental goal of supporting the patient with ECMO. This can be monitored by observing routine laboratory indices of hepatic, renal, and cardiac function and by monitoring $S\bar{v}O_2$ and the patient's acid-base status. Tissue perfusion is dependent on adequate blood oxygen content and delivery, which is influenced by the native cardiac output and the ECMO pump flow rate. In a high-oxygen-demand state, the $S\bar{v}O_2$ may decrease from the normal 75%; assuming the oxygen carrying capacity of the blood is adequate, meaning there is sufficient hemoglobin, the delivery can be enhanced by increasing the ECMO flow rate.

During the acute postcannulation phase, the patient may require ECMO pump flow rates between 100 and 150 mL/kg, which represents approximately 70% to 80% of cardiac output. The patient's acid-base status may correct slowly or quickly depending on the disease and the severity of illness in the pre-ECMO period. For instance, a patient with severe sepsis and profound metabolic acidosis will take longer to stabilize than a newborn with a primary respiratory problem. A septic patient may require higher ECMO flow rates, chemical buffering, and blood transfusions to resolve the acidemia.

LABORATORY TESTS

Laboratory tests are routinely sampled and monitored during an ECMO course and include complete blood counts, blood gases, and coagulation studies. The interaction of blood with a foreign surface in the ECMO circuit affects platelets the most. Thrombocytopenia is common with ECLS because of abnormal platelet activation and consumption.[88] Adequate hemoglobin and hematocrit levels are necessary to ensure sufficient oxygen content and delivery. Coagulation studies, including prothrombin time and fibrinogen levels, are closely monitored to maintain a balance between coagulation and anticoagulation. Plasma-free hemoglobin, a biomarker for hemolysis, is also studied, because elevated levels have been shown to cause renal dysfunction, increased blood transfusions, and an increased risk for mortality.[89]

NEUROLOGIC ASSESSMENT

Traditionally, ECMO patients were heavily sedated and occasionally chemically paralyzed to prevent inadvertent decannulation, which made neurologic assessment more difficult. Although current trends emphasize using less sedation, neurologic injury continues to be a significant concern and a primary risk factor for morbidity and mortality in patients receiving ECMO. The origin of neurologic injury may be from both the underlying condition and changes in cerebral perfusion during ECMO. Additionally, risk factors such as acute hypoxia-ischemia after cardiac arrest and ECPR are of concern. A randomized controlled trial evaluating the neuroprotective effects of therapeutic hypothermia did not result in improved outcomes in children up to 2 years old.[90] This trial included common neonatal indications for ECMO; however, it did not include infants who received cooling after CHD surgery or ECPR. Accordingly, there has been substantial

interest in neurologic monitoring during ECMO, but there is a lack of consensus on protocols to this end. The use of serial head ultrasounds is a standard of practice for infants on ECMO, but this requires the presence of an open anterior fontanel. Other methods of neurologic monitoring include electroencephalography, near-infrared spectroscopy, and plasma brain injury biomarkers. Evidence supporting the efficacy of these methods alone or in combination is limited to mostly observational studies with modest sample sizes and significant heterogeneity among subjects' ages and diagnoses.[91] The availability of portable head computed tomography (CT) has provided a welcome alternative in the diagnosis of suspected neurologic injury. Moreover, many of these patients are acutely ill and unstable, and transport to radiology may not always be feasible.[92]

RESPIRATORY SUPPORT

There is a lack of universal consensus on strategies of providing mechanical ventilation support to patients receiving ECLS. Regardless of the approach, the general idea is to provide respiratory support while minimizing the risk of ventilator-induced lung injury. The goals of respiratory support vary depending on the reason for ECMO, primarily cardiac or primarily respiratory.

A patient requiring ECMO for a primarily cardiac reason is not likely to have significant pulmonary issues, in which case the ventilator strategy is to maintain lung function as near to normal as possible. In a cardiac patient who has significant pre-ECMO pulmonary edema from heart failure, higher levels of positive end-expiratory pressure (PEEP) may be applied until the heart is fully supported and the edema clears.[93]

In patients with a primarily respiratory indication for ECMO, the approach is to achieve what is commonly referred to as "lung rest." In these patients, the pre-ECMO scenario likely would have necessitated the use of high mean airway pressures and advanced modes that would be near injurious—hence the need for ECMO. Once ECMO is established, the ventilator is adjusted to achieve a strictly lung-protective approach.[94] In a large metaanalysis of adults with ARDS receiving ECMO for hypoxemic respiratory failure, ΔP (inspiratory plateau pressure minus PEEP level) was the only ventilator parameter that was independently associated with in-hospital mortality.[95] It is important to note that there may be differences in the pathophysiology, progression, severity of illness, and comorbidities between children and adults with ARDS.[96] Thus larger adult studies may be useful to extrapolate from, but prospective studies in children are still needed to elucidate optimal settings. An example of "resting ventilator settings" would be PCV-SIMV 12 to 15 breaths per minute; positive inspiratory pressure (PIP) 20 to 25 cm H_2O; PEEP 6 to 10 cm H_2O with an Fio_2 of 0.40. Alternatively, a patient requiring ECMO for a primary air leak is maintained on very low ventilator settings to promote complete healing of the leak, and for the most recalcitrant air leaks, only PEEP may be used. Other respiratory support includes routine artificial airway care.

In VA support, the ventilator Fio_2 is usually maintained at 0.40 to ensure that the coronary arteries receive oxygenated blood, because reinfused blood preferentially streams to the descending aorta, whereas coronary perfusion is predominantly from the ascending limb. Therefore, blood returning to the left atrium will have a higher Pao_2 with the ventilator set to 0.40 as opposed to 0.21.

FLUID AND NUTRITION

Maintaining a neutral fluid balance is challenging on ECMO, because patients generally receive liberal amounts of fluid for hemodynamic support and resuscitation preceding ECMO initiation. Once ECMO has been established, patients require periodic replacement of blood components and supplemental fluid associated with medications and nutrition. In patients with essentially normal renal function, a neutral fluid balance can typically be achieved with supplementary diuretics. Unfortunately, many patients receiving ECMO have other organ dysfunction that may be attributed to LCOS, a reduction of peripheral perfusion to the kidneys, and severe hypoxemia preceding ECMO support. Additionally, the systemic inflammatory response after the initiation of ECMO may further exacerbate the development of multiple system organ failure.[97]

Preserving renal function is an important goal in the management of patients receiving ECMO; however, a subset of these patients may develop acute kidney injury. If renal insufficiency persists despite diuretic therapy, **hemofiltration** or renal replacement therapy can be integrated into the ECMO circuit to facilitate fluid removal. In addition, the need for renal replacement therapy has been associated with higher mortality and complicates liberation from ECMO.[98]

It is recognized that neonates are born with few nutritional reserves, and for those who require ECMO, it is particularly challenging to achieve optimal weight gain because of their underlying illness and fluid intolerance. The optimal route and timing for the delivery of nutrition in infants and children receiving ECMO are not well established. Enteral nutrition (EN) is the preferred method of calorie, protein, and micronutrient delivery but may be avoided because of concerns that gastric motility is impaired by vasopressors, sedatives, and paralytics. Several small retrospective studies have documented the safety of EN in neonates and children. Current neonatal guidelines recommend initiating parenteral nutrition in the setting of clinical lability and transitioning to EN when stability has been

Box 19-3 General Clinical Management Guidelines

ANTICOAGULATION WITH CONTINUOUS HEPARIN INFUSION
- Ensure safe and therapeutic dose
  - Activated clotting time 180 to 220 seconds
  - Antifactor Xa activity 0.3 to 0.7
  - Antithrombin III more than 50%

HEMODYNAMIC MONITORING
- Heart rate
- Blood pressure
- Filling pressures
- Temperature
- Spo_2

ORGAN PERFUSION
- Renal function
- Liver function tests

LABORATORY TESTS
- Gas exchange
  - Arterial blood gases
  - Lactic acid
  - Hematologic

NEUROLOGIC ASSESSMENTS
- Pupillary reflexes
- Pain and comfort
- Imaging

RESPIRATORY SUPPORT
- Lung-protective ventilation
- Airway clearance

FLUID AND NUTRITION
- Balance intake and output
- Assess gastric motility

achieved.[99] There is a paucity of data describing the optimal nutritional requirements for pediatric ECMO patients. Moreover, underweight status has been reported as an independent predictor for in-hospital mortality in these patients, suggesting the need for prospective studies to elaborate further on the metabolic status of children receiving ECMO.[100] See Box 19-3 for an overview of general clinical management.

LIBERATION FROM EXTRACORPOREAL MEMBRANE OXYGENATION

Once ECMO support is established and the patient is stable, much of the care, ongoing assessments, and procedures are routine and driven by standardized prescriber orders and treatment algorithms. As the patient's condition improves, the focus is directed toward assessing the patient's ability to be separated from ECMO support. There are two approaches, weaning and periodic testing, and these fundamental approaches apply to both cardiac and respiratory applications.

With respect to VA ECMO, weaning is considered to be the gradual reduction of ECMO flow rates with concomitant gradual increases in ventilator support. This approach is amenable to the respiratory patient and theoretically parallels the improvement in lung function. Once ECMO flow rates are reduced to around 20 to 30 mL/kg, ECMO support is considered minimal. At this point, if reasonable ventilator settings result in adequate gas exchange, the patient is isolated from the ECMO circuit. Additionally, if the patient is on VV ECMO, the sweep gas can be disconnected from the membrane to assess respiratory function without reducing to minimal ECMO flows.

An alternative approach is to maintain ECMO support and lung rest until evidence exists that the patient may be able to be supported without ECMO. In the patient with respiratory failure, this can be evaluated by serial lung compliance checks, chest radiograph appearance, and the need to add more carbon dioxide into the sweep gas as more native carbon dioxide removal has occurred. The next step is to increase the ventilator settings to clinically safe and acceptable levels and then to perform a trial separation from ECMO. During the separation, serial blood gases are obtained to assess gas exchange on the chosen ventilator settings. A set of decannulation criteria are established, and if the patient meets these requirements, ECMO is discontinued.

Each approach has its merits, and neither has been shown to have any significant advantages over the other. Weaning gradually returns the work of the lungs, whereas the periodic test imposes more work in a shorter period. During weaning, there may be less time spent at true lung rest settings, and the ECMO circuit is at lower flows for a longer duration, which may lead to more stagnation and clotting.

In cardiac patients, weaning is considered when signs of improved heart function become apparent or pathologies such as shunt obstruction or residual defect have been corrected.[101] ECMO blood flow is reduced in increments to condition the heart and allow it to gradually resume native cardiac output. Quite often, an echocardiogram is used to assess ventricular function while ECMO flows are reduced. Once ventricular function, hemodynamic parameters, and pulmonary mechanics are within acceptable limits, the ECMO circuit is clamped off with the cannulas in place, effectively separating the patient from the circuit. To prevent stagnation of blood, ECMO flows are maintained using the bridge, and the cannulas are flushed periodically to minimize thrombus formation. If the patient's hemodynamic profile and gas exchange are acceptable over a finite period (e.g., 1-2 hours), then decannulation is considered.

The goal of assessing a patient's readiness to be liberated from ECMO is to verify that the ventilator support or hemodynamic support needed to keep the patient stable without ECMO is not too extreme. For instance, if high mean airway pressures are required to

achieve desired clinical targets in a patient with respiratory failure, the underlying condition may not have fully reversed and ECMO should be continued. Similarly, if high doses of vasoactive agents are required to maintain the blood pressure of a patient with cardiac failure, the heart may not be ready to assume most of the work.

Although a subsequent ECMO course is possible, it is technically challenging, has added risk, and is associated with poor survival outcomes, especially in the presence of CHD or renal failure.[102, 103] Therefore, the parameters for weaning and trialing off ECMO need to provide the clinician with information that supports the decision to discontinue ECMO without added morbidity. Once decannulation is indicated, it often occurs at the bedside, and to a lesser degree the operating room.

COMPLICATIONS

Complications associated with ECMO are generally related to equipment and technical issues or are more physiologic in nature and can be attributed to the patient's blood being exposed to the foreign surface of the ECMO circuit. There is a balance of achieving anticoagulation to abate thrombus formation and maintaining circuit integrity while minimizing the risks of bleeding. Moreover, this equilibrium must be maintained while the underlying reason for ECMO use is reversed, thus longer runs may be subject to more complications.

TECHNICAL

One of the duties of an ECMO specialist is to monitor the functions of the ECMO system and use troubleshooting procedures to address circuit malfunctions.[104] One important aspect is to assess the patient's ability to remain stable without ECMO support should the patient need to be isolated so that a repair or circuit change can be executed. Few ECMO circuit problems arise that require the patient to be acutely removed from support, with the rare exception of a sudden, unplanned decannulation, a tubing or component rupture, or a witnessed air embolism. Most circuit interventions can be executed in a logical and methodical manner and with minimal interruption in support. Troubleshooting procedures are developed for replacement of the entire circuit or components such as the roller pump tubing, membrane oxygenators, connectors, and hemofilters.[105]

The durable components of an ECMO system, such as the pump, water bath, and adjunct monitors, are subject to mechanical failure and may need to be replaced, and standby equipment is maintained as a precaution. The ECMO pump typically has a battery backup in the event of a power failure. Manual cranking devices are also available and can substitute for the mechanical action of the pump if a sudden failure occurs and battery backup malfunctions. The water pump can cease to pump water and cause the patient to become hypothermic, which would be remedied by replacing the water pump. Other monitoring devices are not as critical and will not cause potential patient harm if they malfunction.

PHYSIOLOGIC

The most concerning patient complication that can occur, particularly in newborns, is an intracranial hemorrhage (ICH). The use of ECMO in newborns has greater risks because of anticoagulation requirements and cerebral blood flow changes associated with ligation of the right internal jugular vein and the right common carotid artery. As previously mentioned, during the ECMO course, newborns receive serial head ultrasounds to identify the presence of ICH and to gauge the progression. A slightly premature newborn who experiences periods of hypoxemia and acidosis is even more susceptible. Strategies to minimize the risk of an ICH include continuous blood pressure monitoring, avoidance of hypertensive periods, and strict anticoagulation parameters.

In the early ECMO era, infants born at less than 35 weeks of gestation seemed to have a higher incidence of ICH, which led to the recommendation that ECMO be limited to infants born at 36 weeks of gestation or later. To address this concern and be able to offer ECMO to more neonates, Wilson and colleagues investigated the use of aminocaproic acid, an antifibrinolytic drug that prevents the degradation of thrombus formation.[31] The use of this medication greatly reduced the incidence of ICH, allowed the use of ECMO in infants born before 36 weeks of gestation, and decreased the incidence of postoperative bleeding in patients with CDH. One drawback to the use of aminocaproic acid is that it did result in increased thrombus formation in the ECMO circuit, which required more circuit interventions.

Bleeding is the predominant complication associated with ECMO. In addition to ICH, bleeding can occur at cannula sites; at surgical incisions; and at oropharyngeal, pleural, or any other intravenous or access point in the patient. Bleeding usually can be controlled by closely monitoring coagulation studies, maintaining strict anticoagulation parameters, and replacing deficient blood components such as: platelets, plasma, and cryoprecipitate.

OUTCOMES

Surviving the ECMO course without added morbidity and surviving to hospital discharge without any disability are the main objectives of ECMO. When considering survival as an outcome in neonates and pediatric patients, it is important to understand that many of these patients have failed traditional therapies and would have died without ECMO. In a systematic review by Mugford et al. that compared ECMO to

conventional therapy for neonatal respiratory failure, survival to discharge with ECMO was 77% versus 44%.[12] This equates to the prevention of one death for every three infants supported with ECMO.

As previously mentioned, the application of pediatric ECMO has increased exponentially, and this group has demonstrated more heterogeneity in age, diagnosis, and presence of comorbidities than the neonatal group. In a 15-year retrospective review of the ELSO registry, Zabrocki et al. found that predictors of pediatric respiratory failure mortality included increased age, renal or liver failure, immunodeficiency, pertussis, and PARDs secondary to sepsis. Patients requiring ECMO for status asthmaticus, aspiration pneumonia, or respiratory syncytial virus had significantly higher rates of survival: 83%, 71%, and 70%, respectively.[106] Although it is a difficult decision to withhold ECMO based solely upon diagnosis, the potential long-term implications in terms of functionality, development, financial burden, and quality of life should also be taken into consideration and vary considerably among reasons for ECMO. Survival to discharge outcomes are displayed in Table 19-2.

Aside from the initial reason for ECMO, there are a multitude of other factors that contribute to positive patient outcomes. ECMO centers with a higher annual volume of cases have been associated with both lower cost and improved mortality for children receiving ECMO.[107] This reduction of mortality has been attributed to a better organizational structure, multidisciplinary provider experience, and ECMO protocols and processes. Additionally, higher-volume centers may facilitate further development in teaching, ECMO management, and overall efficiency.

Since the inception of ECMO more than 40 years ago, technologic improvements and a better understanding of patient management have allowed for the current widespread application in infants, children, and adults. The ELSO registry describes an overall survival to discharge rate of 56%, out of 86,287 cases over the past 26 years.[14] These figures represent a significant number of patients who would not have survived in the absence of this therapy.

Table 19-2 Overall Summary of ECMO Use in Neonates and Pediatric Patients: Extracorporeal Life Support Organization, ECLS Registry Report[14]

SURVIVAL AFTER ECMO		
INDICATION FOR ECMO	**NUMBER OF PATIENTS**	**SURVIVAL TO HOSPITAL DISCHARGE**
Neonatal		
Respiratory	29,942	21,948 (73%)
Cardiac	7,169	2,938 (40%)
ECPR	1,532	1,028 (40%)
Pediatric		
Respiratory	8,070	4,632 (57%)
Cardiac	9,362	4,758 (50%)
ECPR	3,399	1,414 (41%)

ECLS, Extracorporeal Life Support Organization; *ECMO*, extracorporeal membrane oxygenation; *ECPR*, extracorporeal cardiopulmonary resuscitation.

Clinical Highlight

BACKGROUND

A 35-week, 4.6-kg previously healthy twin girl, now 3 months old, was admitted to the intensive care unit after being intubated at a different hospital. She had an elevated white blood cell count from 25 to 90 (thousand) in the past 24 hours and tested positive for pertussis. On arrival, she was receiving ventilation on the following conventional settings: PIP 46, PEEP 10, heart rate 36 beats/minute, Fio_2 1. On these settings, her exhaled tidal volume was 5 mL/kg, with a venous pH of 7.10 and Pco_2 of 98. Her chest radiograph demonstrated mild hyperinflation on the right and evolving multifocal infiltrates on the left. Three hours later, she was transitioned to High-frequency oscillatory ventilation (HFOV) Δ 73 f 12 Mean Airway Pressure ($\overline{P}_{aw}$) 30 cm H_2O Fio_2 1. The arterial blood gas on these settings was pH 7.19, Pco_2 54, Pao_2 44, bicarbonate 20 mmol/L. With the addition of iNO at 20 parts per million, the OI decreased from 68 to 56; however, this improvement in oxygenation was not sustained. An echocardiogram was obtained and revealed neutral septal position with a dilated and mildly dysfunctional right ventricular function. Hemodynamically, she exhibited tachycardia in the 200s and had adequate blood pressure on 5 μg/kg/minute of dopamine. Given her progressive clinical deterioration, general surgery was called to cannulate to VV ECMO. A VVDL was placed in the right internal jugular vein, and ECMO flow was established at 100 mL/kg. The ventilator settings were reduced to PIP 20, PEEP 10, rate 10 beats/minute, and Fio_2 0.4. After 38 hours, her hemodynamic status declined, necessitating conversion to VA ECMO. Her course was complicated by a grade 1 infarct of the parietooccipital region and multiple pneumothoraces. After 24 days, she separated from ECMO on PC-SIMV: Pressure-Controlled Synchronize Intermittent Ventilation, PIP: Peak Inspiratory Pressure 30, PEEP: Positive End-Expiratory Pressure 6, heart rate 30, Fio_2: fraction of inspired oxygen .6 5-6 mL/kg.

DISCUSSION

This is an example of ECMO use in an infant with severe respiratory failure secondary to pertussis who failed advanced therapies, including HFOV and iNO. The patient was initially supported with VV ECMO until her hemodynamic status warranted conversion to VA ECMO.

WHY WAS ECMO USED IN THIS PATIENT, AND WHAT WERE THE CLINICAL GOALS?

The OI suggested that the severity of illness was high and could have potentially resulted in death. ECMO was appropriately applied and allowed lung-protective ventilation strategies to be used. The diagnosis of pertussis alone has been associated with increased mortality, and the odds of survival are further reduced in the setting of recurrent pneumothorax and prolonged ECMO. On two occasions, ventilator support was reduced to a PEEP of 15 cm H_2O for 5 to 7 days to allow the lung to heal.

Clinical Highlight

BACKGROUND

A 3.5-kg male infant diagnosed with hypoplastic left heart syndrome (HLHS) was transferred to the cardiac ICU after placement of a Blalock-Taussig shunt. The respiratory therapist noted a large gradient between the Pco_2 and $ETCO_2$. Eight hours after surgery, progressive hypotension, persistent metabolic acidosis, and hypoxia were noted. An arterial blood gas revealed a pH of 7.21, Pco_2 of 41, Pao_2 of 31, bicarbonate level of 18 mmol/L, and lactate level of 22 mmol/L. The $ETCO_2$ now displayed a tension of 10 mm Hg, and the patient was severely hypotensive, prompting the initiation of CPR. After a couple of minutes, the medical team was unable maintain a satisfactory blood pressure, so the decision for ECPR was made. VA ECMO using a transthoracic approach was selected because the patient had very poor cardiac function and the sternum was freshly opened, providing immediate access. A venous cannula was surgically inserted into the patient's right atrium and an arterial cannula into the aorta. A crystalloid-primed ECMO circuit was connected to the coordinating cannulas, and the blood flow rate was titrated to clinically acceptable arterial blood pressures with sweep gases adjusted to achieve acceptable blood gases. This patient was also actively cooled to 34°C by the heat exchanger for neuroprotective purposes. Anticoagulation was initiated once hemodynamics had stabilized. Over the course of the next several hours, the patient's cardiac function improved. An echocardiography study was obtained that demonstrated moderate dysfunction. Anticoagulation was maintained, hemostasis achieved, and ECMO circuit integrity and function closely monitored. After 2 days, the patient was successfully separated from ECMO and the sternum was surgically reconciled. He continued to make forward progress and was extubated the following day to a nasal cannula.

DISCUSSION

This is a typical example of ECPR in a neonate with HLHS after stage 1 repair. The patient was supported with ECMO while heart recovery occurred and was successfully weaned from ECMO without any associated sequelae.

WHY WAS ECMO USED IN THIS PATIENT, AND WHAT WERE THE CLINICAL GOALS?

The severe hypotension, rise in lactate, and loss of $ETCO_2$ were indicative of shunt thrombosis and diminished pulmonary blood flow. ECMO was promptly and appropriately applied, which allowed time for shunt patency to be restored and improvement in cardiac function while supporting adequate gas exchange and preserving end-organ perfusion.

Key Points

- The ECMO system is a modified form of cardiopulmonary bypass designed for long-term use. It consists of a contiguous loop of tubing with drainage and reinfusion limbs. Blood is mechanically pumped through an artificial lung that augments gas exchange.
- ECMO is used to support newborns, infants, children, and adults with respiratory or cardiac failure who do not respond to conventional treatment.
- There are two modes of ECMO support, venous–venous and venous–arterial. Venous–venous is primarily used to support lung function, whereas venous–arterial supports both heart and lung function.
- Monitoring ECMO entails the usual critical care parameters, such as hemodynamics, laboratory and radiologic studies, and patient comfort; the mechanical aspects of the ECMO system; and anticoagulation.
- ECMO is associated with mechanical and technical complications and patient-related complications such as bleeding.

Assessment Questions

1. Which of the following patients meets the criteria for ECMO?
   - **A.** Male born at 25 weeks of gestation with Respiratory distress syndrome (RDS) receiving continuous positive airway pressure
   - **B.** Full-term male with an OI of 15 requiring HFOV
   - **C.** Female born at 27 weeks with Bronchopulmonary dysplasia requiring (BDP) Conventional mechanical ventilation (CMV)
   - **D.** Full-term female with an Oxygenation Index (OI) of 34 requiring INO: inhaled nitric oxide
2. Which of the following correctly describes the path that a red blood cell travels through an ECMO circuit?
   - **A.** Membrane oxygenator, pump, venous cannula
   - **B.** Arterial cannula, pump, membrane oxygenator
   - **C.** Pump, membrane oxygenator, venous cannula
   - **D.** Venous cannula, pump, membrane oxygenator
3. Which of the following is an advantage of using a VV double-lumen cannula in an infant with persistent pulmonary hypertension (PPHN) of the newborn?
   - **A.** Carotid artery ligation is not needed.
   - **B.** Cardiac function is supported.
   - **C.** Higher ECMO flow rates can be used.
   - **D.** Anticoagulation is easier to achieve.
4. Which of the following best describes the difference between a roller pump and a centrifugal pump?
   - **A.** Centrifugal pumps are gravity dependent.
   - **B.** Roller pumps are nonocclusive.
   - **C.** Centrifugal pumps require additional blood.
   - **D.** Roller pumps operate by compression and displacement.
5. Which of the following best describes the difference between silicone membranes and microporous membranes?
   - **A.** Microporous membranes provide better gas exchange.
   - **B.** Silicone membranes require less priming volume.
   - **C.** Microporous membranes have lower resistance.
   - **D.** Silicone membranes are easier to prime and deair.

6. Which of the following best describes the essential components of an ECMO system?
   - **A.** Roller pump, high-frequency ventilator, membrane oxygenator
   - **B.** Microporous membrane, centrifugal pump, circuit, cannulas
   - **C.** Silicone membrane, circuit, ACT point-of-care device
   - **D.** Svo_2 monitor, centrifugal pump, heparin infusion
7. Which of the following is used to monitor anticoagulation?
   - **A.** Activated clotting time
   - **B.** Hematocrit and hemoglobin levels
   - **C.** Platelet count
   - **D.** Arterial blood gases
8. Which of the following best describes the modes of ECMO support?
   - **A.** VV provides only cardiac support.
   - **B.** VA supports both lung and heart function.
   - **C.** VA is only for patients with cardiac failure.
   - **D.** VV provides better oxygenation.
9. Which of the following is the main objective for using ECMO in a patient with viral pneumonia?
   - **A.** To provide lung-protective ventilation
   - **B.** To use high mean airway pressures
   - **C.** To provide lung-recruitment maneuvers
   - **D.** To improve the $Paco_2$
10. Which of the following is the main goal of ECMO?
    - **A.** To support cardiac function
    - **B.** To support lung function
    - **C.** To provide adequate tissue oxygen delivery
    - **D.** To remove carbon dioxide

REFERENCES

1. Betit P. Extracorporeal membrane oxygenation: quo vadis? *Respir Care*. 2009;54(7):948-957.
2. Gibbon Jr JH. Application of a mechanical heart and lung apparatus to cardiac surgery. *Minn Med*. 1954;37(3):171-185; passim.
3. Bartlett RH. John H Gibbon Jr Lecture. Extracorporeal life support: Gibbon fulfilled. *J Am Coll Surg*. 2014;218(3): 317-327.
4. Kolobow T, Bowman RL. Construction and evaluation of an alveolar membrane artificial heart-lung. *Trans Am Soc Artif Intern Organs*. 1963;9:238-243.
5. Hill JD, O'Brien TG, Murray JJ, et al. Prolonged extracorporeal oxygenation for acute post-traumatic respiratory failure (shock-lung syndrome). Use of the Bramson membrane lung. *N Engl J Med*. 1972;286(12):629-634.
6. Zapol WM, Snider MT, Hill JD, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. *JAMA*. 1979;242(20):2193-2196.
7. Bartlett RH, Gazzaniga AB, Jefferies MR, Huxtable RF, Haiduc NJ, Fong SW. Extracorporeal membrane oxygenation (ECMO) cardiopulmonary support in infancy. *Trans Am Soc Artif Intern Organs*. 1976;22:80-93.
8. Bartlett RH, Andrews AF, Toomasian JM, Haiduc NJ, Gazzaniga AB. Extracorporeal membrane oxygenation for newborn respiratory failure: forty-five cases. *Surgery*. 1982; 92(2):425-433.
9. Bartlett RH, Roloff DW, Cornell RG, Andrews AF, Dillon PW, Zwischenberger JB. Extracorporeal circulation in neonatal respiratory failure: a prospective randomized study. *Pediatrics*. 1985;76(4):479-487.
10. O'Rourke PP, Crone RK, Vacanti JP, et al. Extracorporeal membrane oxygenation and conventional medical therapy in neonates with persistent pulmonary hypertension of the newborn: a prospective randomized study. *Pediatrics*. 1989; 84(6):957-963.
11. UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation. UK Collaborative ECMO Trial Group. *Lancet*. 1996;348(9020):75-82.
12. Mugford M, Elbourne D, Field D. Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants. *Cochrane Database Syst Rev*. 2008(3):CD001340.
13. Shanley CJ, Hirschl RB, Schumacher RE, et al. Extracorporeal life support for neonatal respiratory failure. A 20-year experience. *Ann Surg*. 1994;220(3):269-280; discussion 281-282.
14. Extracorporeal Life Support Organization. *International Registry*. Available at: http://www.elso.org. Accessed April 2017.
15. Henderson-Smart DJ, De Paoli AG, Clark RH, Bhuta T. High frequency oscillatory ventilation versus conventional ventilation for infants with severe pulmonary dysfunction born at or near term. *Cochrane Database Syst Rev*. 2009(3):CD002974.
16. Konduri GG, Vohr B, Robertson C, et al. Early inhaled nitric oxide therapy for term and near-term newborn infants with hypoxic respiratory failure: neurodevelopmental follow-up. *J Pediatr*. 2007;150(3):235-240, 240. e1.
17. Kinsella JP, Abman SH. High-frequency oscillatory ventilation augments the response to inhaled nitric oxide in persistent pulmonary hypertension of the newborn: Nitric Oxide Study Group. *Chest*. 1998;114(1 suppl):S100.
18. Farrow KN, Fliman P, Steinhorn RH. The diseases treated with ECMO: focus on PPHN. *Semin Perinatol*. 2005;29(1): 8-14.
19. Keijzer R, Puri P. Congenital diaphragmatic hernia. *Semin Pediatr Surg*. 2010;19(3):180-185.
20. Betit P, Craig N. Extracorporeal membrane oxygenation for neonatal respiratory failure. *Respir Care*. 2009;54(9): 1244-1251.
21. Stevens TP, van Wijngaarden E, Ackerman KG, Lally PA, Lally KP, Congenital Diaphragmatic Hernia Study Group. Timing of delivery and survival rates for infants with prenatal diagnoses of congenital diaphragmatic hernia. *Pediatrics*. 2009;123(2):494-502.
22. Harting MT, Lally KP. The Congenital Diaphragmatic Hernia Study Group registry update. *Semin Fetal Neonatal Med*. 2014; 19(6):370-375.

23. Haile DT, Schears GJ. Optimal time for initiating extracorporeal membrane oxygenation. *Semin Cardiothorac Vasc Anesth*. 2009;13(3):146-153.
24. Ortega M, Ramos AD, Platzker AC, Atkinson JB, Bowman CM. Early prediction of ultimate outcome in newborn infants with severe respiratory failure. *J Pediatr*. 1988;113(4): 744-747.
25. Bayrakci B, Josephson C, Fackler J. Oxygenation index for extracorporeal membrane oxygenation: is there predictive significance? *J Artif Organs*. 2007;10(1):6-9.
26. Hui TT, Danielson PD, Anderson KD, Stein JE. The impact of changing neonatal respiratory management on extracorporeal membrane oxygenation utilization. *J Pediatr Surg*. 2002;37(5):703-705.
27. Fliman PJ, deRegnier RA, Kinsella JP, Reynolds M, Rankin LL, Steinhorn RH. Neonatal extracorporeal life support: impact of new therapies on survival. *J Pediatr*. 2006;148(5): 595-599.
28. Tiruvoipati R, Pandya H, Manktelow B, et al. Referral pattern of neonates with severe respiratory failure for extracorporeal membrane oxygenation. *Arch Dis Child Fetal Neonatal Ed*. 2008;93(2):F104-107.
29. Kinsella JP, Abman SH. Inhaled nitric oxide and high frequency oscillatory ventilation in persistent pulmonary hypertension of the newborn. *Eur J Pediatr*. 1998;157(suppl 1): S28-S30.
30. Chapman RL, Peterec SM, Bizzarro MJ, Mercurio MR. Patient selection for neonatal extracorporeal membrane oxygenation: beyond severity of illness. *J Perinatol*. 2009;29(9):606-611.
31. Wilson JM, Bower LK, Fackler JC, Beals DA, Bergus BO, Kevy SV. Aminocaproic acid decreases the incidence of intracranial hemorrhage and other hemorrhagic complications of ECMO. *J Pediatr Surg*. 1993;28(4):536-540; discussion 540-541.
32. Costello JM, Cooper DS, Jacobs JP, et al. Intermediate-term outcomes after paediatric cardiac extracorporeal membrane oxygenation—what is known (and unknown). *Cardiol Young*. 2011;21(suppl 2):118-123.
33. Paden ML, Rycus PT, Thiagarajan RR, ELSO Registry. Update and outcomes in extracorporeal life support. *Semin Perinatol*. 2014;38(2):65-70.
34. Brogan TV, Zabrocki L, Thiagarajan RR, Rycus PT, Bratton SL. Prolonged extracorporeal membrane oxygenation for children with respiratory failure. *Pediatr Crit Care Med*. 2012;13(4):e249-e254.
35. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet*. 2009;374(9698):1351-1363.
36. Dalton HJ, Macrae DJ, Pediatric Acute Lung Injury Consensus Conference Group. Extracorporeal support in children with pediatric acute respiratory distress syndrome: proceedings from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med*. 2015;16(5 suppl 1): S111-S117.
37. Butt W, MacLaren G. Extracorporeal membrane oxygenation 2016: an update. *F1000Res*. 2016;5:2-6
38. Green TP, Timmons OD, Fackler JC, Moler FW, Thompson AE, Sweeney MF. The impact of extracorporeal membrane oxygenation on survival in pediatric patients with acute respiratory failure. Pediatric Critical Care Study Group. *Crit Care Med*. 1996;24(2):323-329.
39. Mehta NM, Turner D, Walsh B, et al. Factors associated with survival in pediatric extracorporeal membrane oxygenation—a single-center experience. *J Pediatr Surg*. 2010;45(10): 1995-2003.
40. Flori HR, Glidden DV, Rutherford GW, Matthay MA. Pediatric acute lung injury: prospective evaluation of risk factors associated with mortality. *Am J Respir Crit Care Med*. 2005; 171(9):995-1001.
41. Di Nardo M, MacLaren G, Marano M, Cecchetti C, Bernaschi P, Amodeo A. ECLS in pediatric cardiac patients. *Front Pediatr*. 2016;4:109.
42. Cooper DS, Jacobs JP, Moore L, et al. Cardiac extracorporeal life support: state of the art in 2007. *Cardiol Young*. 2007; 17(suppl 2):104-115.
43. Bautista-Hernandez V, Thiagarajan RR, Fynn-Thompson F, et al. Preoperative extracorporeal membrane oxygenation as a bridge to cardiac surgery in children with congenital heart disease. *Ann Thorac Surg*. 2009;88(4): 1306-1311.
44. Thiagarajan RR. Extracorporeal membrane oxygenation for cardiac indications in children. *Pediatr Crit Care Med*. 2016; 17(8 suppl 1):S155-S159.
45. Chandler HK, Kirsch R. Management of the low cardiac output syndrome following surgery for congenital heart disease. *Curr Cardiol Rev*. 2016;12(2):107-111.
46. Mascio CE, Austin EH, Jacobs JP, et al. Perioperative mechanical circulatory support in children: an analysis of the Society of Thoracic Surgeons Congenital Heart Surgery Database. *J Thorac Cardiovasc Surg*. 2014;147(2):658-664; discussion 664-665.
47. Burke CR, McMullan DM. Extracorporeal life support for pediatric heart failure. *Front Pediatr*. 2016;4:115.
48. de Caen AR, Berg MD, Chameides L, et al. Part 12: Pediatric Advanced Life Support: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care (Reprint). *Pediatrics*. 2015; 136(suppl 2):S176-S195.
49. Kane DA, Thiagarajan RR, Wypij D, et al. Rapid-response extracorporeal membrane oxygenation to support cardiopulmonary resuscitation in children with cardiac disease. *Circulation*. 2010;122(11 suppl):S241-S248.
50. Raymond TT, Cunnyngham CB, Thompson MT, et al. Outcomes among neonates, infants, and children after extracorporeal cardiopulmonary resuscitation for refractory inhospital pediatric cardiac arrest: a report from the National Registry of Cardiopulmonary Resuscitation. *Pediatr Crit Care Med*. 2010;11(3):362-371.
51. Ryerson LM, Guerra GG, Joffe AR, et al. Survival and neurocognitive outcomes after cardiac extracorporeal life support in children less than 5 years of age: a ten-year cohort. *Circ Heart Fail*. 2015;8(2):312-321.
52. Allan CK, Thiagarajan RR, Beke D, et al. Simulation-based training delivered directly to the pediatric cardiac intensive care unit engenders preparedness, comfort, and decreased anxiety among multidisciplinary resuscitation teams. *J Thorac Cardiovasc Surg*. 2010;140(3):646-652.
53. Gehrmann LP, Hafner JW, Montgomery DL, Buckley KW, Fortuna RS. Pediatric extracorporeal membrane oxygenation: an introduction for emergency medicine physicians. *J Emerg Med*. 2015;49(4):552-560.
54. Dalton HJ. Extracorporeal life support: moving at the speed of light. *Respir Care*. 2011;56(9):1445-1453; discuiion 1453-1456.
55. Rais-Bahrami K, Van Meurs KP. Venoarterial versus venovenous ECMO for neonatal respiratory failure. *Semin Perinatol*. 2014;38(2):71-77.
56. Reeb J, Olland A, Renaud S, et al. Vascular access for extracorporeal life support: tips and tricks. *J Thorac Dis*. 2016; 8(suppl 4):S353-S363.
57. Sidebotham D, Allen SJ, McGeorge A, Ibbott N, Willcox T. Venovenous extracorporeal membrane oxygenation in adults: practical aspects of circuits, cannulae, and procedures. *J Cardiothorac Vasc Anesth*. 2012;26(5):893-909.
58. Pettignano R, Fortenberry JD, Heard ML, et al. Primary use of the venovenous approach for extracorporeal membrane

oxygenation in pediatric acute respiratory failure. *Pediatr Crit Care Med*. 2003;4(3):291-298.
59. Bamat NA, Tharakan SJ, Connelly JT, et al. Venoarterial extracorporeal life support for neonatal respiratory failure: indications and impact on mortality. *ASAIO J*. 2016; 63(4):490-495.
60. Mathis CA, Powell AE, Holloway RD, Shah S, Goldberg SP, Boston US. Alternative cannulation strategy for pediatric ECMO. *J Card Surg*. 2011;26(4):444-445.
61. Otsu T, Merz SI, Hultquist KA, et al. Laboratory evaluation of a double lumen catheter for venovenous neonatal ECMO. *ASAIO Trans*. 1989;35(3):647-650.
62. Javidfar J, Brodie D, Wang D, et al. Use of bicaval dual-lumen catheter for adult venovenous extracorporeal membrane oxygenation. *Ann Thorac Surg*. 2011;91(6):1763-1768; discussion 1769.
63. de Bucourt M, Teichgräber UK. Image guided placement of extracorporeal life support through bi-caval dual lumen venovenous membrane oxygenation in an interventional radiology setting—initial experience. *J Vasc Access*. 2012;13(2): 221-225.
64. Raman L, Dalton HJ. Year in Review 2015: extracorporeal membrane oxygenation. *Respir Care*. 2016;61(7):986-991.
65. Abrams D, Javidfar J, Farrand E, et al. Early mobilization of patients receiving extracorporeal membrane oxygenation: a retrospective cohort study. *Crit Care*. 2014;18(1):R38.
66. Skinner SC, Hirschl RB, Bartlett RH. Extracorporeal life support. *Semin Pediatr Surg*. 2006;15(4):242-250.
67. Palanzo D, Qiu F, Baer L, Clark JB, Myers JL, Undar A. Evolution of the extracorporeal life support circuitry. *Artif Organs*. 2010;34(11):869-873.
68. Maslach-Hubbard A, Bratton SL. Extracorporeal membrane oxygenation for pediatric respiratory failure: history, development and current status. *World J Crit Care Med*. 2013;2(4): 29-39.
69. MacLaren G, Combes A, Bartlett RH. Contemporary extracorporeal membrane oxygenation for adult respiratory failure: life support in the new era. *Intensive Care Med*. 2012;38(2):210-220.
70. Khoshbin E, Westrope C, Pooboni S, et al. Performance of polymethyl pentene oxygenators for neonatal extracorporeal membrane oxygenation: a comparison with silicone membrane oxygenators. *Perfusion*. 2005;20(3):129-134.
71. Talor J, Yee S, Rider A, Kunselman AR, Guan Y, Undar A. Comparison of perfusion quality in hollow-fiber membrane oxygenators for neonatal extracorporeal life support. *Artif Organs*. 2010;34(4):E110-E116.
72. Undar A, Wang S, Palanzo DA. Impact of polymethylpentene oxygenators on outcomes of all extracorporeal life support patients in the United States. *Artif Organs*. 2013; 37(12):1080-1081.
73. Lehle K, Philipp A, Hiller KA, et al. Efficiency of gas transfer in venovenous extracorporeal membrane oxygenation: analysis of 317 cases with four different ECMO systems. *Intensive Care Med*. 2014;40(12):1870-1877.
74. Jacobs S, De Somer F, Vandenplas G, Van Belleghem Y, Taeymans Y, Van Nooten G. Active or passive bio-coating: does it matters in extracorporeal circulation? *Perfusion*. 2011;26(6): 496-502.
75. Van Meurs KP, Mikesell GT, Seale WR, Short BL, Rivera O. Maximum blood flow rates for arterial cannulae used in neonatal ECMO. *ASAIO Trans*. 1990;36(3):M679-M681.
76. Selewski DT, Cornell TT, Blatt NB, et al. Fluid overload and fluid removal in pediatric patients on extracorporeal membrane oxygenation requiring continuous renal replacement therapy. *Crit Care Med*. 2012;40(9):2694-2699.
77. Bhatt N, Osborn E. Extracorporeal gas exchange: the expanding role of extracorporeal support in respiratory failure. *Clin Chest Med*. 2016;37(4):765-780.
78. Hoganson DM, Gazit AZ, Boston US, et al. Paracorporeal lung assist devices as a bridge to recovery or lung transplantation in neonates and young children. *J Thorac Cardiovasc Surg*. 2014;147(1):420-426.
79. Lorts A, Zafar F, Adachi I, Morales DL. Mechanical assist devices in neonates and infants. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu*. 2014;17(1):91-95.
80. Dipchand AI, Mahle WT, Tresler M, et al. Extracorporeal membrane oxygenation as a bridge to pediatric heart transplantation: effect on post-listing and post-transplantation outcomes. *Circ Heart Fail*. 2015;8(5):960-969.
81. Kirklin JK, Bennett Pearce F, Dabal RJ, Carlo WF. Mechanical circulatory support: strategies and outcomes in pediatric congenital heart disease. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu*. 2014;17(1):62-68.
82. Saini A, Spinella PC. Management of anticoagulation and hemostasis for pediatric extracorporeal membrane oxygenation. *Clin Lab Med*. 2014;34(3):655-673.
83. Oliver WC. Anticoagulation and coagulation management for ECMO. *Semin Cardiothorac Vasc Anesth*. 2009;13(3): 154-175.
84. Stocker CF, Horton SB. Anticoagulation strategies and difficulties in neonatal and paediatric extracorporeal membrane oxygenation (ECMO). *Perfusion*. 2016;31(2):95-102.
85. Bembea MM, Schwartz JM, Shah N, et al. Anticoagulation monitoring during pediatric extracorporeal membrane oxygenation. *ASAIO J*. 2013;59(1):63-68.
86. Protti A, L'Acqua C, Panigada M. The delicate balance between pro-(risk of thrombosis) and anti-(risk of bleeding) coagulation during extracorporeal membrane oxygenation. *Ann Transl Med*. 2016;4(7):139.
87. Kotani Y, Chetan D, Rodrigues W, et al. Left atrial decompression during venoarterial extracorporeal membrane oxygenation for left ventricular failure in children: current strategy and clinical outcomes. *Artif Organs*. 2013;37(1): 29-36.
88. Lim HS, Howell N, Ranasinghe A. Extracorporeal life support: physiological concepts and clinical outcomes. *J Card Fail*. 2017;23(2):181-196.
89. Meyer AD, Wiles AA, Rivera O, et al. Hemolytic and thrombocytopathic characteristics of extracorporeal membrane oxygenation systems at simulated flow rate for neonates. *Pediatr Crit Care Med*. 2012;13(4):e255-e261.
90. Field D, Juszczak E, Linsell L, et al. Neonatal ECMO study of temperature (NEST): a randomized controlled trial. *Pediatrics*. 2013;132(5):e1247-e1256.
91. Bembea MM, Felling R, Anton B, Salorio CF, Johnston MV. Neuromonitoring during extracorporeal membrane oxygenation: a systematic review of the literature. *Pediatr Crit Care Med*. 2015;16(6):558-564.
92. LaRovere KL, Brett MS, Tasker RC, Strauss KJ, Burns JP, Pediatric Critical Nervous System P. Head computed tomography scanning during pediatric neurocritical care: diagnostic yield and the utility of portable studies. *Neurocrit Care*. 2012;16(2):251-257.
93. Schmidt M, Pellegrino V, Combes A, Scheinkestel C, Cooper DJ, Hodgson C. Mechanical ventilation during extracorporeal membrane oxygenation. *Crit Care*. 2014;18(1): 203.
94. Gattinoni L, Tonetti T, Quintel M. How best to set the ventilator on extracorporeal membrane lung oxygenation. *Curr Opin Crit Care*. 2017;23(1):66-72.
95. Serpa Neto A, Schmidt M, Azevedo LC, et al. Associations between ventilator settings during extracorporeal membrane oxygenation for refractory hypoxemia and outcome in patients with acute respiratory distress syndrome: a pooled individual patient data analysis: mechanical ventilation during ECMO. *Intensive Care Med*. 2016;42(11): 1672-1684.

96. Khemani RG, Smith LS, Zimmerman JJ, Erickson S, Pediatric Acute Lung Injury Consensus Conference G. Pediatric acute respiratory distress syndrome: definition, incidence, and epidemiology: proceedings from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med*. 2015;16(5 suppl 1):S23-S40.
97. Villa G, Katz N, Ronco C. Extracorporeal membrane oxygenation and the kidney. *Cardiorenal Med*. 2015;6(1):50-60.
98. Antonucci E, Lamanna I, Fagnoul D, Vincent JL, De Backer D, Silvio Taccone F. The impact of renal failure and renal replacement therapy on outcome during extracorporeal membrane oxygenation therapy. *Artif Organs*. 2016;40(8):746-754.
99. Desmarais TJ, Yan Y, Keller MS, Vogel AM. Enteral nutrition in neonatal and pediatric extracorporeal life support: a survey of current practice. *J Pediatr Surg*. 2015;50(1):60-63.
100. Anton-Martin P, Papacostas M, Lee E, Nakonezny PA, Green ML. Underweight status is an independent predictor of in-hospital mortality in pediatric patients on extracorporeal membrane oxygenation. *J Parenter Enteral Nutr*. 2016;42(1):104-111.
101. Schwartz S, Floh AA. Is this heart going to work? *Pediatr Crit Care Med*. 2014;15(9):909-910.
102. Fisher JC, Stolar CJ, Cowles RA. Extracorporeal membrane oxygenation for cardiopulmonary failure in pediatric patients: is a second course justified? *J Surg Res*. 2008;148(1):100-108.
103. Shuhaiber J, Thiagarajan RR, Laussen PC, Fynn-Thompson F, del Nido P, Pigula F. Survival of children requiring repeat extracorporeal membrane oxygenation after congenital heart surgery. *Ann Thorac Surg*. 2011;91(6):1949-1955.
104. Fleming GM, Gurney JG, Donohue JE, Remenapp RT, Annich GM. Mechanical component failures in 28,171 neonatal and pediatric extracorporeal membrane oxygenation courses from 1987 to 2006. *Pediatr Crit Care Med*. 2009;10(4):439-444.
105. Darling E, Searles B. Oxygenator change-out times: the value of a written protocol and simulation exercises. *Perfusion*. 2010;25(3):141-143; discussion 144-145.
106. Zabrocki LA, Brogan TV, Statler KD, Poss WB, Rollins MD, Bratton SL. Extracorporeal membrane oxygenation for pediatric respiratory failure: survival and predictors of mortality. *Crit Care Med*. 2011;39(2):364-370.
107. Faraoni D, Nasr VG, DiNardo JA, Thiagarajan RR. Hospital costs for neonates and children supported with extracorporeal membrane oxygenation. *J Pediatr*. 2016;169:69-75. e61.
108. Butt W, MacLaren G. Extracorporeal membrane oxygenation. *F1000Prime Rep*. 2013;5:55.
109. Meyer A, Strüber M, Fischer S. Advances in extracorporeal ventilation. *Anesthesiol Clin*. 2008;26(2):381-391, viii.

20 Pharmacology

Liza Li, Jessica White

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. Identify pharmacokinetic parameters that differ between pediatric and adult patients.
2. Discuss the place in therapy of β_2-adrenergic agonists in the treatment of asthma, chronic obstructive pulmonary disease (COPD), and exercise-induced bronchospasms.
3. Identify potential adverse events observed with the use of inhaled short-acting β-adrenergic agonists.
4. Explain the place in therapy of inhaled long-acting β_2-adrenergic agonists.
5. Explain administration issues with inhalation of corticosteroids.
6. Discuss the place in therapy of the leukotriene modifiers.
7. Discuss the mechanism of action of the mucolytic agents.
8. Discuss the place in therapy of antiviral and immunomodulatory agents commonly used in the treatment of pediatric viral infections.
9. Discuss the place in therapy of aerosolized antimicrobials used in the treatment of infectious respiratory diseases.

Key Terms

agonist
arachidonic acid
cation
Churg-Strauss syndrome
dysphonia
hirsutism
hypertonic
hypothalamic-pituitary-adrenal (HPA) axis
minimum inhibitory concentration
mucolytic
parenteral
pharmacokinetic
racemic
sympathomimetic
tolerance

This chapter introduces concepts of developmental pharmacology and reviews pharmacologic agents commonly used in pediatric airway diseases. The mechanism of action, side effect profiles, dosage ranges, place in therapy, and specific administration techniques are reviewed where appropriate.

Before the Pediatric Research Equity Act (PREA) and exclusivity provision of the Best Pharmaceuticals for Children Act (BPCA), approximately 20% of drugs approved by the Food and Drug Administration (FDA) were labeled for pediatric use.[1] Since passed into law in 2003, the PREA grants the FDA authority to require pediatric studies of a new drug if the FDA determines the product is likely to be used in a substantial number of pediatric patients. They can also require pediatric studies if the product can potentially provide a meaningful benefit in the pediatric population over existing treatments. On the other hand, the BPCA is a voluntary pediatric exclusivity provision of the FDA Modernization Act of 1997 that has done more to spur pediatric studies than any other regulatory initiative. This provision allows pharmaceutical companies to qualify for an additional 6 months of marketing exclusivity or patent protection if they perform studies in children as requested by the FDA. As a result, there have been significant advances in pediatric research that have provided new information about pediatric clinical pharmacology, drug safety, and effectiveness.

DEVELOPMENTAL PHARMACOLOGY

Advances in pediatric clinical pharmacology stem from the influence of physiologic and **pharmacokinetic** differences between children and adults. Pediatric dosage regimens cannot be simply extrapolated from adult data and corrected for body weight because of significant age-related differences in pharmacokinetic principles specific to children. Human growth is not a linear process, because age-associated changes in body composition and organ function are dynamic and can be discordant during the first decade of life.[2]

Drug absorption, distribution, and metabolism vary greatly in neonatal and pediatric patients. Developmental changes in absorptive surfaces such as the gastrointestinal (GI) tract, skin, and pulmonary tree can affect the absorption rate and bioavailability of a drug. Changes in intraluminal pH in different segments of the GI tract can influence the relative amount of the drug available for absorption. Gastric pH is increased in neonates, infants, and young children and will reach adult pH values by 2 years of age. Gastric motility is the primary determinant for the rate of drug to be dispersed along the small intestine, which is decreased in neonates and reaches adult levels in infants and children.[1-3] After a drug is absorbed, it is distributed to a variety of body compartments depending on its physiochemical properties. In neonates and infants, an increase in the total body water/fat ratio contributes to a higher volume of distribution for hydrophilic drugs (i.e., gentamicin), thus requiring larger weight-based doses to achieve therapeutic concentrations.[2,4,5] Furthermore, delayed maturation of drug-metabolizing enzyme activity may account for the marked toxicity of drugs in the very young. The metabolic enzyme that is involved in the metabolism of more than 50% of medications is called *cytochrome (CYP) 3A4.* Although it accounts for approximately 30% of total hepatic CYP, its activity is very low at birth and will increase to nearly 20% of adult values at 1 month of age and approximately 75% of adult values at 1 year of age.[4-6] Disease states such as cystic fibrosis have also been shown to alter drug absorption and have unique pharmacokinetic characteristics that would warrant different dosing regimens.

β-ADRENERGIC AGONISTS

MECHANISM OF ACTION

Norepinephrine is a potent α and β_1 **agonist** that has relatively little action on $\beta_2$receptors. However, structural changes and additions to the parent structure of norepinephrine result in compounds with a higher affinity for either α or β receptors and a prolonged duration of action. Therefore norepinephrine is the parent compound of all the β_2-agonists because additions and substitutions of molecular entities on the terminal amine group will alter the β-receptor activity.[7]

Activation of β-adrenergic receptor sites on airway smooth muscle results in activation of adenylyl cyclase, which increases the production of cyclic adenosine monophosphate (cAMP), resulting in bronchial smooth muscle relaxation and skeletal muscle stimulation. β agonists can also inhibit the release of inflammatory mediators through stabilization of the mast cell membrane, which will slow the progression of the inflammatory cascade (Figure 20-1).

PLACE IN THERAPY

β_2-adrenergic agonists are the cornerstone treatment of bronchoconstriction in asthma, chronic obstructive pulmonary disease (COPD), and exercise-induced bronchospasms. Fast- and short-acting agents are best used for rescue of symptoms, whereas long-acting agents are best used for maintenance therapy. Expert guidelines recommend standard treatment of acute episodes of bronchospasms, and exacerbations of asthma should include short-acting β_2-agonists (i.e., albuterol, levalbuterol).[8] Administration using a handheld metered-dose inhaler (MDI) with a spacer device (high dose: 4-8 puffs) is at least equivalent to nebulized $\beta_2\beta_2$-agonist therapy in children and adults.[9-11] Long-acting β_2-agonists (i.e., salmeterol, formoterol) are used concomitantly with glucocorticoids for children who fail to achieve adequate asthma control with a medium-dose inhaled

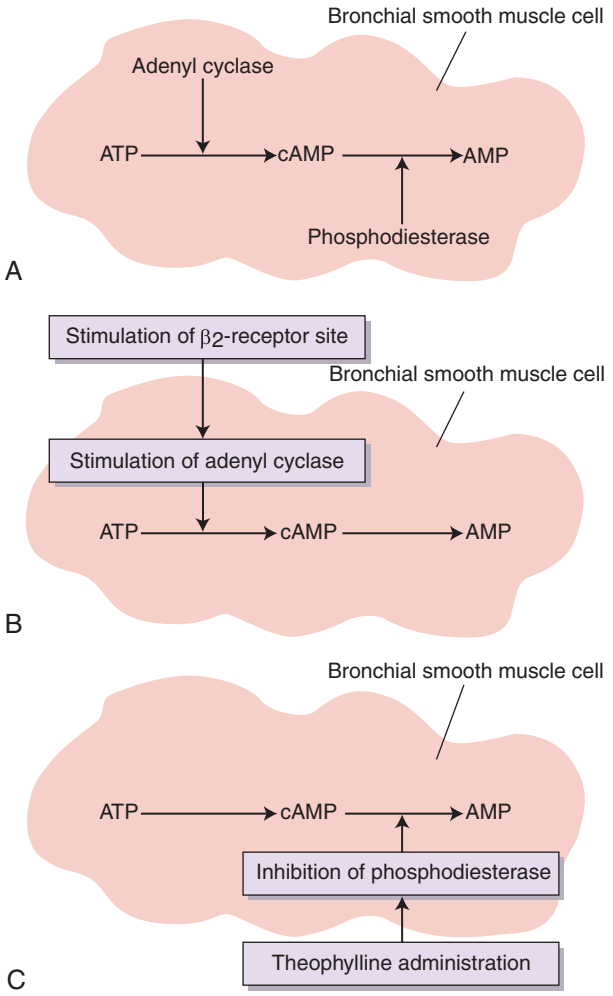


FIGURE 20-1 **A,** Sympathetic mechanisms controlling bronchial muscle tone. The enzyme adenyl cyclase is the catalyst for the conversion of adenosine triphosphate *(ATP)* to cyclic adenosine monophosphate *(cAMP).* The enzyme phosphodiesterase breaks down cAMP into adenosine monophosphate *(AMP).* Increased levels of cAMP result in relaxation of bronchial smooth muscle. Decreased levels of cAMP lead to spasm of susceptible bronchial smooth muscle. **B,** Bronchial muscle receptors are called β_2 receptor sites. Stimulation of these sites results in stimulation of the enzyme adenyl cyclase, which produces an increased level of cAMP, resulting in bronchodilation. **C,** Administration of the methylxanthine theophylline inhibits the enzyme phosphodiesterase, which inhibits the breakdown of cAMP and results in increased levels of cAMP and bronchodilation.

glucocorticoid.[8] The addition of systemic therapy to inhaled β_2-agonist therapy has been used with some success; however, there is no evidence to support the isolated use of a **parenteral** β_2-agonist to treat severe asthma exacerbations.[12,13]

In 2010 the FDA announced that in accordance with long-standing US obligations under the Montreal Protocol on Substances that Deplete the Ozone Layer, MDIs that contain chlorofluorocarbons (CFCs) as a propellant could no longer be manufactured or sold as of 2013.[14] Because of this mandate, manufacturers of short-acting β_2-agonists have since switched to hydrofluoroalkane (HFA)–propelled MDIs. Lung deposition of drug particles with HFA-propelled inhalers may be greater than or at least equivalent to CFC-propelled inhalers.[15,16]

ADVERSE EVENTS

At recommended doses, aerosol administrations are selective β_2 receptors with minimal systemic adverse events. Adverse events occur through excessive activation of β-adrenergic receptors when high doses of aerosolized selective β_2-adrenergic agonists are used or with the use of nonselective β-adrenergic agonists.

The most common adverse effect observed with the use of selective agents are tremors caused by stimulation of the β_2 receptors in skeletal muscle, which is less likely with inhalational therapy than parenteral or oral therapy.[17,18] Tachycardia and vasodilation are observed when β receptors are stimulated on the heart and peripheral vasculature. Upon initiation and with high-dose treatment, a reduction of serum potassium concentrations can be seen.[19] Hypokalemia is caused by a transient activation of the sodium-potassium pump and the transport of potassium intracellularly, which may predispose the heart to toxic effects such as arrhythmias.[19,20] Headache, nervousness, dizziness, palpitations, cough, nausea, vomiting, and throat irritation may also occur.

Regular β_2-agonist use in patients with asthma may potentially result in **tolerance** to the drug's bronchodilating effects, which can be associated with poorer disease control.[21,22] Chronic administration of selective β_2-adrenergic agonists will create tolerance by reducing the density of β_2 receptors and the binding affinity to the receptors.[22] Tolerance primarily reduces duration of bronchodilation as opposed to peak response.

Overuse of inhaled β_2-agonists has been associated with increased risk of mortality from asthma, specifically in those patients using two or more canisters of rescue inhaler each month.[8] The cardiotoxic potential of β_2-agonists may increase the risk of mortality, as may overreliance on medication and the patient's comfort level with β_2-agonist use. Control of symptoms may cause the patient to postpone obtaining adequate medical care in the presence of worsening asthma. With the use of a powerful bronchodilator, the perceived need for corticosteroid therapy may not be realized.[23] Concerns about overuse have led to the recommendation that β agonists be used only on an "as needed" basis in the treatment of acute episodes.[8,24,25] In addition, the association of development of serious adverse events is greater in children who regularly use long-acting β-agonists.[26-28]

SELECTIVE AGENTS

Selective agents have a higher specific affinity for β_2 receptors, with minimal effect on β_1 receptors, so less stimulation of the heart rate is observed. Several β-adrenergic agonists are available for the management of airway obstruction; they differ in β_2 selectivity, potency, elimination half-life, and availability of dosage formulations.

Dosage and Administration

Table 20-1 lists the bronchodilators available in inhalation form that are commonly used in pediatric patients. Generally, weight-based dosing of inhaled medications may not be appropriate for young children because of the low deposition of medication in the lungs. Standard weight-based dose of nebulized albuterol are, less than 10 kg: 1.25 mg; 10 to 30 kg: 2.5 mg, and more than 30 kg: 5 mg.

For asthma exacerbations, inhaled β_2-agonists, most commonly albuterol, can be administered continuously

Table 20-1 Inhaled Bronchodilators[8]

AVAILABLE FORMULATIONS	PEDIATRIC DOSE	ADVERSE EVENTS	ADMINISTRATION COMMENTS
Short-Acting β_2-Agonists			
Albuterol HFA 90 μg/puff	Asthma exacerbations: 4-8 puffs every 20 min for 3 doses, then 1-4 puffs every 1-4 h PRN Maintenance; as needed for symptoms: 2 puffs every 4-6 h PRN	Tachycardia, tremor, nervousness, hypokalemia, headache, palpitations, dizziness, nausea, vomiting	Drug of choice for acute bronchospasms. MDI requires periodic cleaning. Use large volume nebulizers for continuous administration.
Albuterol nebulizer solution 0.63 mg/3 mL, 1.25 mg/3 mL, 2.5 mg/3 mL, 5 mg/mL	Asthma exacerbations: 0.15 mg/kg (min: 2.5 mg/dose) every 20 min for 3 doses, then 0.15-0.3 mg/kg (max:10 mg/dose) every 1-4 h PRN As needed for symptoms: <5 years: 0.63-2.5 mg every 4-6 h PRN >5 years: 1.25-5 mg every 4-6 h PRN		May mix with cromolyn solution, budesonide inhalant suspension, or ipratropium nebulizer solution. Some nebulizer solution concentration may be premixed with NS; double check individual package information.
Levalbuterol HFA 45 μg/puff	Asthma exacerbations: 4-8 puffs every 20 min for 3 doses, then every 1-4 h; Maintenance dose: 1-2 puffs every 4-6 h PRN (max, 12 puffs/day)		Some nebulizer solution concentrations may be premixed with NS; double check individual package information.
Levalbuterol nebulizer solution 0.31 mg/3 mL, 0.63 mg/ 3 mL, 1.25 mg/3 mL, 1.25 mg/0.5 mL	Asthma exacerbations: 0.075 mg/kg (min dose 1.25 mg) every 20 min for 3 doses, then 0.075-0.15 mg/kg (max 5 mg/dose) every 1-4 h PRN Maintenance therapy: infants <5 years: 0.31-1.25 mg every 4-6 h PRN 5-11 years: 0.31-0.63 mg every 8 h PRN >12 years: 0.63-1.25 mg every 8 h PRN		
Long-Acting β_2-Agonists			
Salmeterol powder for inhalation: 50 μg/puff	≥4 years old-adolescent; maintenance therapy: 1 puff (50 μg) every 12 h	Prolonged QT interval, tachycardia, palpitations, dizziness, nausea, vomiting	Do not blow into inhaler after dose is activated.
Formoterol dry powder inhaler (capsules): 12 μg/capsule	≥5 years old-adolescent; maintenance therapy: 1 capsule (12 μg) every 12 h (max, 2 doses daily)	Tachycardia, tremor, nervousness, nausea, vomiting, headache, hypertension, dizziness, viral chest infection, fatigue tonsillitis	Do not blow into inhaler after dose is activated. Each capsule is for single use only and should not be taken orally.
Racemic epinephrine nebulizer solution: 2.25% (0.5 mL)	0.5 mL diluted with 3-5 mL of NS (max: 12 inhalations in 24 h); administer over ~15 minutes every 3-4 h PRN	Tachycardia, tremor, dizziness, nausea, vomiting, headache, nervousness, palpitations	Not recommended for routine management and treatment of asthma. Protect from light. Solution should be discarded if it contains a precipitate or is discolored.

Continued

Table 20-1 Inhaled Bronchodilators—cont'd

AVAILABLE FORMULATIONS	PEDIATRIC DOSE	ADVERSE EVENTS	ADMINISTRATION COMMENTS
Anticholinergics			
Ipratropium bromide Nebulizer solution: 0.2% (2.5 mL) Intranasal: 0.03% and 0.06%	Asthma exacerbations: 0.25-0.5 mg every 20 min for 3 doses, then PRN <12 years old: maintenance: 0.25-0.5 mg every 6-8 h PRN ≥12 years old: maintenance: 0.25 mg every 6 h PRN	Dry mouth, headache, dizziness, cough, blurred vision, drying of secretions	Protect from light. May mix in same nebulizer with albuterol. Multiple doses in the emergency department provide additive benefit when administered with albuterol.
Ipratropium bromide HFA: 17 μg/puff	Asthma exacerbations: 4-8 puffs every 20 min for 3 doses; then PRN Maintenance: 1-2 puffs every 6 h (max, 12 puffs/day)		
Systemic β_2-Agonists			
Terbutaline Aqueous 1 mg/mL	Subcutaneous: 0.005 mg/kg (max: 0.4 mg/dose) every 20 min for 3 doses then every 2-6 h PRN Continuous infusion: Load: 2-10 μg/kg intravenously 1 time Maintence: 0.08 mg/kg/hr–0.4 μg/kg/min	Tachycardia, tremor, dizziness, nausea, vomiting, headache, nervousness, palpitations	No proven advantage of systemic therapy over aerosol.
Epinephrine 1:1000 (1 mg/mL)	Subcutaneous: 0.01 mg/kg up to 0.3-0.5 mg every 20 min for 3 doses		Protect from light. Solution should be discarded if it contains a precipitate or is discolored.

HFA, Hydrofluoroalkane; *MDI,* metered-dose inhaler; *PRN,* as needed; *pwd,* powder; *soln,* solution.

or intermittently, via a nebulizer or an MDI with a spacer. Children with moderate exacerbations usually require inhaled short-acting agents every 1 to 3 hours; however, patients who require treatments more frequently should be considered for continuous albuterol nebulization. Patients with a lack of response or worsening of respiratory parameters will require more frequent treatments. Those who display improvement should have the interval between the treatments increased. In addition to the regularly scheduled β_2-agonist treatment, "as needed" treatments should be available for episodes of acute bronchospasm or worsening respiratory distress.[8] Long-acting agents can provide bronchodilation for up to 12 hours when administered as an aerosol.

Albuterol

Although the name suggested by the World Health Organization (WHO, Geneva, Switzerland) is *salbutamol,* albuterol is the official generic name in the United States. Albuterol is indicated for the treatment and prevention of bronchospasms and is available in a variety of dosage forms. The most common reported adverse reactions to aerosolized albuterol are upper respiratory infections, rhinitis, pharyngitis, nausea, throat irritation, cough, and anxiety.[29,30]

Levalbuterol

Albuterol is composed of both (R)- and (S)-isomers of albuterol. Levalbuterol is the active isomer of albuterol (R-albuterol) and is indicated for the treatment or prevention of bronchospasms in adults and children.[31,32] In studies of asthma treatment in pediatric patients, levalbuterol has been compared with both **racemic** albuterol and placebo.[33] At doses of 0.31 and 0.63 mg, levalbuterol produced an equipotent degree of bronchodilation, as measured by percent change from predose forced expiratory volume at 1 second (FEV_1), as comparable doses of 1.25 and 2.5 mg of racemic albuterol. This same study found that 0.63 mg of levalbuterol was equipotent to 1.25 mg of racemic albuterol, and 1.25 mg of levalbuterol was equipotent to 2.5 mg of racemic albuterol. Therefore there is no demonstrable difference in terms of safety or effectiveness between levalbuterol and albuterol.[34,35]

Levalbuterol is supplied as an MDI or in concentrated solution for nebulization that does not require dilution before administration. Each actuation of the MDI delivers 59 μg levalbuterol tartrate (equivalent to 45 μg of levalbuterol free base) from the actuator mouthpiece. The recommended MDI dose for treatment of acute bronchospasms or prevention of asthmatic symptoms is two inhalations (90μg) repeated every 4 to 6 hours; however, for some patients one

inhalation every 4 hours may be sufficient.[32] The suggested nebulization dosage for children on an "as needed" basis is dependent on their age. The solution should be stored in a protective foil pouch and discarded if the solution is not colorless.[31]

Adverse events in patients receiving levalbuterol are similar to those observed with racemic albuterol. Despite administration of larger equipotent albuterol doses, there is no clinically significant difference between levalbuterol and racemic albuterol in the effect on heart rate.[36] However, the incidence of tremor and nervousness has been reported to be slightly less when using 0.63 mg of levalbuterol.[37]

Terbutaline

Terbutaline is the only selective β_2-agonist available in parenteral form for the emergency treatment of status asthmaticus in critically ill children.[38] Its structural formula differs from that of albuterol in that it has a dihydroxybenzene group instead of a benzene ring, with etahydroxymethyl and parahydroxyl groups. It is available as an oral tablet and a sterile aqueous solution for parenteral (subcutaneous and intravenous) administration. Effects are observed rapidly after inhalation or parenteral administration and can persist for up to 3 to 4 hours after inhalation.

In most institutions, terbutaline is reserved for the management of acute episodes of severe asthma or in critically ill children. Although the manufacturer does not recommend use of inhaled terbutaline, in patients younger than 12 years of age doses of 0.2 mg/kg of terbutaline solution given by compressed air–powered nebulizer have resulted in a mean 55% improvement in FEV_1 at 1 hour.[39] Continuously nebulized terbutaline has also been reported to be safely administered to children in a pulmonary intensive care setting.[40] Terbutaline administered intravenously as a continuous infusion or repeated subcutaneous injections have been reported effective in the treatment of refractory status asthmaticus in pediatric patients refractory to more conventional treatments.[41,42] The aqueous solution is supplied in a 2-mL clear glass ampule containing 1 mg of terbutaline sulfate per 1 mL of solution. The ampules must be protected from light and stored at room temperature. Parenteral terbutaline loses much of its β_2 selectivity; therefore cardiovascular effects are common. Tachycardia is a common dose-limiting adverse effect and is mostly observed when using doses in the upper range of normal.[39]

INHALED LONG-ACTING β_2-AGONISTS

Long-acting β_2-agonists (LABAs) have a duration of action of at least 12 hours and have an onset of action that occurs approximately 30 minutes after intake for asthma.[43] Salmeterol and formoterol are the agents of choice for nocturnal asthma in patients who remain symptomatic despite standard management. Furthermore, studies in adolescents indicate that LABAs have the potential of improving overall asthma control when added to corticosteroids for patients who are inadequately controlled with inhaled corticosteroids alone.[43-50] LABA should not be used for acute symptom relief. It is imperative that, when beginning treatment with LABA, patients are counseled to discontinue any regular use of a short-acting β_2-agonist and to use the shorter acting agent for symptomatic, quick relief during acute episodes only. NAEPP asthma guidelines discourage use for exercise-induced bronchospasm because of the risk of LABA disguising poorly controlled persistent asthma with frequent chronic use.

Adverse reactions to LABAs include tremor, tachycardia, arrhythmias, palpitation, nervousness, agitation, headache, muscle cramps, dizziness, fatigue, insomnia, dry mouth, nausea, hypokalemia, hyperglycemia, and metabolic acidosis.[51] Although uncommon after administration at recommended doses, LABA can produce a clinically significant cardiovascular effect in some patients. Changes in the electrocardiogram include flattening of the T wave, prolongation of the QT interval, and ST-segment depression. Adverse events occur more often in children (ages 5 to 12 years) in need of daily bronchodilator and antiinflammatory treatment and include viral infection, rhinitis, tonsillitis, gastroenteritis, abdominal pain, nausea, and dyspepsia.

Salmeterol

Salmeterol is indicated for long-term maintenance treatment of asthma and prevention of bronchospasm, including exercise-induced bronchospasm (EIB), in patients 4 years of age and older. It is generally used as an adjunct to inhaled corticosteroid therapy for long-term control of asthma symptoms, nocturnal asthma symptoms, and EIB.[8] Pediatric patients should use a combined product that contains both an inhaled corticosteroid and a LABA to treat the multiple mechanisms that produce airway disease.

Salmeterol is available as a single agent in the form of a dry powder inhaler (DPI) or in fixed-dose combinations with ICS fluticasone as a DPI and MDI.[51] Studies suggest that for patients with inadequate symptom control who are receiving low to medium doses of inhaled corticosteroids, it may be more beneficial to add salmeterol than to increase the dose of inhaled corticosteroid.[52,53]

Formoterol

Formoterol is indicated for long-term, twice-daily (morning and evening) administration in the maintenance treatment of asthma and prevention of bronchospasm in adults and children 5 years of age and older.[54,55] Formoterol is available as a single agent in a hard gelatin capsule containing a dry powder blend of 12 μg of formoterol and 25 mg of lactose that is intended for oral inhalation only.[56] Prescribers should use caution with patients with severe milk protein allergy. Formoterol is also available in a solution for

nebulization and in an MDI in combination with budesonide approved for use in those 12 years of age and older.[57]

Formoterol is a highly selective β_2-agonist, whereas salmeterol is a partial agonist. In single-dose studies, when compared with salmeterol, formoterol had a shorter onset of action but similar duration of action.[54,55] In the treatment of asthma, differences between formoterol and salmeterol are not likely to produce clinically significant differences if used in combination with inhaled corticosteroids. However, in a randomized, placebo-controlled trial of patients with COPD receiving twice-daily formoterol, an increase of FEV_1 was significantly inferior to patients receiving once daily indacaterol.[58] Currently indicated for adults with COPD, indacaterol is a promising once-daily LABA currently being studied in pediatric patients with moderate to severe asthma.[59]

NONSELECTIVE AGENTS

Epinephrine

Epinephrine (adrenaline) is a potent **sympathomimetic** that acts on both α- and β-adrenergic receptors. Effects of epinephrine reproduce adrenal medullary stimulation and can be described by the phrase *fight or flight*. Its effects on target organs, including the heart, and the vascular system and respiratory tract are diverse and extremely complex. Stimulation of the αreceptors results in vasoconstriction and a reduction of mucosal and submucosal congestion and edema. The β-adrenergic effects result from stimulation of adenyl cyclase and increased cAMP production, which results in reduction of airway smooth muscle spasms (see Figure 20-1).

Parenteral epinephrine plays a vital role in cardiopulmonary resuscitation and reversal of hypersensitivity reactions.[60-64] Epinephrine is ineffective after oral administration because it is quickly metabolized, and absorption is rapid after parenteral and inhaled administration. Acting at β_2 receptors on bronchial smooth muscle, effects after nebulized administrations are restricted to the respiratory tract, thus making it useful in the treatment of postintubation and infectious croup.[65-67] In children with an acute asthma exacerbation, a metaanalysis of randomized trials failed to show a benefit of nebulized epinephrine over albuterol or terbutaline in an emergency setting.[68]

Epinephrine for injection is available in multiple dosage strengths: 1 mg/mL, 0.1 mg/mL, and 0.5 mg/mL. The solution for inhalation of racemic epinephrine is 2.5 mg/mL (2.25%). Every precaution must be taken not to confuse the solution designed for parenteral administration, because inadvertent injection can be fatal. A plastic or glass dropper should be used to prepare the dose, because the solution reacts on contact with metals. Epinephrine should be protected from light, because oxidation will turn the drug pink, then brown in color. Common adverse effects include tachycardia, palpitations, nervousness, tremor, insomnia, headache, loss of appetite, and nausea.[69]

ANTICHOLINERGICS

MECHANISM OF ACTION

The parasympathetic nervous system plays a major role in regulating airway homeostasis and bronchomotor tone. Various noxious stimuli have been demonstrated to increase parasympathetic activity, resulting in bronchoconstriction. Anticholinergics inhibit parasympathetic nerve impulses by selectively blocking the binding of the neurotransmitter acetylcholine to its receptor site in nerve cells. The nerve fibers of the parasympathetic system are responsible for the involuntary movements of smooth muscles present in the gastrointestinal tract, urinary tract, and lungs[70] (Figure 20-2).

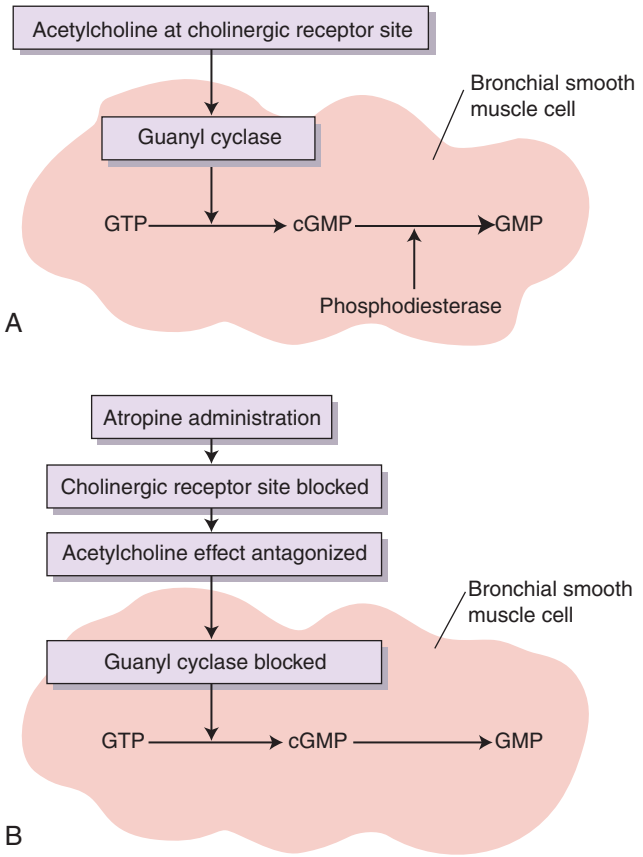


FIGURE 20-2 **A,** Parasympathetic mechanisms controlling bronchial smooth muscle tone. Stimulation of the parasympathetic system causes the release of acetylcholine at the cholinergic receptor site. Acetylcholine stimulates the enzyme guanyl cyclase to convert guanosine triphosphate *(GTP)* to cyclic guanosine monophosphate *(cGMP)*. Phosphodiesterase then breaks down cGMP to guanosine monophosphate *(GMP)*. High cGMP levels result in bronchoconstriction. **B,** Administration of an anticholinergic (atropine) antagonizes the acetylcholinergic effect and prevents cGMP from forming. This relieves the bronchoconstriction.

PLACE IN THERAPY

Anticholinergics are used to treat a variety of respiratory disorders in children, including asthma and chronic bronchitis.[8] Oral and parenteral administration of anticholinergics can be used to inhibit salivation and excessive secretions of the respiratory tract and treat chronic drooling associated with neurologic conditions. Inhaled anticholinergics are effective bronchodilators, but not as effective as β_2-agonists, and only attenuate allergen-induced asthma and EIB. Inhaled ipratropium is indicated only as adjunctive therapy in severe acute asthma not completely responsive to β_2-agonists alone, whereas tiotropium is indicated for bronchospasms associated with COPD in adults.

IPRATROPIUM BROMIDE

Aerosolized ipratropium is not sufficiently effective to be used as a single agent in the treatment of acute bronchospasms. When administered to children with severe asthma exacerbations, multiple doses of ipratropium and a β-agonist reduced the number of hospitalizations and improved overall lung function.[71] Although the addition of inhaled ipratropium bromide to inhaled β-agonist therapy has proven effective in the emergency department setting, studies during hospital admissions have not revealed added benefit.[72,73] Therefore ipratropium bromide is not recommended as standard therapy during hospitalizations for asthma exacerbations.

Dosage and Administration

Ipratropium bromide is available in a variety of dosage forms, including a nasal spray, an MDI, and a nebulizer solution. The nasal spray is used only for symptomatic relief of rhinorrhea associated with allergic and nonallergic rhinitis; it does not relieve nasal congestion, sneezing, or postnasal drip.[74] The nebulizer solution vials are packaged in a foil pouch and must be protected from light. The inhalation solution can be mixed in the nebulizer with albuterol solution for nebulizer if used within 1 hour. Recommended dosing and administration comments regarding inhaled anticholinergics are listed in Table 20-1.

Ipratropium is also available premixed with albuterol in a solution for nebulization and as an MDI.[75] It is important to note that the recommended dose is based on the ipratropium component.[8] The MDI contains soya lecithin and should not be used in patients allergic to soya lecithin or related food products such as soybeans and peanuts.[76]

Adverse Events

Ipratropium bromide is an anticholinergic agent that is a quaternary ammonium derivative of atropine. Quaternary compounds are poorly absorbed across mucosal membranes and the blood–brain barrier; therefore inhalation of ipratropium results in opening of the bronchi with minimal systemic effects.[77] The most common adverse reactions are dry mouth, cough, headache, nausea, dizziness, blurred vision, and drying of secretions. Skin flushing, tachycardia, acute angle–closure glaucoma, and palpitations have also been reported.

GLYCOPYRROLATE

Dosage and Administration

Glycopyrrolate belongs to a class of drugs known as the *antimuscarinics* that function by blocking muscarinic receptors and inhibiting cholinergic transmission. Glycopyrrolate is available in an oral and parenteral formulation used specifically to inhibit salivation and excessive secretions of the respiratory tract. The enteral dose for control of secretions in children is 40 to 100 μg/kg three or four times daily. The intramuscular and intravenous dosage is 4 to 10 μg/kg every 3 to 4 hours. Glycopyrrolate is also used to counter the muscarinic effects of neostigmine and pyridostigmine during reversal of neuromuscular blockade. Contraindications to glycopyrrolate are similar to other anticholinergic medications, including narrow-angle glaucoma, severe ulcerative colitis, tachycardia, paralytic ileus, and myasthenia gravis.

Adverse Events

The parenteral formulation of glycopyrrolate contains benzyl alcohol, which has been associated with "gasping syndrome" (the quick inhalation and exhalation of breaths—much like gulping for air) in neonates after administration of large amounts of benzyl alcohol (more than 99 mg/kg/day).[78,79] Adverse reactions include thickening of bronchial secretions, tachycardia, behavioral changes, palpitations, drowsiness, headache, and ataxia. Extreme caution should be used in infants, patients with Down syndrome, and children with spastic paralysis or brain damage because of the potential hypersensitivity to the antimuscarinic effects.

CORTICOSTEROIDS

MECHANISM OF ACTION

Although the term *corticosteroids* is used for most endogenous steroids, it is a general term that includes both glucocorticoids and mineralocorticoids. Glucocorticoids (i.e., cortisol) control carbohydrate, fat, and protein metabolism and also have antiinflammatory properties. Mineralocorticoids (i.e., aldosterone) control electrolyte and water levels, primarily by promoting sodium retention in the kidney.

Pharmacology of the corticosteroids is extremely complex and can ultimately affect almost all body systems. Corticosteroids are highly lipophilic and readily cross cell membranes to combine with glucocorticoid receptors found in the cytoplasm of most cells throughout the body. Corticosteroids act by controlling the rate of protein synthesis, depress the migration of polymorphonuclear leukocytes and fibroblasts, reverse capillary permeability, and stabilize

lysosomal membranes to prevent or control inflammation processes. Corticosteroids also increase the number and responsiveness of β_2-adrenergic receptors to β_2-adrenergic stimulation, therefore reducing hypersecretion, airway edema, and exudation. Cellular effects of corticosteroids are immediate but may require 4 to 12 hours before any clinical response is noted.[80]

PLACE IN THERAPY

Corticosteroids are potent antiinflammatory agents used in a variety of disease states, including the management of asthma in pediatric and adult patients. Inhaled corticosteroids have a high antiinflammatory potency, approximately 1000-fold greater than endogenous cortisol.[81] Inhalation therapy allows the topical administration of the potent antiinflammatory directly at the site of action, which reduces the risk of adverse events observed with systemic corticosteroid therapy. The Expert Panel Report 3 (EPR-3) on asthma states that inhaled corticosteroids are the most effective antiinflammatory agents available for persistent asthma, and inhaled corticosteroids are the only therapy proven to reduce the risk of death from asthma.[8] Of note, inhaled corticosteroids are not as effective as systemic therapy for severe asthma exacerbations and should not be used as a substitute for systemic corticosteroid therapy.

Systemic corticosteroids are a vital component in the treatment of exacerbations of asthma because of their ability to decrease airway inflammation and secretions. In the emergency department, intravenous and oral corticosteroids are first-line therapy.[8,82,83] There is no added benefit of using intravenous dosing in a pediatric patient if the patient is able to tolerate oral dosing; thus oral administration is preferred.[84]

DOSAGE AND ADMINISTRATION

Corticosteroids are available in a variety of dosage forms and are listed in Table 20-2 along with the potential

Table 20-2 Corticosteroid Agents

AGENT	AVAILABLE FORMULATIONS	ADVERSE EVENTS	ADMINISTRATION COMMENTS
Inhaled Corticosteroids			
Beclomethasone dipropionate Budesonide Fluticasone	MDI: 40 μg/puff, 80 μg/puff Flexhaler DPI: 90 μg/puff, 180 μg/puff Suspension for nebulization: 0.25 mg/2 mL, 0.5 mg/2 mL; 1 mg/2 mL DPI: 50 μg/blister, 100 μg/blister, 250 μg/blister HFA: 44 μg/puff, 110 μg/puff, 220 μg/puff	Hoarseness, dry throat, **dysphonia,** cough, oropharyngeal candidiasis (thrush)	Patients should be instructed to rinse mouth with water after administration. Most children younger than 4 years cannot provide sufficient inspiratory flow for adequate lung deliver of DPI.
Combined Inhaled Corticosteroid and Long-Acting β_2-Agonist			
Fluticasone/Salmeterol Budesonide/Formoterol	HFA (MDI): 45 μg/21 μg, 115 mcg/21 μg, 230 μg/21 μg Diskus (DPI): 100 μg/50 μg, 250 μg/50 mcg, 500 μg/50 μg HFA (MDI): 80 μ/4.5 μgg, 160 μg/4.5 μg	See individual ingredients	Should not be used for acute symptom relief or asthma exacerbations. Most children younger than 4 years cannot provide sufficient inspiratory flow for adequate lung delivery of the DPI.
Oral Systemic Corticosteroids*			
Prednisone Prednisolone Methylprednisolone	Tablets: 1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, 50 mg Solution: 5 mg/5 mL Tablets: 5 mg Solution: 5 mg/5 mL, 15 mg/5 mL Tablets: 2 mg, 4 mg, 8 mg, 16 mg, 32 mg	Short-term use: reversible glucose metabolism, fluid retention, weight gain, mood alteration, hypertension, peptic ulcer Long-term use: HPA axis suppression, growth suppression, hypertension, Cushing syndrome	Children on low-dose therapy experience fewer behavioral side effects. Other systemic corticosteroids such as hydrocortisone and dexamethasone given in equipotent daily doses are likely to be as effective.

*Recommended dosing is equivalent for all listed preparations.
DPI, Dry powder inhaler; *HFA,* hydrofluoroalkane; *HPA,* hypothalamic–pituitary–adrenal; *inh,* inhaled; *max,* maximum; *MDI,* metered-dose inhaler; *neb,* nebulization; *soln,* solution.

adverse events. Inhalational dosages are often increased depending on the age of the patient and his or her response to therapy. Once asthma symptoms are under control, the starting dose is adjusted to the lowest effective dose to reduce the possibility of side effects. Maximal benefit may not be achieved for 1 to 2 weeks or longer after starting treatment. There are significant differences in efficacy and safety of the available inhalation formulations. These differences result from differences in the chemical entity, potency, and pharmacokinetic profile. It is important to counsel the patient to rinse the mouth with water after each administration to decrease drug deposition in the mouth and local adverse events (e.g., thrush).

For asthma exacerbations, dosages of systemic corticosteroid therapy vary from 1 to 2 mg/kg/day, with a maximum daily dose of 60 mg/day of prednisone.[8] The most commonly used intravenous agent is methylprednisolone; oral forms of hydrocortisone, dexamethasone, prednisone, and prednisolone are also available. Pharmacologic and adverse effects of corticosteroids are dependent on the dose and duration of therapy. There is minimal risk of long-term adverse events if systemic agents are used for short periods (4 to 5 days). Because of potential suppression of the **hypothalamic-pituitary-adrenal (HPA) axis,** systemic doses should be tapered in patients who require a course longer than 10 days.[8,80] The lowest effective dose should be used in patients requiring chronic corticosteroid therapy.

ADVERSE EVENTS

As stated earlier, the likelihood of systemic side effects increases when corticosteroids are used at high doses or for a long duration. Chronic use of corticosteroids produces a dose-dependent suppression of adrenal axis steroid production and may potentially impair growth in pediatric patients into adulthood.

The effects of inhaled corticosteroids on linear growth have extensively been described in literature.[85-88] Treatment with inhaled beclomethasone was associated with prepubertal growth impairment, but suppression was limited to 1.5 cm/year in children treated with beclomethasone at 400 μg/day. Subsequent studies have shown that inhaled corticosteroid therapy combined with systemic corticosteroid therapy does not clinically affect final adult height.[88,89] Many studies to determine the effects on growth have significant design limitations. Delayed or impaired growth may be a result of the disease itself; the question remains as to whether the treatment or the underlying disease is the true determinant of linear growth reduction. Further studies have proved that even with this initial reduction in linear growth, the long-term effects do not last. In long-term follow-up, patients with a history of inhaled corticosteroid use achieved a height that fell within the expectation based on hereditary models.[84]

A majority of side effects attributed to corticosteroids are primarily seen with systemic therapy and not inhalational therapy. After corticosteroid inhalation, local adverse events include oropharyngeal candidiasis, **dysphonia,** cough, wheezing, and dry throat. The dysphonia appears to be the result of a direct effect of the steroid on the musculature that controls the vocal cords. Proper inhalation technique such as using a holding chamber device (i.e., spacer) or rinsing the mouth after each inhalation may help decrease the risk of local adverse events.

Major limitations to the long-term use of systemic corticosteroids include HPA axis suppression, Cushing syndrome, osteoporosis, myopathies, glaucoma, cataracts, gastritis, hypertension, **hirsutism,** electrolyte imbalances, glucose intolerance, skin atrophy, and immunosuppression, increasing the risk of opportunistic infections. Varicella infection (chickenpox) or measles may lead to serious or even fatal complications in children taking chronic systemic corticosteroids. If long-term systemic therapy is warranted, considerable care must be taken to avoid exposure to potential infectious diseases.

LEUKOTRIENE MODIFIERS

MECHANISM OF ACTION

Release of histamine and leukotrienes is triggered by exposure of allergens from mast cells, which are located throughout the walls of the respiratory tract. The synthesis of leukotrienes is dependent on lipoxygenation of **arachidonic acid,** a fatty acid found in cell membranes, by 5-lipoxygenase.[90,91] The leukotrienes work to constrict airway smooth muscle and increase vascular permeability, leading to airway edema, mucus production, and activation of inflammatory cells in the airways of patients with asthma.[92] Mast cell degranulation and leukotrienes are believed to be integral causes of exercise-induced bronchospasms after either drying or cooling of the airways.[93]

Current US FDA-approved oral leukotriene-modifying agents are listed in Table 20-3. Classes of leukotriene modifiers are based on their site of action: leukotriene receptor antagonists (zafirlukast, montelukast) and leukotriene synthesis inhibitors (zileuton). Zafirlukast and montelukast act by selectively antagonizing leukotriene binding to its cellular receptor, cysteinyl leukotriene receptor ($CysLT_1$), which prevents a cascade that leads to constriction of bronchial smooth muscle. Zileuton acts as a potent and selective inhibitor of leukotriene formation by inhibiting 5-lipoxygenase, the enzyme responsible for converting arachidonic acid to the cysteinyl leukotrienes.[94-96]

PLACE IN THERAPY

Treatment with leukotriene modifiers is associated with improved asthma symptoms and pulmonary function, including improvement in FEV_1.[20] Pediatric

Table 20-3 Leukotriene-Modifying Agents

AGENT	AVAILABLE FORMULATIONS	ADVERSE EVENTS	ADMINISTRATION COMMENTS
Zileuton	600-mg tablet, 600-mg 12-hour extended release tablet	Elevated liver enzymes, reversible hepatitis, and hyperbilirubinemia	Extended-release tablet should not be crushed, cut, or chewed. Zileuton increases serum theophylline and warfarin concentrations.
Zafirlukast Montelukast	10-mg and 20-mg tablet 4-mg or 5-mg chewable tablet, 10-mg tablet, 4-mg granule packet	Headache, elevated liver enzymes, reversible hepatitis NOTE: Rare cases of eosinophilic vasculitis (Churg-Strauss) have been reported.	Administer at least 1 hour before or 2 hours after a meal. Patients with both asthma and allergic rhinitis should take their dose in the evening. Montelukast granules are not intended to be dissolved in liquid and must be administered within 15 minutes of opening the packet.

studies demonstrate the usefulness of leukotriene modifiers in mild asthma and attenuation of exercise-induced bronchoconstriction. Leukotriene receptor antagonists are not an alternative to using short-acting β-adrenergic agonists during an asthma exacerbation but are recommended to be continued during an asthma exacerbation.[8]

Zileuton is approved for use in children older than 12 years and is used less commonly than other leukotriene modifiers because of a need to regularly monitor liver enzymes and drug–drug interactions. It is the only leukotriene synthesis inhibitor currently approved for use. Zileuton is effective in the treatment of cold air–induced, aspirin-intolerant, exercise-induced, and nocturnal asthma.[97] Zileuton reduces asthma symptoms, and the supplemental use of β agonists improves FEV_1 values and may have an additive effect with inhaled steroids.[98]

Leukotriene receptor antagonists montelukast and zafirlukast are useful as steroid-sparing agents for patients with difficult-to-control asthma. Although an inhaled corticosteroid has been shown to provide better control in patients with persistent asthma, leukotriene receptor antagonists are viable alternatives secondary to their ease of use and better adherence.[99] The most widely used leukotriene inhibitor, montelukast, is FDA approved for control of asthma in children 12 months of age or older and treatment of rhinitis in children 6 months of age or older. Zafirlukast is administered twice daily and approved for children older than 5 years. Use of montelukast or zafirlukast can reduce asthma symptoms and bronchial hyperreactivity and potentially decrease use of β agonists and systemic corticosteroids in children with intermittent or persistent asthma.[100-103] Recent pediatric studies of montelukast use in respiratory syncytial virus (RSV) bronchiolitis have shown promising results. Patients with RSV-positive bronchiolitis receiving daily montelukast demonstrated fewer daytime coughs and a delay in exacerbation compared with placebo-treated controls.[104]

ZILEUTON

Dosage and Administration

Zileuton is available as a 600-mg tablet and an extended-release 600-mg tablet. The recommended dosage in adults and children 12 years and older is 600-mg four times per day for a total daily dose of 2400 mg, or 1200 mg twice daily with an extended-release tablet. Zileuton should be taken with meals and at bedtime but can be taken with or without food. The extended-release tablet should not be crushed, cut, or chewed. Zileuton is a cytochrome P-450 enzyme substrate and as such will affect the plasma concentration of other substrates metabolized by the P-450 system such as theophylline, propranolol, and warfarin.

Adverse Events

The most common side effects are abdominal pain, upset stomach, and nausea. Zileuton is associated with threefold or greater elevations of liver enzymes (serum aminotransferase) in 2% to 4% of patients.[105] The elevations usually occur during the first 3 months of treatment and return to normal when zileuton is discontinued. Therefore liver function should be evaluated before starting zileuton, monthly for the first 3 months of treatment, then every 3 months for the first year, and periodically thereafter.

MONTELUKAST AND ZAFIRLUKAST

Dosage and Administration

Montelukast is available as both a 4-mg and 5-mg chewable cherry-flavored tablet, as well as a 10-mg film-coated tablet. The dose for children 2 to 5 years old is one 4-mg tablet daily. The dose for children 6 to 14 years old is one 5-mg tablet daily. The dose for adolescents (15 years and older) and adults is one 10-mg tablet daily. Montelukast is dosed once daily in the evening as 4-mg or 5-mg chewable tablets for ages 2 to 5 years and 6 to 14 years, respectively. A 10-mg tablet is available for adolescents older than 15 years. The initial response after a single dose of montelukast occurs in 3 to 4 hours with a duration of action up to 24 hours. Montelukast has also been shown to

improve symptoms when used in combination with loratadine for the treatment of seasonal allergic rhinitis.

Zafirlukast is rapidly absorbed after oral administration, with a response in approximately 3 hours. The duration of action is approximately 10 hours. Clinical trials demonstrated that zafirlukast improved daytime asthma symptoms, nighttime awakenings, rescue β-agonist use, FEV_1, and morning peak expiratory flow rate.[92] Zafirlukast is not a bronchodilator and is not used to treat acute episodes of asthma. Because food reduces the bioavailability, zafirlukast should be taken on an empty stomach or approximately 1 hour before or 2 hours after meals. Zafirlukast can inhibit the metabolism of warfarin; therefore patients receiving warfarin anticoagulant therapy concomitantly with zafirlukast should have their prothrombin time closely monitored and adjusted accordingly.

Adverse Events

Leukotriene modifiers are appealing because of their excellent safety profile for long-term control of mild persistent asthma in children. The most common side effect is headache. Other side effects of leukotriene receptor antagonists include mild fatigue, fever, abdominal pain, gastroenteritis, heartburn, dizziness, and rash.

Elevation of liver enzymes, progressing to hepatitis and hepatic failure, has occurred in patients using zafirlukast. Most incidents occurred while using doses four times higher than the recommend dose; however, similar cases have occurred in patients receiving the recommended daily dose.

In rare cases, patients may present with clinical features of vasculitis consistent with **Churg-Strauss syndrome,** which typically have been reported in patients undergoing a reduction in oral corticosteroid medication. Resolution of symptoms occurred when the agent was discontinued and corticosteroid therapy resumed.[106-109] Although further studies are needed to determine the extent of the association, many believe that the syndrome is unmasked after withdrawal of the corticosteroid.[110]

METHYLXANTHINES

THEOPHYLLINE

Mechanism of Action

The chemical structure of theophylline is similar to dietary caffeine with a mechanism of action that is not completely understood. Theophylline is believed to competitively inhibit phosphodiesterase, the enzyme that degrades cAMP. Increased concentrations of cAMP may mediate the observed bronchodilation (see Figure 20-1). Other proposed mechanisms of action include inhibition of the release of intracellular calcium and competitive antagonism of the bronchoconstrictor adenosine. As a result, theophylline relaxes smooth muscle, stimulates the central nervous system and cardiac muscle, increases mucociliary transport and diaphragmatic contractility, and acts on the kidneys to promote diuresis.[7]

Place in Therapy

Theophylline has both bronchodilatory and antiinflammatory properties, with potential steroid-sparing and immunomodulatory effects.[111,112] The role of theophylline in the management of childhood asthma has been decreasing because of serious adverse effects. Theophylline is not recommended for acute asthma exacerbations but can be used as an alternative to inhaled corticosteroids for children with mild persistent asthma.[8]

Dosage and Administration

Theophylline is available in a multitude of dosage formulations and strengths, with great variation in the recommended dosing guidelines based on patient age. Sustained-release preparations generally provide more consistent drug levels and allow dosing once, twice, or three times daily, favoring patient compliance. Theophylline is rapidly absorbed, with wide variations in clearance because of differences in hepatic metabolism. Multiple factors increase the clearance rate of theophylline and result in higher dose requirements, including smoking, hyperthyroidism, and concurrent use of medications such as phenobarbital and rifampin. Factors that can decrease clearance and lead to toxicity include hypothyroidism, congestive heart failure, liver failure, and the use of oral contraceptives and various antibiotics, including ciprofloxacin and erythromycin.

Because of the wide interpatient variability of theophylline clearance, routine serum theophylline level monitoring is vital. Doses are adjusted based on serum concentrations, with a goal of 5 to 15 μg/mL when drug concentrations approach steady state. Steady state occurs approximately 48 hours after the administration of the same dose of theophylline.[8]

Adverse Events

The use of theophylline to treat chronic childhood asthma is problematic because of potentially serious short-term and long-term adverse events. Dose-related acute toxicities include tachycardia, nausea, vomiting, supraventricular tachycardia, central nervous system stimulation, seizures, headache, and electrolyte disturbances. Adverse events seen at therapeutic serum concentrations include insomnia, gastric upset, and hyperactivity.[8,113]

MAST CELL STABILIZERS

CROMOLYN SODIUM

Mechanism of Action

Although the complete mechanism of action of cromolyn is unknown, it does inhibit mast cell degranulation after exposure to antigens, therefore blocking

the release of histamine and leukotrienes. These actions serve to inhibit the early asthmatic response through stabilization of the mast cell membrane. Cromolyn has no intrinsic bronchodilator, antihistaminic, anticholinergic, or vasoconstrictor activity.[7]

Place in Therapy

The EPR-3 on asthma recommends cromolyn sodium for treatment of mild and moderate persistent asthma.[8] Inhaled corticosteroids are superior to cromolyn as controller therapy for mild persistent asthma in children. Although there are some studies in which cromolyn compared favorably to other therapies, a systematic review of trials of cromolyn versus placebo found no clear therapeutic effect.[114,115]

Dosage, Administration, and Adverse Events

Cromolyn sodium is only available as a nebulizer solution. The recommended dosage of the solution for nebulization in children older than 2 years is 20 mg (one 2-mL ampule) three to four times daily. The ampule must be protected from light and should not be used it if it contains a precipitate or becomes discolored. Serious adverse events after cromolyn administration are relatively rare; however, the most commonly reported include cough, nasal congestion, nausea, throat irritation, and sneezing.[116]

MAGNESIUM SULFATE

MECHANISM OF ACTION

Magnesium is an abundant intracellular **cation** and a cofactor in more than 300 enzymatic and cellular reactions in the body. Magnesium relaxes smooth muscle and can cause depression of the central nervous system. When given intravenously, magnesium promotes bronchodilation by competing for binding sites with calcium ions, essentially acting as a competitive calcium channel blocker.[117]

PLACE IN THERAPY

Magnesium sulfate is generally reserved for patients in the emergency department or those having life-threatening exacerbations who remain in the severe category after 1 hour of intensive conventional therapy.[8] Clinical studies have proven safe improvements of spirometric indices during severe asthma exacerbations when magnesium sulfate is used in addition to standard therapy in the emergency department.[118-120] Nebulized magnesium sulfate has also been used successfully with and without β_2-agonists in the treatment of acute asthma.[121,122]

DOSAGE, ADMINISTRATION, AND ADVERSE EVENTS

The intravenous dose of magnesium sulfate for bronchodilation as adjunctive treatment in an acute severe asthma exacerbation is 25 to 50 mg/kg, with a maximum of 2 g given as a single dose.[8] Oral administrations are not commonly used for asthma exacerbations; however, it is important to note that a 1-g dose of magnesium sulfate is equivalent to 98.6 mg (8.12 mEq) of elemental magnesium if magnesium sulfate is used to treat hypomagnesemia.

Dose-related facial flushing and vasodilation can occur, as well as infusion-related hypotension and vasodilation. Other adverse events of magnesium sulfate include fatigue, somnolence, respiratory depression, and blunting of deep tendon reflexes. As the magnesium serum level diminishes, deep tendon reflexes return in reverse order of attenuation.

MUCOLYTIC AND HYDRATING AGENTS

N-ACETYLCYSTEINE (MUCOMYST)

Mechanism of Action

The viscosity of mucous secretions in the lungs depends on the concentrations of mucoprotein and the presence of disulfide bonds between these macromolecules and DNA. N-acetylcysteine (NAC) acts to split the sulfide bonds in the macromolecules, thereby decreasing viscosity and elasticity of airway mucus, allowing for removal by normal chest physiotherapy.[123] The action of N-acetylcysteine is pH dependent, with mucolytic action significant at pH ranges of 7.0 to 9.0.[124]

Place in Therapy

Oral and aerosolized NAC is indicated as a **mucolytic** agent used as adjunctive therapy for pulmonary complications involving abnormal or viscid mucous secretions such as bronchopulmonary disease, pulmonary complications of surgery, and cystic fibrosis (CF).[125] Use of mucolytics to clear secretions in patients with non–cystic fibrosis bronchiectasis is controversial and uncertain.[126,127] Intravenous and oral formulations of acetylcysteine are used as emergent antidotes in acetaminophen overdose to prevent or lessen hepatic injury after ingestion of a hepatotoxic quantity of acetaminophen.[128]

Dosage, Administration, and Adverse Events

NAC is available as either a 10% or 20% solution. The recommended aerosolized dose of *NAC* in children is 3 to 5 mL of the 20% solution. The 20% solution should be diluted with an equal volume of water or normal saline and administered by nebulizer three or four times per day. The 10% solution may be used undiluted. The aerosolized solution should be administered separately, because it is incompatible with several other medications. A slight color change (light purple) may occur with opened vials but does not affect the safety or efficacy of the solution.[129]

Adverse events reported with *NAC* include stomatitis, vomiting, hemoptysis, bronchospasm, and severe

rhinorrhea. It has an unpleasant, pungent odor that may lead to an increased incidence of nausea.[124]

DORNASE ALFA

Mechanism of Action

An additional factor that contributes to viscous mucus in patients with CF is extracellular DNA. Bacterial cell death and subsequent cell lysis release DNA into the extracellular environment, which works to thicken airway secretions. Dornase alfa is a highly purified solution of recombinant human deoxyribonuclease I (rhDNase), an enzyme that selectively cleaves DNA, facilitating mucus clearance in the lung.[130]

Place in Therapy

By decreasing the size and viscosity of DNA in sputum, dornase alfa has been demonstrated to reduce mucous obstruction and improve pulmonary function in patients with CF. Studies have shown that daily administration of dornase alfa results in a definite improvement in the FEV_1 above baseline.[131] Furthermore, administration of dornase alfa in patients with CF also resulted in a significant reduction in the number of patients experiencing respiratory tract infections requiring parenteral antibiotics.[132-134]

Dosage, Administration, and Adverse Events

Dornase alfa is indicated as an adjunct to standard therapies to improve pulmonary function in the management of patients 5 years of age and older with CF. The recommended dose for most patients with CF is 2.5 mg by nebulizer once daily; however, some patients may benefit from twice-daily treatments. Although dornase alfa is not approved in children younger than 5 years, there are small studies in children as young as 3 months of age with similar reported efficacy and adverse events.[135,136] Because of inactivation, dornase alfa ampules should be kept refrigerated and not diluted or mixed with other medications in the nebulizer.[137]

Common adverse events have included voice alteration, pharyngitis, laryngitis, rash, and chest pain. Other less common adverse events include respiratory symptoms, flu syndrome, malaise, hypoxia, and weight loss.[137] Interestingly, when aerosolized dornase alfa is administered in healthy subjects and patients with CF, a lack of an allergic response or serum antibodies has been demonstrated.[138]

HYPERTONIC SALINE

Mechanism of Action

Several hypotheses have been postulated to explain the mechanism by which hypertonic saline works in pulmonary diseases. Proposed mechanisms include alteration of mucus viscosity by osmotic absorption of water from the submucosa, restoration of airway surface liquid, and irritant properties that stimulate cough and mucociliary clearance of mucociliary secretions.[139]

Place in Therapy

Hypertonic saline is considered a hydrator and not a mucolytic agent. Hypertonic saline has been studied in several chronic lung disease states as a means of mobilizing secretions, with most of the literature supporting use in patients with CF. Ultrasonic nebulization of 7% hypertonic saline in patients with CF with moderate obstructive lung disease has been shown to increase mucociliary clearance.[140,141] On the other hand, studies in non-CF bronchiectasis have been unclear. A recent Cochrane review found no papers worthy of analysis; however, some studies have shown benefit if added to other mucus-clearance technologies.[142,143] Further studies on the long-term efficacy of hypertonic saline therapy and optimal hypertonic saline concentration are warranted.

Dosage, Administration, and Adverse Events

A variety of hypertonic saline concentrations has been used in conjunction with inspiratory positive ventilation. The 3% and 7% nebulized solutions are most often used. The usual dose for 3% nebulized solution is 3 to 4 mL via nebulizer up to every 4 hours as needed. The usual dose of the 7% nebulized solution used in patients with CF is 4 mL via nebulizer twice daily. Studies administering hypertonic saline used various types of nebulizers, including jet and ultrasonic nebulizers.[140,145,146] Hypertonic saline should not be mixed with any of the standard bronchodilators or adjunctive agents. The most commonly reported side effect is cough; however, bronchospasms and pulmonary edema have also been reported. Prophylactic bronchodilator administration is recommended to prevent the potential bronchospasms.[140]

ANESTHETICS

KETAMINE

Mechanism of Action

The mechanism of action for ketamine appears to be a selective interruption of the association pathways of the brain. The resulting bronchodilation may be of sympathetic origin. There is also a parasympathetic limb of action whereby ketamine diminishes acetylcholine activity on bronchial smooth muscle, resulting in bronchodilation.[147,148]

Place in Therapy

Ketamine is an anesthetic agent that produces anesthesia, sedation, and amnesia without significant respiratory depression. Because of its bronchodilating effects, ketamine has been used as part of rapid-sequence intubation in pediatric patients with status asthmaticus. It has also been used as a combined bronchodilator and sedative in patients with asthma requiring mechanical ventilation. In the setting of quickly deteriorating asthma, ketamine may be one of several last-resort medications to prevent placing

the patient on mechanical ventilation. In general, the use of ketamine should be viewed as third- or fourth-line therapy.[149]

Dosage, Administration, and Adverse Events

Ketamine is given through a central venous catheter as a continuous infusion with a normal dose for sedation of 5 to 20 μg/kg/minute. For bronchodilation, the starting dose may be very low and titrated to effect.[150,151] For sedation or minor procedures, the dose is 0.5 to 1 mg/kg. The duration of action of a single dose can last up to 10 to 20 minutes. Parenteral administrations should not exceed 0.5 mg/kg/minute and should be given no faster than 60 seconds to minimize risk of respiratory depression and pressor response.[152]

Adverse events seen with ketamine include increased sympathomimetic activity, seizures, delirium, increased laryngeal secretions, and respiratory depression. During the recovery phase, unusual dreams and hallucinations have been reported. Premedication with midazolam (less than 0.1 mg/kg) can attenuate this effect. Intubation equipment must be readily available before administering ketamine, because the sedative effects may result in respiratory failure and the need for emergency intubation. Epinephrine should also be available for possible bradycardia.

AEROSOLIZED ANTIMICROBIALS

The delivery of aerosolized antibiotics is a vital component of treatment for several respiratory disorders, including CF, non-CF bronchiectasis, and pneumonia.[144] Aerosol delivery of antibiotics reduces the likelihood of systemic adverse events and is often used for targeted antimicrobial delivery to a site of infection.[153] However, the delivery of aerosolized antimicrobials to infants and children is complicated by several anatomic and physiologic differences in their respiratory systems compared with adults.

Several factors influence the ultimate amount of drug delivered to the appropriate anatomic region within the lung, including properties of the delivery device, aerosol particles, disease state, administration technique, and the drug's specific pharmacologic properties. The pharmacologic effect of a drug is dependent on the site of deposition within the lung, the rate of drug clearance from the airway, and the site of infection.[154] To be effective, drug particles must withstand the forces required to generate the aerosol and often must penetrate a mucus layer (i.e., biofilm) and airway mucosa to reach their target receptor sites or cells.

Pulmonary manifestations as a result of colonization of *Pseudomonas aeruginosa* in patients with CF have independently been associated with a decline in lung function and death.[155] Therapies, including aerosolized antimicrobials, can potentially decrease organism burden or eliminate colonization, improving clinical outcomes of patients with CF.[153,156] Strategies for optimal use of aerosolized antimicrobials differ depending on the status of the patient. Eradication of airway pathogens is most likely early in the disease; once the patient has been colonized, suppressive therapy is unlikely to eradicate the organism but may potentially reduce disease complications. Chronic suppressive therapy cycles between 28-days-on and 28-days-off therapy designed to suppress bacterial burden, which has been shown to improve lung function, quality of life, and hospitalization rates.[157]

Addition of inhaled antimicrobials to the armamentarium of antibiotics may help address the problematic increase in antimicrobial resistance. Antimicrobial classes such as aminoglycosides, β-lactams, and antivirals have all been aerosolized with various degrees of efficacy; however, only a few commercial formulations currently exist for this route of administration.[153] Usual doses and administration comments for nebulized antimicrobials are listed in Table 20-4.

TOBRAMYCIN

Mechanism, Place in Therapy, and Adverse Events

Tobramycin is an aminoglycoside antibiotic typically used to treat gram-negative infections, including *P. aeruginosa*. Tobramycin is bactericidal by binding to ribosomal subunits, which in turn inhibits bacterial protein synthesis. An inhalation formulation of tobramycin solution (Tobi) was approved by the FDA in 1998 primarily for chronic suppressive therapy in patients with CF. Use of nebulized tobramycin can improve FEV_1 by 7.8% to 12% in patients with CF and potentially eradicate *P. aeruginosa* from the respiratory tract in early colonization and in young patients.[157-159] Several clinical studies have also shown a reduction in hospitalizations for acute exacerbations as well as in the parenteral use of antipseudomonal antibiotics in patients with CF with varying degrees of disease severity.[157-159] Tobramycin inhalation solution is indicated for patients with CF older than 6 years with *P. aeruginosa* infection and an FEV_1 between 25% and 75% of predicted values.[160] Aerosolized tobramycin has also played a role in the treatment of hospital-acquired pneumonia and treatment of acute exacerbations and suppression for non-CF bronchiectasis[153] (TOBI PODHALER [tobramycin] capsule [package insert]. Novartis Pharmaceuticals Corporation, East Hanover, NJ, 2013).

Peak sputum levels of aerosolized tobramycin can exceed 10 to 25 times the **minimum inhibitory concentration** (MIC) of bacterial pathogens; however, systemic exposure and incidence of systemic adverse events are relatively low. Cough, pharyngitis, increased sputum production, rhinitis, and dyspnea are the most commonly reported adverse effects.[161]

Table 20-4 Aerosolized Antimicrobial Agents

ANTIMICROBIAL	ANTIMICROBIAL CLASS	USUAL DOSAGE	ADMINISTRATION COMMENTS
Tobramycin inhalational solution	Aminoglycoside	150-300 mg every 12 hours (do not administer doses <6 hours apart) in repeated cycles of 28 days on followed by 28 days off with Pari LC Plus	Doses should be administered at least 6 hours apart. Ampules should be kept in the refrigerator and protected from light.
Tobramycin inhalation powder	Aminoglycoside	Inhalation of the contents of four 28 mg capsules twice-daily (do not administer doses <6 hours apart) for 28 days on followed by 28 days off using the Podhaler device.	Capsules must not be swallowed and should always be stored in the blister and removed immediately before use.
Aztreonam lysine (Cayston)	Monobactam	75 mg three times daily (at least 4 hours apart) in repeated cycles of 28 days on followed by 28 days off with Altera nebulizer system	Use of a bronchodilator before administration is recommended. Incompatible with other nebulizer medications.
Colistimethate	Polymyxin	75-150 mg twice daily	Solution should be used promptly after reconstitution.
Pentamidine	Antiprotozoal	≥5 years and adolescents: 300 mg every 4 weeks with Respirgard II nebulizer	Safety and efficacy dependent on appropriately sized face mask. Do not mix with other nebulizer solutions.

A tobramycin inhalation powder (TIP) has recently been approved by the FDA designed to relieve the high treatment burden and improve patient adherence in patients with CF with chronic pulmonary *P. aeruginosa* infections. The inhalation powder formulation is a light, porous particle using PulmoSphere technology designed to deliver the tobramycin in a capsule-based dry powder inhaler over 5 minutes without the need for any device cleaning.[188] Clinical studies in patients older than 6 years have shown that systemic exposure to TIP is comparable with the tobramycin inhalation solution, as is efficacy, and TIP had higher treatment satisfaction scores, a shorter duration of administration, and a higher rate of cough.[189,190]

AZTREONAM LYSINE

Mechanism, Place in Therapy, and Adverse Events

Aztreonam is a relatively old monobactam antibiotic that historically has been used intravenously to treat gram-negative bacteria by binding to the cell wall penicillin-binding proteins, leading to cell wall destruction. The parenteral formulation contains arginine to stabilize the formulation's pH; however, repeated exposure to arginine has been shown to cause airway inflammation and coughing.[162,163] The nebulized aztreonam solution (Cayston) is a newly formulated lyophilized lysine salt approved for chronic suppressive therapy of respiratory symptoms in patients with CF. Aztreonam lysine is indicated for patients 7 years and older with FEV_1 between 25% and 75% of predicted values not colonized with *Burkholderia cepacia*. The inhaled formulation of aztreonam is only administered using the Altera nebulizer system, which is designed to produce appropriate-sized particles to achieve high sputum and low systemic concentrations over a treatment period of 2 to 3 minutes. Nebulized aztreonam is dosed three times a day at least 4 hours apart, consistent with other antibiotics that require multiple daily doses secondary to the time-dependent killing.[164] Interestingly, patients with mild lung impairment treated for 4 weeks with inhaled aztreonam did not demonstrate significant improvement in respiratory symptoms; however, patients with an FEV_1 lower than 90% experienced a greater response.[165] Open-label studies of eradication of early *P. aeruginosa* in pediatric patients are currently under way.

Because nebulized aztreonam is fairly new to US markets, most adverse events reported are based on observations from clinical trials and may not reflect the rates observed in a clinical setting. The most common adverse reactions reported were cough, nasal congestion, wheezing, and pharyngolaryngeal pain. Short-acting bronchodilators provide a greater reduction in *P. aeruginosa* density as well as improved FEV_1 and sputum drug concentrations when administered between 15 minutes and 4 hours before each dose.[166,167]

COLISTIMETHATE

Mechanism, Place in Therapy, and Adverse Events

Colistimethate sodium is a polymyxin antibiotic that acts as a cationic detergent damaging bacterial cytoplasmic membranes of gram-negative organisms, causing

leakage of intracellular substances and eventually cell death. Colistin has been aerosolized for several years for eradication and chronic suppression of *P. aeruginosa.* Coincidently, there is a paucity of large, randomized, controlled studies, but colistin has been reported to be used therapeutically in prevention or eradication of bacteria in CF, treatment of hospital-acquired pneumonia, and suppressive therapy in non-CF bronchiectasis.[153] The Cystic Fibrosis Foundation Pulmonary Guidelines Committee found insufficient evidence to recommend for or against the use of colistin for chronic *P. aeruginosa* infection, but the agent was included in the European guidelines on inhaled medications in CF.[160,168]

Compared with other nebulized antimicrobials, colistin has a higher rate and severity of pulmonary adverse events, nephrotoxicity, and bronchospasms. After reconstitution of colistimethate, the drug molecule is hydrolyzed into two active components, polymyxin E1 and polymyxin E2. In animal models, polymyxin E1 can cause localized inflammation of the airway epithelia and eosinophilic infiltration. When colistimethate is used for inhalational therapy, the colistimethate solution should be used promptly after reconstitution to limit the potential risk of lung toxicity.

PENTAMIDINE

Mechanism, Place in Therapy, and Adverse Events

Pneumocystis jirovecii (formerly known as *Pneumocystis carinii*) pneumonia is an opportunistic infection that historically had a high rate of mortality, which has since decreased because of the routine use of prophylaxis. *P. carinii* is an animal commensal, whereas *P. jirovecii* is the human commensal and pathogen. PCP as an acronym for *Pneumocystis* pneumonia has been retained since the change in nomenclature.[169,170] In severe cases of PCP, such as adult patients requiring mechanical ventilation, mortality can approach up to 50%; PCP is associated with an even higher rate of mortality in children.[171] Disease states associated with immunosuppression are typical candidates for *Pneumocystis* prophylaxis, including patients with human immunodeficiency virus (HIV), solid organ transplant recipients, and patients with hematologic malignancies.

Pentamidine is categorized as an antiprotozoal and acts by interfering with protein synthesis by inhibiting oxidative phosphorylation of nucleotides and nucleic acids into protozoa RNA and DNA.[172] Clinical trials have proven a slight inferiority of aerosolized pentamidine compared with trimethoprim-sulfamethoxazole, which has led to the Infectious Disease Society of America, Centers for Disease Control and Prevention (CDC), and American Academy of Pediatrics to recommend aerosolized pentamidine as a secondary alternative for prevention of PCP in patients with HIV infection.[173] Aerosolized pentamidine is not recommended for the treatment of PCP because of limited efficacy and more frequent relapses.[173]

Aerosol administration of pentamidine is associated with fewer systemic adverse events than oral administration of prophylactic agents. Respiratory symptoms include cough, wheezing, shortness of breath, and reversible bronchospasms. Other effects include fatigue, dizziness or lightheadedness, fever, throat irritation, conjunctivitis, decreased appetite, nephrotoxicity, glucose intolerance, and allergic reactions.[172] Nebulized pentamidine should be administered in a negative pressure room and through a Respigard II, which routes exhaled breaths through a microfilter to avoid potential adverse events to health care workers in the immediate treatment area.

ANTIVIRAL AGENTS

RIBAVIRIN

Mechanism, Place in Therapy, and Adverse Events

Ribavirin is a synthetic nucleoside analogue that disrupts viral protein synthesis through inhibition of messenger ribonucleic acid (mRNA) expression. Oral ribavirin is used in combination with parenteral pegylated interferon alfa-2a for treatment of chronic hepatitis C. Nebulized ribavirin is the only FDA-approved agent for the treatment of hospitalized infants and children with respiratory syncytial virus (RSV) lower respiratory tract infections (see Chapter 26).[174] However, routine use is not recommended and should be reserved for life-threatening RSV infections because of lack of consistent efficacy data and potential risks to health care workers administering the aerosol.[175-177] Nebulized ribavirin has also been used in treating severe influenza virus infections; however, it does not appear to be beneficial other than reducing the duration of fever in hospitalized children.[178]

In nonmechanically ventilated infants, aerosolized ribavirin should be administered in an oxygen hood from the small particle aerosol generator (SPAG-2). Special precautions are essential with mechanically ventilated patients to prevent complications and to reduce the risk of crystalline precipitation in the circuit. The use of one-way valves in the inspiratory lines, a breathing circuit filter in the expiratory line, and frequent monitoring and filter placement are effective in preventing these complications and subsequent ventilator dysfunction.

Adverse events attributed to nebulized ribavirin are uncommon but can include sudden deterioration and adverse cardiovascular effects. The most common reported adverse events include conjunctival irritation, rash, and transient wheezing. Techniques to reduce environmental exposure are highly recommended to reduce risk of toxicity to the health care provider and surrounding staff. Ribavirin is FDA pregnancy

category X; thus pregnant women should not directly care for patients receiving aerosolized ribavirin. Because aerosolized particles of ribavirin can precipitate on contact lenses, the use of protective goggles or glasses is recommended.[174]

IMMUNOMODULATORS

PALIVIZUMAB

Mechanism, Place in Therapy, and Adverse Events

Palivizumab is a humanized monoclonal antibody with neutralizing activity against the F protein of RSV. It is given intramuscularly on a monthly basis at a dose of 15 mg/kg/dose throughout the annual RSV season. Typically, RSV activity is between November and March, with a peak in January or February. Communities in the southern United States, particularly Florida, tend to experience earlier onsets of RSV. Palivizumab has demonstrated benefit in protecting against RSV hospitalization in premature infants with underlying prematurity, chronic lung disease of infancy, and congenital heart disease.[179-181] Five monthly doses of palivizumab provides more than 20 weeks of protective serum antibody concentrations.[182] However, cost considerations have led to restrictive guideline recommendations for high-risk infants from the American Academy of Pediatrics, including full-term and premature infants with either chronic lung disease, congenital heart disease, or congenital abnormalities of the airway.[175]

Adverse reactions to palivizumab are extremely rare. The most common reported reactions include rash, fever, local injection site reactions, and, rarely, anaphylaxis.[182]

OMALIZUMAB

Mechanism, Place in Therapy, and Adverse Events

Omalizumab is a recombinant humanized monoclonal anti-IgE antibody that binds to the same receptor of the IgE molecule on basophils and mast cells. In turn, omalizumab inhibits the release of free IgE from mast cells in response to an allergen exposure and has been shown to decrease the incidence of asthma exacerbations.[183] Subcutaneous omalizumab is recommended as adjunctive therapy in patients 12 years and older who have allergies and severe persistent asthma that is inadequately controlled with the combination of high-dose inhaled corticosteroids and long-acting β-agonists.[8] There is no indication for the use of omalizumab in the treatment of other allergic conditions, including the relief of acute bronchospasms or status asthmaticus.[183]

Adverse reactions include headache, dizziness, fatigue, and local injection site reactions. Although rare, anaphylactic reactions have occurred after the first and subsequent doses in patients who presented no identifiable triggers. Patients should be monitored, and medications for treatment of severe allergic reactions should be readily available.[183]

INVESTIGATIONAL AGENTS

BRONCHODILATORS

Simplifying pharmacologic regimens to bronchodilating agents is fundamental to increasing patient compliance and controlling symptoms of asthma and COPD. The potential of a single drug with a long duration of action or with a bifunctional mechanism of action presents a new approach to the treatment of restrictive respiratory diseases.

Aclidinium bromide is a novel long-acting anticholinergic agent that recently obtained FDA approval for long-term maintenance treatment of bronchospasms associated with COPD.[184] When compared with other bronchodilatory agents in vitro, aclidinium demonstrated potent anticholinergic activity comparable to both tiotropium and ipratropium. Aclidium displayed a faster onset of action than tiotropium and a significantly longer duration of action versus ipratropium, allowing for a 24-hour duration of action.[185] Clinical studies evaluating dose efficacy and safety have resulted in improvements in bronchodilation, health status, and dyspnea in patients with COPD with a relatively low incidence of adverse events compared with placebo.[186]

Secondary to the proven clinical efficacy of inhaled anticholinergics and β_2-agonists, there has been recent interest in the development of combining both pharmacologic agents for the treatment of asthma and COPD. GSK-961081 is a novel long-acting muscarinic receptor antagonist/β_2-adrenergic receptor agonist (MABA) bronchodilator that is currently in clinical studies. GSK-961081 has a dual mechanism of action that covalently links a muscarinic antagonist and a β_2-agonist within a single drug molecule. In phase I randomized double-blind, placebo-controlled studies of healthy volunteers, GSK961081 was generally well tolerated and demonstrated evidence of bronchodilation more than 24 hours after a single dose and after seven consecutive daily doses.[187] Phase 2 studies with GSK-96108 are currently under way.

ANTIMICROBIALS

The emerging recognition of aerosol antibiotics' role as an integral part of treatment regimens in patients with chronic airway infections has stimulated several efforts in drug development research. There have been significant advances in the development of novel aerosolized antibiotic formulations, including a liposomal aminoglycoside and fluoroquinolone inhalation solution that are in various stages of clinical development.

Amikacin is an aminoglycoside antibiotic with a similar mechanism of action to tobramycin; it is currently in phase III studies. Liposomal amikacin is being

developed as an inhaled treatment option for gram-negative infections aerosolized with an eFlow nebulizer. Theoretically this novel formulation is advantageous because the liposomes have been shown to penetrate biofilms in vitro, which would allow for sustained high drug concentrations in the lung and potentially improve compliance and clinical outcomes.[191] Once-daily doses of the liposomal amikacin have been shown to be equivalent to twice-daily tobramycin in rat lung models, and a sustained effect in FEV_1 versus placebo has been observed in human clinical studies.[191,192]

Inhalational levofloxacin is a fluoroquinolone antibiotic that acts by inhibiting DNA gyrase of bacterial pathogens and promoting breakage of bacterial DNA strains. In contrast to other antimicrobials, in vitro studies of aerosolized levofloxacin in patients with CF demonstrated effectiveness against P. aeruginosa in the presence of sputum and biofilm and in anaerobic environments.[193,194] Further clinical studies have also demonstrated promising results in patients with CF with reductions in *P. aeruginosa* density and patient need for additional antipseudomonal antibiotics, as well as improvements in FEV_1.[195,196]

Case Study

A 50-kg, 15-year-old boy with a history of asthma presents to the emergency department (ED) with dyspnea with audible wheezing and tachypnea. The patient has taken his prescribed medications of albuterol and montelukast at home with no relief of symptoms before presenting to the ED.

A physical examination revealed a heart rate of 110 beats per minute and a respiratory rate of 40 breaths per minute with signs of accessory muscle use. Auscultation revealed decreased breath sounds with inspiratory and expiratory wheezing. Sa_{O_2} was 83% on room air. An arterial blood gas (ABG) was ordered with the following results: pH of 7.5, Pa_{CO_2} of 27 mm Hg, and Pa_{O_2} of 75 mm Hg.

Which of the following is the best treatment regimen for this patient's asthma exacerbation? (NOTE: More than one answer may be acceptable.)

1. Oxygen to achieve Sa_{O_2} 90% or higher
2. Levalbuterol 3.75 mg via nebulizer every 20 minutes for 3 doses
3. Salmeterol 1 puff (50 μg) every 30 minutes
4. Ipratropium 25 mg via nebulizer every 20 minutes for 3 doses

See Evolve Resources for answers.

Key Points

- Adult dosage regimens are not always appropriate for pediatric patients, because there are several pharmacokinetic differences between children and adults, such as the gastric motility, volume of distribution, and age-dependent activity of drug-metabolizing enzymes.
- β-adrenergic agonists are the cornerstone treatment of bronchoconstrictions in pediatric asthma, COPD, and exercise-induced bronchospasms. Short-acting selective agents are used for acute relief of symptoms and asthma exacerbations. There is no evidence to support the isolated use of parenteral β_2-agonists to treat severe asthma exacerbations.
- The most common adverse effect observed with the use of β-adrenergic agonists is tremors through excessive activation of β_2 receptors in skeletal muscle. Tachycardia and vasodilation are also observed when β receptors are stimulated on the heart and peripheral vasculature.
- Hypokalemia can occur by transient activation of the sodium-potassium pump and transport of potassium intracellularly. Headache, nervousness, dizziness, palpitations, cough, nausea, vomiting, and throat irritation may also occur.
- LABAs have a duration of action of at least 12 hours, with an onset of action that occurs approximately 30 minutes after administration. Aerosolized LABAs, anticholinergics, leukotriene modifiers, and corticosteroids are used for maintenance of asthma symptoms and should not be used for acute symptom relief.
- Oropharyngeal candidiasis is often an adverse effect in patients receiving corticosteroids by inhalation. It is important to counsel patients to rinse their mouth with water after each administration to help reduce the chance of local adverse events.
- Montelukast is the most widely used leukotriene modifier and is indicated for treatment in children 6 months or older. Zileuton has been shown to be effective in the treatment of cold air–induced, aspirin-intolerant, exercise-induced bronchospasms and nocturnal asthma. Zafirlukast and montelukast are effective in improving asthma symptoms and treating allergic rhinitis and should be considered in patients with poor inhaler technique and those who are noncompliant with inhaled corticosteroid therapy.
- NAC acts by splitting sulfide bonds in DNA that leads to a reduction in viscosity and elasticity of airway mucus. Dornase alfa is an enzyme that selective cleaves DNA, facilitating mucus clearance in the lung.
- Nebulized ribavirin is the only FDA-approved agent for the treatment of hospitalized infants and children with respiratory syncytial virus (RSV) lower respiratory tract infections. Palivizumab and omalizumab are monoclonal antibodies used for RSV prophylaxis and treatment of asthma, respectively. Palivizumab is indicated for infants at high risk for an RSV infection, including those with chronic lung disease, congenital heart disease, or congenital abnormalities of the airway. Subcutaneous omalizumab is recommended as adjunctive therapy in patients who have allergies and severe persistent asthma that is not adequately controlled with conventional therapy.
- Tobramycin and aztreonam are typically used for chronic suppressive therapy in patients with CF colonized with *P. aeruginosa.* Chronic suppressive therapy cycles between 28-days-on and 28-days-off therapy to suppress bacterial burden. Pentamidine is used for prophylaxis for PCP pneumonia caused by *P. jirovecii,* most commonly for patients with a suppressed immune system.

Assessment Questions

See Evolve Resources for answers.

1. Which of the following is a *true* statement?
   - I. Fast- and short-acting β-adrenergic agents are best used for rescue of symptoms, whereas long-acting agents are best used for maintenance therapy.
   - II. Levalbuterol is more safe and efficacious than albuterol for the treatment of bronchospasms in adults and children.
   - III. Administration using a handheld MDI with a spacer device is equivalent to nebulized β_2-agonist therapy in children and adults.
   - IV. For an acute asthma exacerbation, albuterol is not recommended to be administered continuously through a nebulizer.

   A. I, II, and III
   B. I and III
   C. II and IV
   D. Only III
2. Overuse of short-acting inhaled β_2-agonists has been associated with increased mortality from asthma. Which of the following are considered short-acting β_2-agonists?
   A. Racemic epinephrine, formoterol, albuterol
   B. Formoterol, salmeterol, levalbuterol
   C. Albuterol, levalbuterol, salbutamol
   D. Formoterol, salmeterol, salbutamol, levalbuterol
3. Which of the following is a *true* statement?
   A. Gastric pH is increased in neonates than in adults.
   B. Larger weight-based doses are sometimes required in pediatrics because of a higher volume of distribution.
   C. Metabolic enzymes involved in metabolizing medications will reach close to adult values at 1 year of age.
   D. Disease states such as cystic fibrosis have unique pharmacokinetic characteristics that warrant different dosing regimens.
   E. A, B, and C
4. JF is a 15-year-old girl with mild persistent asthma who is being discharged from the hospital with a prescription of salmeterol/fluticasone. Which of the following is important to counsel the patient on before initiating treatment?
   - I. Long-term use may lead to HPA axis suppression
   - II. Rinse the mouth with water after each administration
   - III. Should not be used for acute symptoms of asthma

   A. I and II
   B. II and III
   C. III
   D. I, II, and III
5. Which of the following is a *true* statement regarding leukotriene modifiers?
   A. Zafirlukast prevents bronchoconstriction by antagonizing leukotriene binding to the $CysLT_1$ receptor.
   B. Theophylline and warfarin are contraindicated with zileuton.
   C. Leukotriene modifiers are efficacious in short-term control of mild persistent asthma in children.
   D. Zafirlukast should be administered with food to increase bioavailability.
6. Which of the following is commonly used to increase mucociliary clearance in patients with bronchiolitis and cystic fibrosis by absorbing water from the submucosa of the airway wall lining, which allows thick mucus to be expectorated more easily?
   A. NAC
   B. Albuterol
   C. 3% hypertonic sodium chloride
   D. Dornase alpha
7. JW, a 12-year-old boy with a history of poorly controlled asthma, presents to the emergency department in acute respiratory distress. Which of the following combinations of inhalation solution is safe to mix together in the nebulizer?
   - I. Albuterol and ipratropium
   - II. Hypertonic saline and cromolyn
   - III. Levalbuterol and budesonide

   A. I and II
   B. II and III
   C. I and III
   D. I, II, and III
8. BM is a premature neonate born at 23 weeks with bronchopulmonary dysplasia who qualifies for immunoprophylaxis of a lower respiratory tract infection. _____ is the monoclonal antibody indicated for immunoprophylaxis of premature infants for _____respiratory virus.
   A. Omalizumab, metapneumovirus
   B. Dornase alfa, rotavirus
   C. Palivizumab, respiratory syncytial virus
   D. Cromolyn, herpes simplex virus
9. Which of the following is a *true* statement?
   A. Drug absorption is the primary determinant for the rate of drug to be dispersed along the small intestine in infants and children.
   B. Patients requiring three or more canisters of a short-acting β_2-agonist per month are at a higher risk of mortality from asthma as a result of tolerance and lessened bronchodilatory effects.
   C. The parenteral form of aztreonam contains lysine and should not be used for aerosolization, because repeated exposure has been shown to cause airway inflammation.
   D. Hypertonic saline is a hydrating agent used as adjunctive therapy for pulmonary complications involving viscid mucus secretions.
10. Which of the following is the mechanism of action for amikacin?
    A. Inhibits DNA gyrase of bacterial pathogens and promotes breakage of bacterial DNA strains
    B. Binds to bacterial ribosomal subunits, which inhibits protein synthesis
    C. Disrupts protein synthesis through inhibition of messenger ribonucleic acid (mRNA) expression
    D. Inhibits oxidative phosphorylation of nucleotides and nucleic acids into RNA and DNA

REFERENCES

1. U.S. Food & Drug Administration. *Pediatric Product Development*. 2012. Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm. Accessed 9/05/2012.
2. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology–drug disposition, action, and therapy in infants and children. *N Engl J Med*. 2003;349(12):1157-1167.
3. Gupta M, Brans YW. Gastric retention in neonates. *Pediatrics*. 1978;62(1):26-29.
4. Shimada T, Yamazaki H, Mimura M, Inui Y, Guengerich FP. Interindividual variations in human liver cytochrome P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic chemicals: studies with liver microsomes of 30 Japanese and 30 Caucasians. *J Pharmacol Exp Ther*. 1994; 270(1):414-423.
5. Wrighton SA, Stevens JC. The human hepatic cytochromes P450 involved in drug metabolism. *Crit Rev Toxicol*. 1992; 22(1):1-21.
6. Johnson TN, Tucker GT, Rostami-Hodjegan A. Development of CYP2D6 and CYP3A4 in the first year of life. *Clin Pharmacol Ther*. 2008;83(5):670-671.
7. Cazzola M, Page CP, Calzetta L, Matera MG. Pharmacology and therapeutics of bronchodilators. *Pharmacol Rev*. 2012; 64(3):450-504.
8. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. *J Allergy Clin Immunol*. 2007;120(suppl 5):S94–S138.
9. Leversha AM, Campanella SG, Aickin RP, Asher MI. Costs and effectiveness of spacer versus nebulizer in young children with moderate and severe acute asthma. *J Pediatr*. 2000;136(4):497-502.
10. Pollart SM, Compton RM, Elward KS. Management of acute asthma exacerbations. *Am Fam Physician*. 2011;84(1):40-47.
11. Cates CJ, Crilly JA, Rowe BH. Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. *Cochrane Database Syst Rev*. 2006;(2):CD000052.
12. Browne GJ, Lam LT. Single-dose intravenous salbutamol bolus for managing children with acute severe asthma in the emergency department: reanalysis of data. *Pediatr Crit Care Med*. 2002;3(2):117-123.
13. Gao Smith F, Perkins GD, Gates S, et al. Effect of intravenous beta-2 agonist treatment on clinical outcomes in acute respiratory distress syndrome (BALTI-2): a multicentre, randomised controlled trial. *Lancet*. 2012;379(9812):229-235.
14. U.S. Food & Drug Administration. *Asthma and COPD Inhalers That Contain Ozone-depleting CFCs to be Phased Out; Alternative Treatments Available*. 2010. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm208302.htm. Accessed 9/05/2012.
15. Leach CL, Colice GL. A pilot study to assess lung deposition of HFA-beclomethasone and CFC-beclomethasone from a pressurized metered dose inhaler with and without add-on spacers and using varying breathhold times. *J Aerosol Med Pulm Drug Deliv*. 2010;23(6):355-361.
16. Leach CL, Davidson PJ, Hasselquist BE, Boudreau RJ. Lung deposition of hydrofluoroalkane-134a beclomethasone is greater than that of chlorofluorocarbon fluticasone and chlorofluorocarbon beclomethasone: a cross-over study in healthy volunteers. *Chest*. 2002;122(2):510-516.
17. Cockcroft DW. Inhaled beta2-agonists and airway responses to allergen. *J Allergy Clin Immunol*. 1998;102(5):S96-S99.
18. Dolovich M. Aerosol delivery to children: what to use, how to choose. *Pediatr Pulmonol Suppl*. 1999;18:79-82.
19. Salpeter SR, Ormiston TM, Salpeter EE. Cardiovascular effects of beta-agonists in patients with asthma and COPD: a meta-analysis. *Chest*. 2004;125(6):2309-2321.
20. Leikin JB, Linowiecki KA, Soglin DF, Paloucek F. Hypokalemia after pediatric albuterol overdose: a case series. *Am J Emerg Med*. 1994;12(1):64-66.
21. Carroll WD, Jones PW, Boit P, Clayton S, Cliff I, Lenney W. Childhood evaluation of salmeterol tolerance–a double-blind randomized controlled trial. *Pediatr Allergy Immunol*. 2010;21(2 Pt 1):336-344.
22. Salpeter SR, Ormiston TM, Salpeter EE. Meta-analysis: respiratory tolerance to regular beta2-agonist use in patients with asthma. *Ann Intern Med*. 2004;140(10):802-813.
23. Spitzer WO, Suissa S, Ernst P, et al. The use of beta-agonists and the risk of death and near death from asthma. *N Engl J Med*. 1992;326(8):501-506.
24. Smith L. Childhood asthma: diagnosis and treatment. *Curr Probl Pediatr*. 1993;23(7):271-305.
25. Kornecki A, Shemie SD. Bronchodilators and RSV-induced respiratory failure: agonizing about beta2 agonists. *Pediatr Pulmonol*. 1998;26(1):4-5.
26. Cates CJ, Lasserson TJ, Jaeschke R. Regular treatment with formoterol and inhaled steroids for chronic asthma: serious adverse events. *Cochrane Database Syst Rev*. 2009;(2):CD006924.
27. Cates CJ, Cates MJ. Regular treatment with salmeterol for chronic asthma: serious adverse events. *Cochrane Database Syst Rev*. 2008;(3):CD006363.
28. Rodrigo GJ, Moral VP, Marcos LG, Castro-Rodriguez JA. Safety of regular use of long-acting beta agonists as monotherapy or added to inhaled corticosteroids in asthma. A systematic review. *Pulm Pharmacol Ther*. 2009;22(1):9-19.
29. *PROVENTIL Oral Inhalation Solution, Albuterol Sulfate oral Inhalation Solution* [package insert]. Kenilworth, NJ: Schering Corporation; 2002.
30. *PROAIR HFA Oral Inhalation Aerosol, Albuterol Sulfate Oral Inhalation Aerosol* [package insert]. Horsham, Penn: L. Teva Respiratory; 2010.
31. *XOPENEX Inhalation Solution, Levalbuterol Hydrochloride Inhalation Solution* [package insert]. Marlborough, Mass: Sepracor Inc; 2004.
32. *XOPENEX HFA Oral Inhalation Aerosol, Levalbuterol Tartrate Oral Inhalation Aerosol* [package insert]. Marlborough, Mass: Sepracor Inc; 2005.
33. Gawchik SM, Saccar CL, Noonan M, Reasner DS, DeGraw SS. The safety and efficacy of nebulized levalbuterol compared with racemic albuterol and placebo in the treatment of asthma in pediatric patients. *J Allergy Clin Immunol*. 1999; 103(4):615-621.
34. Qureshi F, Zaritsky A, Welch C, Meadows T, Burke BL. Clinical efficacy of racemic albuterol versus levalbuterol for the treatment of acute pediatric asthma. *Ann Emerg Med*. 2005;46(1):29-36.
35. Berger WE. Levalbuterol: pharmacologic properties and use in the treatment of pediatric and adult asthma. *Ann Allergy Asthma Immunol*. 2003;90(6):583-591; quiz 591-592, 659.
36. Bio LL, Willey VJ, Poon CY. Comparison of levalbuterol and racemic albuterol based on cardiac adverse effects in children. *J Pediatr Pharmacol Ther*. 2011;16(3):191-198.
37. Scott VL, Frazee LA. Retrospective comparison of nebulized levalbuterol and albuterol for adverse events in patients with acute airflow obstruction. *Am J Ther*. 2003;10(5): 341-347.
38. Wheeler DS, Jacobs BR, Kenreigh CA, Bean JA, Hutson TK, Brilli RJ. Theophylline versus terbutaline in treating critically ill children with status asthmaticus: a prospective, randomized, controlled trial. *Pediatr Crit Care Med*. 2005; 6(2):142-147.
39. *Terbutaline Sulfate Injection* [package insert]. Bedford, Ohio: B.V. Laboratories; 2004.
40. Kelly HW, McWilliams BC, Katz R, Murphy S. Safety of frequent high dose nebulized terbutaline in children with acute severe asthma. *Ann Allergy*. 1990;64(2 Pt 2):229-233.

41. Tipton WR, Nelson HS. Frequent parenteral terbutaline in the treatment of status asthmaticus in children. *Ann Allergy*. 1987;58(4):252-256.
42. Fuglsang G, Pedersen S, Borgström L. Dose-response relationships of intravenously administered terbutaline in children with asthma. *J Pediatr*. 1989;114(2):315-320.
43. Pearlman DS, Chervinsky P, LaForce C, et al. A comparison of salmeterol with albuterol in the treatment of mild-to-moderate asthma. *N Engl J Med*. 1992;327(20):1420-1425.
44. Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Allen & Hanburys Limited UK Study Group. *Lancet*. 1994;344(8917):219-224.
45. Woolcock A, Lundback B, Ringdal N, Jacques LA. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. *Am J Respir Crit Care Med*. 1996;153(5):1481-1488.
46. Pauwels RA, Löfdahl CG, Postma DS. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. *N Engl J Med*. 1997;337(20):1405-1411.
47. Lazarus SC, Boushey HA, Fahy JV, et al. Long-acting beta2-agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial. *JAMA*. 2001;285(20):2583-2593.
48. Gappa M, Zachgo W, von Berg A, et al. Add-on salmeterol compared to double dose fluticasone in pediatric asthma: a double-blind, randomized trial (VIAPAED). *Pediatr Pulmonol*. 2009;44(11):1132-1142.
49. Ni Chroinin M, Lasserson TJ, Greenstone I, Ducharme FM. Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children. *Cochrane Database Syst Rev*. 2009;(3):CD007949.
50. Lemanske Jr RF, Mauger DT, Sorkness CA, et al. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. *N Engl J Med*. 2010;362(11):975-985.
51. *SEREVENT Inhalation Aerosol, Salmeterol Xinafoate Inhalation Aerosol* [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2004.
52. Condemi JJ, Goldstein S, Kalberg C, Yancey S, Emmett A, Rickard K. The addition of salmeterol to fluticasone propionate versus increasing the dose of fluticasone propionate in patients with persistent asthma. Salmeterol Study Group. *Ann Allergy Asthma Immunol*. 1999;82(4):383-389.
53. Murray JJ, Church NL, Anderson WH, et al. Concurrent use of salmeterol with inhaled corticosteroids is more effective than inhaled corticosteroid dose increases. *Allergy Asthma Proc*. 1999;20(3):173-180.
54. Bartow RA, Brogden RN. Formoterol: An update of its pharmacological properties and therapeutic efficacy in the management of asthma. *Drugs*. 1998;55(2):303-322.
55. Pohunek P, Matulka M, Rybnicek O, Kopriva F, Honomichlová H, Svobodová T. Dose-related efficacy and safety of formoterol (Oxis) Turbuhaler compared with salmeterol Diskhaler in children with asthma. *Pediatr Allergy Immunol*. 2004;15(1):32-39.
56. *FORADIL AEROLIZER Inhalation Powder, Formoterol Fumarate Inhalation Powder* [package insert]. Kenilworth, NJ: S. Corporation; 2006.
57. *PERFOROMIST Inhalation Solution, Formoterol Fumarate Inhalation Solution* [package insert]. Napa, Calif: Dey; 2007.
58. Dahl R, Chung KF, Buhl R, et al. Efficacy of a new once-daily long-acting inhaled beta2-agonist indacaterol versus twice-daily formoterol in COPD. *Thorax*. 2010;65(6):473-479.
59. LaForce C, Alexander M, Deckelmann R, et al. Indacaterol provides sustained 24 h bronchodilation on once-daily dosing in asthma: a 7-day dose-ranging study. *Allergy*. 2008;63(1):103-111.
60. Neumar RW, Otto CW, Link MS, et al. Part 8: adult advanced cardiovascular life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122(18 suppl 3):S729-S767.
61. *ISUPREL IV Injection, Isoproterenol HCL IV Injection* [package insert]. Lake Forest, Ill: Hospira; 2004.
62. Kleinman ME, Chameides L, Schexnayder SM, et al. Part 14: pediatric advanced life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122(18 suppl 3):S876-S908.
63. Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol*. 2010;126(3):477-480.e1-42.
64. Kattwinkel J, Perlman JM, Aziz K, et al. Neonatal resuscitation: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Pediatrics*. 2010;126(5):e1400-e1413.
65. Hegenbarth MA. Preparing for pediatric emergencies: drugs to consider. *Pediatrics*. 2008;121(2):433-443.
66. Rosekrans JA. Viral croup: current diagnosis and treatment. *Mayo Clin Proc*. 1998;73(11):1102-1106; discussion 1107.
67. Wright RB, Pomerantz WJ, Luria JW. New approaches to respiratory infections in children. Bronchiolitis and croup. *Emerg Med Clin North Am*. 2002;20(1):93-114.
68. Rodrigo GJ, Nannini LJ. Comparison between nebulized adrenaline and beta2 agonists for the treatment of acute asthma. A meta-analysis of randomized trials. *Am J Emerg Med*. 2006;24(2):217-222.
69. *Epinephrine Oral Inhalation Aerosol* [package insert]. West Roxbury, Mass: Armstrong Pharmaceuticals; 2004.
70. Brunton L. *Manual of Pharmacology and Therapeutics*. New York: McGraw-Hill; 2008.
71. Rodrigo GJ, Rodrigo C. The role of anticholinergics in acute asthma treatment: an evidence-based evaluation. *Chest*. 2002;121(6):1977-1987.
72. Craven D, Kercsmar CM, Myers TR, O'riordan MA, Golonka G, Moore S. Ipratropium bromide plus nebulized albuterol for the treatment of hospitalized children with acute asthma. *J Pediatr*. 2001;138(1):51-58.
73. Goggin N, Macarthur C, Parkin PC. Randomized trial of the addition of ipratropium bromide to albuterol and corticosteroid therapy in children hospitalized because of an acute asthma exacerbation. *Arch Pediatr Adolesc Med*. 2001;155(12):1329-1334.
74. *ATROVENT HFA Oral Inhalation Aerosol, Ipratropium Bromide HFA oral inhalation aerosol* [package insert]. Ridgefield, Conn: Boehringer Ingelheim Pharmaceuticals; 2004.
75. *DUONEB Inhalation Solution, Albuterol Sulfate and Ipratropium Bromide Inhalation Solution* [package insert]. Napa, Calif: Dey; 2005.
76. *COMBIVENT Inhalation Aerosol, Albuterol Sulfate and Ipratropium Bromide Inhalation Aerosol* [package insert]. Ridgefield, Conn: Boehringer Ingelheim Pharmaceutical; 2005.
77. Baigelman W, Chodosh S. Bronchodilator action of the anticholinergic drug, ipratropium bromide (Sch 1000), as an aerosol in chronic bronchitis and asthma. *Chest*. 1977;71(3):324-328.
78. "Inactive" ingredients in pharmaceutical products: update (subject review). American Academy of Pediatrics Committee on Drugs. *Pediatrics*. 1997;99(2):268-278.
79. *CUVPOSA Oral solution, Glycopyrrolate Oral Solution* [package insert]. Atlanta, GA: Shionogi Pharma Inc; 2010.
80. Kelly HW, Murphy S. Corticosteroids for acute, severe asthma. *DICP*. 1991;25(1):72-79.
81. Pedersen S, O'Byrne P. A comparison of the efficacy and safety of inhaled corticosteroids in asthma. *Allergy*. 1997;52(suppl 39):1-34.

82. Edmonds ML, Camargo CA, Pollack CV, Rowe BH. Early use of inhaled corticosteroids in the emergency department treatment of acute asthma. *Cochrane Database Syst Rev*. 2001;(1):CD002308.
83. Rowe BH, Spooner C, Ducharme FM, Bretzlaff JA, Bota GW. Early emergency department treatment of acute asthma with systemic corticosteroids. *Cochrane Database Syst Rev*. 2001;(1):CD002178.
84. Becker JM, Arora A, Scarfone RJ, et al. Oral versus intravenous corticosteroids in children hospitalized with asthma. *J Allergy Clin Immunol*. 1999;103(4):586-590.
85. Allen DB, Bielory L, Derendorf H, Dluhy R, Colice GL, Szefler SJ. Inhaled corticosteroids: past lessons and future issues. *J Allergy Clin Immunol*. 2003;112(suppl 3):S1-S40.
86. Kelly HW, Sternberg AL, Lescher R, et al. Effect of inhaled glucocorticoids in childhood on adult height. *N Engl J Med*. 2012;367(10):904-912.
87. Irwin RS, Richardson ND. Side effects with inhaled corticosteroids: the physician's perception. *Chest*. 2006;130(suppl 1): 41S-53S.
88. Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. *N Engl J Med*. 2000;343(15):1064-1069.
89. Erceg D, Nenadic N, Plavec D, Nogalo B, Turkalj M. Inhaled corticosteroids used for the control of asthma in a "real-life" setting do not affect linear growth velocity in prepubertal children. *Med Sci Monit*. 2012;18(9):CR564-568.
90. Wenzel SE. New approaches to anti-inflammatory therapy for asthma. *Am J Med*. 1998;104(3):287-300.
91. Leff JA, Busse WW, Pearlman D, et al. Montelukast, a leukotriene-receptor antagonist, for the treatment of mild asthma and exercise-induced bronchoconstriction. *N Engl J Med*. 1998;339(3):147-152.
92. Drazen J. Clinical pharmacology of leukotriene receptor antagonists and 5-lipoxygenase inhibitors. *Am J Respir Crit Care Med*. 1998;157(6 Pt 2):S233-237; discussion S247-248.
93. McFadden Jr ER, Gilbert IA. Exercise-induced asthma. *N Engl J Med*. 1994;330(19):1362-1367.
94. Bernstein PR. Chemistry and structure-activity relationships of leukotriene receptor antagonists. *Am J Respir Crit Care Med*. 1998;157(6 Pt 2):S220-225; discussion S225-226, S247-248.
95. Aharony D. Pharmacology of leukotriene receptor antagonists. *Am J Respir Crit Care Med*. 1998;157(6 Pt 2):S214-218; discussion S218-219, S247-248.
96. Aharony D. Pharmacology of leukotriene receptor antagonists. *Am J Respir Crit Care Med*. 1998;157(6 Pt 2):S214-S218; discussion S218-219, S247-248.
97. Chung KF. Leukotriene receptor antagonists and biosynthesis inhibitors: potential breakthrough in asthma therapy. *Eur Respir J*. 1995;8(7):1203-1213.
98. Liu MC, Dubé LM, Lancaster J. Acute and chronic effects of a 5-lipoxygenase inhibitor in asthma: a 6-month randomized multicenter trial. Zileuton Study Group. *J Allergy Clin Immunol*. 1996;98(5 Pt 1):859-871.
99. Courtney AU, McCarter DF, Pollart SM. Childhood asthma: treatment update. *Am Fam Physician*. 2005;71(10): 1959-1968.
100. Hakim F, Vilozni D, Adler A, Livnat G, Tal A, Bentur L. The effect of montelukast on bronchial hyperreactivity in preschool children. *Chest*. 2007;131(1):180-186.
101. Knorr B, Nguyen HH, Kearns GL, et al. Montelukast dose selection in children ages 2 to 5 years: comparison of population pharmacokinetics between children and adults. *J Clin Pharmacol*. 2001;41(6):612-619.
102. Moeller A, Lehmann A, Knauer N, Albisetti M, Rochat M, Johannes W. Effects of montelukast on subjective and objective outcome measures in preschool asthmatic children. *Pediatr Pulmonol*. 2008;43(2):179-186.
103. Horwitz RJ, McGill KA, Busse WW. The role of leukotriene modifiers in the treatment of asthma. *Am J Respir Crit Care Med*. 1998;157(5 Pt 1):1363-1371.
104. Bisgaard H. A randomized trial of montelukast in respiratory syncytial virus postbronchiolitis. *Am J Respir Crit Care Med*. 2003;167(3):379-383.
105. *ZYFLO Oral Tablets, Zileuton Oral Tablets* [package insert]. Lexington, Mass: Critical Therapeutics; 2005.
106. Holloway J, Ferriss J, Groff J, Craig TJ, Klinek M. Churg-Strauss syndrome associated with zafirlukast. *J Am Osteopath Assoc*. 1998;98(5):275-278.
107. Knoell DL, Lucas J, Allen JN. Churg-Strauss syndrome associated with zafirlukast. *Chest*. 1998;114(1):332-334.
108. Wechsler ME, Garpestad E, Flier SR, et al. Pulmonary infiltrates, eosinophilia, and cardiomyopathy following corticosteroid withdrawal in patients with asthma receiving zafirlukast. *JAMA*. 1998;279(6):455-457.
109. Kaliterna DM, Perković D, Radić M. Churg-Strauss syndrome associated with montelukast therapy. *J Asthma*. 2009;46(6):604-605.
110. Keogh KA, Specks U. Churg-Strauss syndrome: clinical presentation, antineutrophil cytoplasmic antibodies, and leukotriene receptor antagonists. *Am J Med*. 2003;115(4): 284-290.
111. Nassif EG, Weinberger M, Thompson R, Huntley W. The value of maintenance theophylline in steroid-dependent asthma. *N Engl J Med*. 1981;304(2):71-75.
112. Magnussen H, Reuss G, Jörres R. Theophylline has a dose-related effect on the airway response to inhaled histamine and methacholine in asthmatics. *Am Rev Respir Dis*. 1987;136(5):1163-1167.
113. *ELIXOPHYLLIN Oral Elixir, Theophylline Anhydrous Oral Elixir* [package insert]. St. Louis, Mo: Forest Pharmaceuticals; 2004.
114. van der Wouden JC, Tasche MJ, Bernsen RM, Uijen JH, de Jongste JC, Ducharme FM. Inhaled sodium cromoglycate for asthma in children. *Cochrane Database Syst Rev*. 2003;(3): CD002173.
115. Shapiro GG, Sharpe M, DeRouen TA, et al. Cromolyn versus triamcinolone acetonide for youngsters with moderate asthma. *J Allergy Clin Immunol*. 1991;88(5):742-748.
116. *INTAL Inhalation Aerosol, Cromolyn Sodium Inhalation Aerosol* [package insert]. Bristol, Tenn: King Pharmaceuticals; 2005.
117. Spivey WH, Skobeloff EM, Levin RM. Effect of magnesium chloride on rabbit bronchial smooth muscle. *Ann Emerg Med*. 1990;19(10):1107-1112.
118. Rowe BH, Bretzlaff JA, Bourdon C, Bota GW, Camargo Jr CA. Magnesium sulfate for treating exacerbations of acute asthma in the emergency department. *Cochrane Database Syst Rev*. 2000;(2):CD001490.
119. Rowe BH, Bretzlaff JA, Bourdon C, Bota GW, Camargo Jr CA. Intravenous magnesium sulfate treatment for acute asthma in the emergency department: a systematic review of the literature. *Ann Emerg Med*. 2000;36(3):181-190.
120. Cheuk DK, Chau TC, Lee SL. A meta-analysis on intravenous magnesium sulphate for treating acute asthma. *Arch Dis Child*. 2005;90(1):74-77.
121. Blitz M, Blitz S, Hughes R, et al. Aerosolized magnesium sulfate for acute asthma: a systematic review. *Chest*. 2005;128(1):337-344.
122. Blitz M, Blitz S, Beasely R, et al. Inhaled magnesium sulfate in the treatment of acute asthma. *Cochrane Database Syst Rev*. 2005;(4):CD003898.
123. Rogers DF. Mucoactive agents for airway mucus hypersecretory diseases. *Respir Care*. 2007;52(9):1176-1193; discussion 1193–1197.
124. *MUCOMYST Inhalation Solution, Acetylcysteine Inhalation Solution* [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2001.

125. Nair GB, Ilowite JS. Pharmacologic agents for mucus clearance in bronchiectasis. *Clin Chest Med*. 2012;33(2):363-370.
126. Grandjean EM, Berthet P, Ruffmann R, Leuenberger P. Efficacy of oral long-term N-acetylcysteine in chronic bronchopulmonary disease: a meta-analysis of published double-blind, placebo-controlled clinical trials. *Clin Ther*. 2000; 22(2):209-221.
127. Decramer M, Rutten-van Mölken M, Dekhuijzen PN, et al. Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo-controlled trial. *Lancet*. 2005;365(9470):1552-1560.
128. Wolf SJ, Heard K, Sloan EP, Jagoda AS. Clinical policy: critical issues in the management of patients presenting to the emergency department with acetaminophen overdose. *Ann Emerg Med*. 2007;50(3):292-313.
129. *Acetylcysteine Oral Solution, Solution for Inhalation, Acetylcysteine Oral Solution, Solution for Inhalation* [package insert]. Columbus, OH: Roxane Laboratories; 2007.
130. Konstan MW, Ratjen F. Effect of dornase alfa on inflammation and lung function: potential role in the early treatment of cystic fibrosis. *J Cyst Fibros*. 2012;11(2):78-83.
131. McCoy K, Hamilton S, Johnson C. Effects of 12-week administration of dornase alfa in patients with advanced cystic fibrosis lung disease. Pulmozyme Study Group. *Chest*. 1996;110(4):889-895.
132. Fuchs HJ, Borowitz DS, Christiansen DH, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group. *N Engl J Med*. 1994;331(10):637-642.
133. Wilmott RW, Amin RS, Colin AA, et al. Aerosolized recombinant human DNase in hospitalized cystic fibrosis patients with acute pulmonary exacerbations. *Am J Respir Crit Care Med*. 1996;153(6 Pt 1):1914-1917.
134. Quan JM, Tiddens HA, Sy JP, et al. A two-year randomized, placebo-controlled trial of dornase alfa in young patients with cystic fibrosis with mild lung function abnormalities. *J Pediatr*. 2001;139(6):813-820.
135. Shah PL, Scott SF, Knight RA, Marriott C, Ranasinha C, Hodson ME, et al. In vivo effects of recombinant human DNase I on sputum in patients with cystic fibrosis. *Thorax*. 1996;51(2):119-125.
136. Geller DE. Aerosolized dornase alfa in cystic fibrosis: is there a role in the management of patients with early obstructive lung disease? *Pediatr Pulmonol*. 1997;24(2):155-158; discussion 159-161.
137. *PULMOZYME Inhalation Solution, Dornase Alfa Inhalation Solution* [package insert]. South San Francisco, Calif: Genentech, Inc; 2005.
138. Aitken ML, Burke W, McDonald G, Shak S, Montgomery AB, Smith A. Recombinant human DNase inhalation in normal subjects and patients with cystic fibrosis. A phase 1 study. *JAMA*. 1992;267(14):1947-1951.
139. Elkins MR, Bye PT. Inhaled hypertonic saline as a therapy for cystic fibrosis. *Curr Opin Pulm Med*. 2006;12(6):445-452.
140. Robinson M, Regnis JA, Bailey DL, King M, Bautovich GJ, Bye PT. Effect of hypertonic saline, amiloride, and cough on mucociliary clearance in patients with cystic fibrosis. *Am J Respir Crit Care Med*. 1996;153(5):1503-1509.
141. Rosenfeld M, Ratjen F, Brumback L, et al. Inhaled hypertonic saline in infants and children younger than 6 years with cystic fibrosis: the ISIS randomized controlled trial. *JAMA*. 2012;307(21):2269-2277.
142. Wills P, Greenstone M. Inhaled hyperosmolar agents for bronchiectasis. *Cochrane Database Syst Rev*. 2006;(2):CD002996.
143. Kellett F, Redfern J, Niven RM. Evaluation of nebulised hypertonic saline (7%) as an adjunct to physiotherapy in patients with stable bronchiectasis. *Respir Med*. 2005;99(1):27-31.
144. Gibson RL, Burns JL, Ramsey BW. Pathophysiology and management of pulmonary infections in cystic fibrosis. *Am J Respir Crit Care Med*. 2003;168(8):918-951.
145. Dellon EP, Donaldson SH, Johnson R, Davis SD. Safety and tolerability of inhaled hypertonic saline in young children with cystic fibrosis. *Pediatr Pulmonol*. 2008;43(11):1100-1106.
146. Elkins MR, Robinson M, Rose BR, et al. A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. *N Engl J Med*. 2006;354(3):229-240.
147. Strube PJ, Hallam PL. Ketamine by continuous infusion in status asthmaticus. *Anaesthesia*. 1986;41(10):1017-1019.
148. Sarma VJ. Use of ketamine in acute severe asthma. *Acta Anaesthesiol Scand*. 1992;36(1):106-107.
149. Allen JY, Macias CG. The efficacy of ketamine in pediatric emergency department patients who present with acute severe asthma. *Ann Emerg Med*. 2005;46(1):43-50.
150. Howton JC, Rose J, Duffy S, Zoltanski T, Levitt MA. Randomized, double-blind, placebo-controlled trial of intravenous ketamine in acute asthma. *Ann Emerg Med*. 1996; 27(2):170-175.
151. Hemming A, MacKenzie I, Finfer S. Response to ketamine in status asthmaticus resistant to maximal medical treatment. *Thorax*. 1994;49(1):90-91.
152. *KETALAR, Ketamine Hydrochloride* [package insert]. Bristol, Tenn: Monarch Pharmaceuticals; 2004.
153. Le J, Ashley ED, Neuhauser MM, et al. Consensus summary of aerosolized antimicrobial agents: application of guideline criteria. Insights from the Society of Infectious Diseases Pharmacists. *Pharmacotherapy*. 2010;30(6):562-584.
154. Le Sou®f P. The meaning of lung dose. *Allergy*. 1999; 54(suppl 49):93-96.
155. Langton Hewer SC, Smyth AR. Antibiotic strategies for eradicating Pseudomonas aeruginosa in people with cystic fibrosis. *Cochrane Database Syst Rev*. 2009;(4):CD004197.
156. Ryan G, Singh M, Dwan K. Inhaled antibiotics for long-term therapy in cystic fibrosis. *Cochrane Database Syst Rev*. 2011;(3):CD001021.
157. Ramsey BW, Pepe MS, Quan JM, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. *N Engl J Med*. 1999;340(1):23-30.
158. Wiesemann HG, Steinkamp G, Ratjen F, et al. Placebo-controlled, double-blind, randomized study of aerosolized tobramycin for early treatment of Pseudomonas aeruginosa colonization in cystic fibrosis. *Pediatr Pulmonol*. 1998;25(2): 88-92.
159. Douglas TA, Brennan S, Gard S, et al. Acquisition and eradication of P. aeruginosa in young children with cystic fibrosis. *Eur Respir J*. 2009;33(2):305-311.
160. Flume PA, O'Sullivan BP, Robinson KA, et al. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *Am J Respir Crit Care Med*. 2007; 176(10):957-969.
161. *TOBI Inhalation Solution, Tobramycin Inhalation Solution* [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2011.
162. Dietzsch HJ, Gottschalk B, Heyne K, Leupoid W, Wunderlich P. Cystic fibrosis: comparison of two mucolytic drugs for inhalation treatment (acetylcysteine and arginine hydrochloride). *Pediatrics*. 1975;55(1):96-100.
163. *AZACTAM IV, IM Injection, Aztreonam IV, IM Injection* [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2007.
164. Oermann CM, Retsch-Bogart GZ, Quittner AL, et al. An 18-month study of the safety and efficacy of repeated courses of inhaled aztreonam lysine in cystic fibrosis. *Pediatr Pulmonol*. 2010;45(11):1121-1134.
165. Retsch-Bogart GZ, Quittner AL, Gibson RL, et al. Efficacy and safety of inhaled aztreonam lysine for airway pseudomonas in cystic fibrosis. *Chest*. 2009;135(5):1223-1232.

166. Retsch-Bogart GZ, Burns JL, Otto KL, et al. A phase 2 study of aztreonam lysine for inhalation to treat patients with cystic fibrosis and Pseudomonas aeruginosa infection. *Pediatr Pulmonol*. 2008;43(1):47-58.
167. *CAYSTON Inhalation Solution, Aztreonam Inhalation Solution* [package insert]. Foster City, Calif: Gilead Sciences; 2012.
168. Heijerman H, Westerman E, Conway S, Touw D, Döring G. Inhaled medication and inhalation devices for lung disease in patients with cystic fibrosis: a European consensus. *J Cyst Fibros*. 2009;8(5):295-315.
169. Sheldon WH. Pulmonary pneumocystis carinii infection. *J Pediatr*. 1962;61:780-791.
170. Long SS. 50 years ago in the Journal of Pediatrics: pulmonary pneumocystis carinii infection. *J Pediatr*. 2012;161(5):798.
171. Cohen DE, Mayer KH. Primary care issues for HIV-infected patients. *Infect Dis Clin North Am*. 2007;21(1):49-70, viii.
172. *NebuPent, Pentamidine Isethionate* [package insert]. Schaumburg, Ill: American Pharmaceutical Partners; 2002.
173. Mofenson LM, Brady MT, Danner SP, et al. Guidelines for the Prevention and Treatment of Opportunistic Infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. *MMWR Recomm Rep*. 2009;58(RR-11):1-166.
174. *Virazole, Ribavirin* [package insert]. Costa Mesa, Calif: Valeant Pharmaceuticals; 1996.
175. Committee on Infectious Diseases, American Academy of Pediatrics, Pickering LK, Baker CJ, Kimberlin DW. *Red Book: 2012 Report of the Committee on Infectious Diseases*. 29th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012.
176. Englund JA, Piedra PA, Ahn YM, Gilbert BE, Hiatt P. High-dose, short-duration ribavirin aerosol therapy compared with standard ribavirin therapy in children with suspected respiratory syncytial virus infection. *J Pediatr*. 1994;125(4):635-641.
177. Meert KL, Sarnaik AP, Gelmini MJ, Lieh-Lai MW. Aerosolized ribavirin in mechanically ventilated children with respiratory syncytial virus lower respiratory tract disease: a prospective, double-blind, randomized trial. *Crit Care Med*. 1994;22(4):566-572.
178. Rodriguez WJ, Hall CB, Welliver R, et al. Efficacy and safety of aerosolized ribavirin in young children hospitalized with influenza: a double-blind, multicenter, placebo-controlled trial. *J Pediatr*. 1994;125(1):129-135.
179. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. The Impact-RSV Study Group. *Pediatrics*. 1998;102(3):531-537.
180. Feltes TF, Cabalka AK, Meissner HC, et al. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. *J Pediatr*. 2003;143(4):532-540.
181. Lacaze-Masmonteil T, Truffert P, Pinquier D, et al. Lower respiratory tract illness and RSV prophylaxis in very premature infants. *Arch Dis Child*. 2004;89(6):562-567.
182. *SYNAGIS IM Injection, Palivizumab IM Injection* [package insert]. Gaithersburg, Md: MedImmune; 2011.
183. *XOLAIR Subcutaneous Solution, Omalizumab Subcutaneous Solution* [package insert]. South San Francisco, Calif: Genetech Inc; 2007.
184. *TUDORZA PRESSAIR Oral Inhalation Powder, Aclidinium Bromide Oral Inhalation Powder*. St Louis, Mo: Forest Pharmaceuticals; 2012.
185. Cazzola M. Aclidinium bromide, a novel long-acting muscarinic M3 antagonist for the treatment of COPD. *Curr Opin Investig Drugs*. 2009;10(5):482-490.
186. Jones PW, Singh D, Bateman ED, et al. Efficacy and safety of twice-daily aclidinium bromide in COPD patients: the ATTAIN study. *Eur Respir J*. 2012;40(4):830-836.
187. Fitzgerald MF, Fox JC. Emerging trends in the therapy of COPD: novel anti-inflammatory agents in clinical development. *Drug Discov Today*. 2007;12(11-12):479-486.
188. Geller DE, Weers J, Heuerding S. Development of an inhaled dry-powder formulation of tobramycin using PulmoSphereTM technology. *J Aerosol Med Pulm Drug Deliv*. 2011;24(4):175-182.
189. Konstan MW, Flume PA, Kappler M, et al. Safety, efficacy and convenience of tobramycin inhalation powder in cystic fibrosis patients: The EAGER trial. *J Cyst Fibros*. 2011;10(1):54-61.
190. Geller DE, Konstan MW, Smith J, Noonberg SB, Conrad C. Novel tobramycin inhalation powder in cystic fibrosis subjects: pharmacokinetics and safety. *Pediatr Pulmonol*. 2007;42(4):307-313.
191. Meers P, Neville M, Malinin V, et al. Biofilm penetration, triggered release and in vivo activity of inhaled liposomal amikacin in chronic Pseudomonas aeruginosa lung infections. *J Antimicrob Chemother*. 2008;61(4):859-868.
192. Okusanya OO, Bhavnani SM, Hammel J, et al. Pharmacokinetic and pharmacodynamic evaluation of liposomal amikacin for inhalation in cystic fibrosis patients with chronic pseudomonal infection. *Antimicrob Agents Chemother*. 2009;53(9):3847-3854.
193. King P, Lomovskaya O, Griffith DC, Burns JL, Dudley MN. In vitro pharmacodynamics of levofloxacin and other aerosolized antibiotics under multiple conditions relevant to chronic pulmonary infection in cystic fibrosis. *Antimicrob Agents Chemother*. 2010;54(1):143-148.
194. King P, Citron DM, Griffith DC, Lomovskaya O, Dudley MN. Effect of oxygen limitation on the in vitro activity of levofloxacin and other antibiotics administered by the aerosol route against Pseudomonas aeruginosa from cystic fibrosis patients. *Diagn Microbiol Infect Dis*. 2010;66(2):181-186.
195. Geller DE, Flume PA, Staab D, et al. Levofloxacin inhalation solution (MP-376) in patients with cystic fibrosis with Pseudomonas aeruginosa. *Am J Respir Crit Care Med*. 2011;183(11):1510-1516.
196. Geller DE, Flume PA, Griffith DC, et al. Pharmacokinetics and safety of MP-376 (levofloxacin inhalation solution) in cystic fibrosis subjects. *Antimicrob Agents Chemother*. 2011;55(6):2636-2640.

Thoracic Organ Transplantation

21

Brian K. Walsh

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. Recognize clinical indications for heart and lung transplantation in childhood.
2. Describe important respiratory complications after heart and lung transplantation.
3. Explain reasons why children can have more complications than adults after thoracic transplantation.
4. Identify reasons for the increased susceptibility of children after lung transplantation to respiratory infections and their complications.

Key Terms

allograft rejection
bronchiolitis obliterans
cardiomyopathy
congenital heart disease
cystic fibrosis
heart-lung transplantation
heart transplantation
lung transplantation
pulmonary hypertension

Thoracic organ transplantation dates back to the 1960s, for the first heart transplant in South Africa, and for the first **lung transplant** in Mississippi. In each case, the recipients survived only a few weeks. Despite the development of improved surgical techniques for thoracic organ transplantation in the 1980s, it was not until effective immunosuppressive regimens became available that there was a significant increase in the number of thoracic organ transplantations[1,2] (Figure 21-1).

In 1982 and 1983, fewer than a dozen pediatric **heart transplants** were performed worldwide each year; by 1990, the number increased to 325, and the worldwide total slowly increased to more than 500 by 2010.[1,3] In contrast, fewer than 10 pediatric lung transplants were performed from 1986 through 1989.[1] Since 1986 through June 2013, the number of pediatric lung transplants worldwide has also increased and reached 2091, and 689 **heart-lung transplants** have been performed, the vast majority of which were in the adolescent age group.[3] In sharp contrast, heart-lung transplantation, which was used for end-stage pulmonary disease because of the relative availability of heart-lung blocks, peaked in 1989 at 61 pediatric transplants per year.[1]

With the advances in surgical technique pioneered by Cooper in Toronto in the 1980s, lung transplantation became the procedure of choice for most forms of end-stage lung disease. It is now rare to consider heart-lung transplantation for isolated pulmonary disease.[4] In the 21st century, heart transplantation is indicated for inoperable congenital heart defects or end-stage myocardial failure. Single or bilateral lung transplantation is used for end-stage pulmonary and pulmonary vascular disease. Heart-lung transplantation is reserved for the uncommon circumstance of combined left ventricular heart failure with pulmonary disease or combined congenital defects of both the heart and lung (Table 21-1).[3,4] In 2010, fewer than 100 heart-lung transplants were performed worldwide, compared with 3500 lung and nearly 4000 heart transplants in all ages.[5] Of the 74 heart-lung transplants performed around the world in 2010, only 7 were performed in individuals younger than 18 years.[3,5]

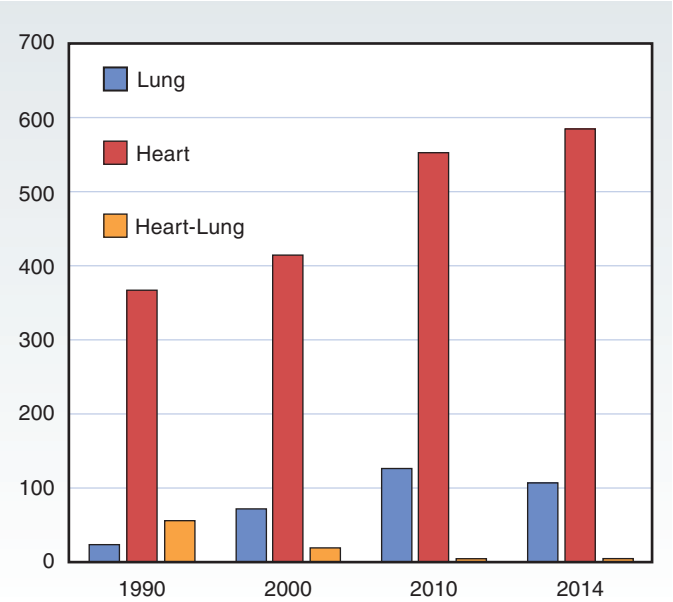


FIGURE 21-1 Relative volume of lung, heart, and heart-lung transplants performed. (Data from The Registry of the International Society for Heart and Lung Transplantation: thirty-second annual pediatric lung and heart–lung transplantation report—2016, *J Heart Lung Transplant* 35[10]:1149–1205, 2016.)

Table 21-1 Pediatric Thoracic Organ Transplantation: Primary Indications

TRANSPLANT TYPE	CLINICAL INDICATION
Heart	Cardiomyopathy **Congenital heart disease**
Bilateral lung	Cystic fibrosis Pulmonary hypertension Interstitial lung disease Pulmonary growth abnormalities Bronchiolitis obliterans
Lung with heart repair	Congenital heart disease with pulmonary hypertension but preserved left ventricular function
Heart-lung	End-stage lung disease with left ventricular failure Irreparable congenital heart disease with pulmonary hypertension or other intrinsic lung disease

Significantly fewer children wait for thoracic organ transplantation than those waiting for kidney or liver transplantation (Figure 21-2). Since the late 1990s, there has been a steady increase in the number of pediatric candidates for solid organ transplantation, but until recently there has been no increase in the number of donors.

In 2003, the Organ Donation Breakthrough Collaborative was formed under public auspices in the United States to enhance organ donation.[6] The average conversion rate—that is, the rate at which families of brain-dead individuals consent to organ donation—was 46% at that time. Examination of best practices suggested that a 75% conversion rate was achievable,

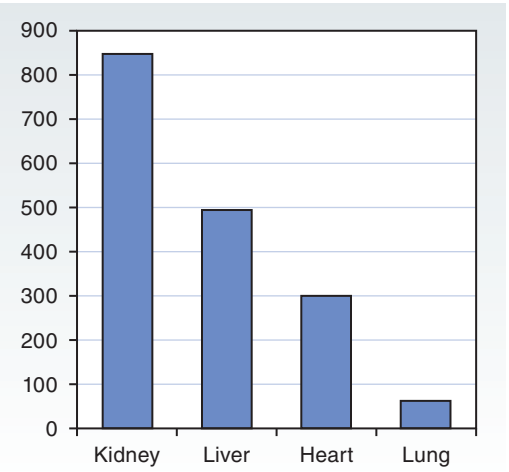


FIGURE 21-2 Numbers of children in the United States awaiting solid organ transplantation by organ type as of February 2013. (Data from http://optn.transplant.hrsa.gov.)

and this goal was formally set in the final report of the collaborative in September 2003. Since that time, there has been a significant increase in donors.

In 2005, the Organ Transplantation Breakthrough Collaborative was formed to increase the number of organs harvested from each donor. In most donors historically, the liver and kidneys were deemed suitable for transplant, but only approximately 25% of the hearts and 10% to 15% of the lungs were deemed healthy enough to be transplanted. Myocardial dysfunction is a common response to the dramatic events related to brain death. In most previously healthy donors, modern donor management, given enough time, results in a return to near-normal cardiac function. On the other hand, lungs are often infected or atelectatic, injured during prolonged intubation and ventilation, or unsuitable because of pulmonary edema, trauma, or aspiration.[7] By the application of best practices, aggressive donor management can increase both heart and lung donation, although it may take longer to manage the donor until the time of recovery.[8,9] In addition, the number of abdominal organs can also be increased by this approach.

It was the goal of the collaborative to extend the use of aggressive donor management protocols across the United States to increase the yield of transplanted organs. One of the mandates of the Organ Transplantation Collaborative was to treat every donor as a thoracic organ donor, with early emphasis on evaluating and resuscitating the lungs and heart after declaration of brain death.

Another innovative approach to the donor shortage includes the use of living donor lobar donation (LDLT) for lung transplantation (using a single lobe each from two taller individuals, commonly but not always parents or relatives).[10] Starnes popularized this surgical approach in the 1990s.[10] In this approach, two healthy biologically related or unrelated older and taller individuals donate a lower lobe to replace the recipient's

native lungs. Despite relative early success, peak volume of living donor lobar transplantation was in 1998 and 1999, with 29 recipients in the United States each year. From 2010 until the present, there has been no more than one reported LDLT surgery per year, according to data from the United Network for Organ Sharing (UNOS).[3,5]

Donation after cardiac death (DCD) has been a rare source of donor organs until recent years.[11] In this clinical scenario, physicians recommend discontinuation of life-sustaining therapy for a terminally ill patient. In some of these patients, especially if there has been a recent central nervous system injury, families sometimes ask about the possibility of organ and tissue donation. If circulatory arrest is anticipated within minutes of withdrawal of ventilatory support, organ donation may be possible. In that situation, the organ procurement center is contacted and recovery surgeons are notified and present in a nearby operating room at the time of extubation. If circulatory arrest occurs within 30 to 60 minutes, kidneys, livers and most recently lungs may be procured for transplantation. In 2009, UNOS documented 33 lung transplants performed in the United States after DCD recovery (Figure 21-3).[12] Rarely, infant heart transplantation has been performed in the DCD setting.[13]

For most children who undergo thoracic organ transplantation, quality of life returns to normal.[14,15] Within weeks after the operation, depending on their pretransplant nutritional and physical state, most patients are able to resume age-appropriate activities with improving exercise tolerance. Cardiac function is generally normal in heart transplant patients.[16] Gas exchange and pulmonary function rapidly return to near normal in the first months after lung transplantation.[14,15] Minor childhood illnesses appear to be well tolerated, although in its initial stage it is often difficult to ascertain whether a febrile illness represents a minor infection, graft rejection, or life-threatening infection in an immunocompromised host. Somatic growth delay can be a problem, at least in part resulting from the administration of prednisone, which is continued lifelong in almost all lung and a subset of heart recipients. However, subsequent growth of the patient as well as the **allograft** is possible, and it is unlikely that the subject will outgrow the transplanted organ.[17]

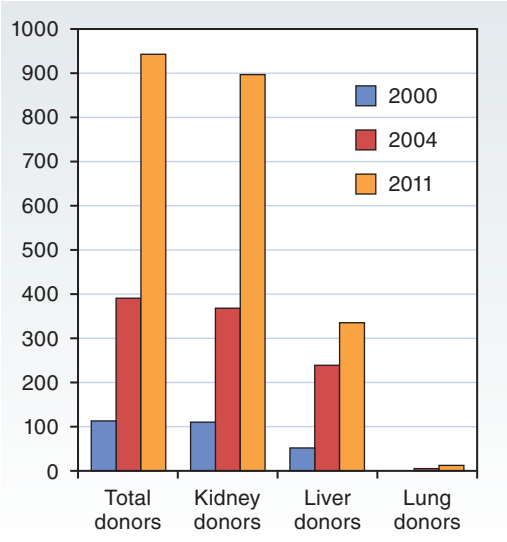


FIGURE 21-3 Volume of kidney, liver, and lung transplants from donors after cardiac death from 2000 to 2009, demonstrating increasing volume for each organ. (Data from http://optn.transplant.hrsa.gov.)

HEART TRANSPLANTATION

In the 1980s the primary indication for heart transplantation was **cardiomyopathy.** However, in more recent years the proportion of transplantations for congenital heart defects has been increasing (Table 21-2).[1] Congenital lesions are the indication for heart transplantation in 55% of patients younger than 1 year worldwide, but only 25% of older children.[5] The operative approach in heart transplantation involves a sternotomy with surgical anastomoses to the venae cavae and aorta. Early postoperative mortality arises from graft failure and, less commonly, cardiac rhythm disorders. The newly denervated implanted heart often has an initial intrinsic rhythm too slow to produce an adequate cardiac output. Thus, a temporary external pacemaker is attached to the heart at the end of each heart transplant operation. Infectious complications, graft rejection, and central nervous system hemorrhage or embolism occur with lower incidence. Early mortality rate after transplantation is higher in younger children, as evidenced by the 25% 1-year mortality rate in recipients younger than 1 year, compared to 10% for the 11- to 18-year age group.[18] Late deaths are caused primarily by coronary vasculopathy (chronic rejection). A small number of deaths in the early and late groups have been related to central nervous system complications such as stroke. The death rate from malignancy (primarily lymphoproliferative disease) increases over time and represents 10% of deaths after 5 years.[18] Other morbidities from heart transplantation that have been reported include hypertension in approximately 40% of individuals, renal insufficiency in 20%, and seizures in 25%.[19-21]

Table 21-2 Indications for Heart Transplantation in North America by Age

	<1 YEAR	1-5 YEARS	1-10 YEARS	11-17 YEARS
Cardiomyopathy	38%	44%	44%	23%
Congenital heart defects	55%	41%	35%	54%
Other	7%	11%	15%	15%
Retransplantation	0.3%	4%	6%	8%

Modified from Yusen RD, Edwards LB, Dipchand AI, et al. The registry of the International Society for Heart and Lung Transplantation: thirty-second annual pediatric lung and heart–lung transplantation report—2016. *J Heart Lung Transplant.* 2016;35(10):1170-1184.

A troublesome and life-limiting problem in long-term heart transplant survivors regardless of age is the development of premature coronary artery disease or coronary vasculopathy, also known as *graft atherosclerosis*.[18] This condition may be asymptomatic and may be discovered only at the time of surveillance coronary angiography, performed annually in most centers. In some patients, the disease can be significant enough to cause myocardial ischemia and may contribute to arrhythmias or sudden death. There is general consensus that premature coronary artery disease is immunologically mediated as a manifestation of chronic graft rejection and therefore may decrease in prevalence with improvements in immunosuppressive regimens.

Neonatal heart transplantation has been successful at some centers. This has been used almost exclusively for hypoplastic left-heart syndrome, which is uniformly fatal if surgical correction or transplantation is not offered. The current experience with either surgical palliation (the Norwood procedure) or transplantation does not clearly indicate which is more appropriate to optimize survival.[20] Although once considered promising, anencephalic infants have not proven to be suitable donors for other neonates.[22] Young infants are less sophisticated hosts by virtue of their relatively immature immune response and therefore might tolerate the immunologic challenge of transplantation more readily than older patients. In fact, many pediatric candidates younger than 18 months can receive hearts across the ABO group barriers with long-term success. The survival rate and duration of survival with good cardiac function appear to be the same for children and adult heart transplant recipients.[18,21]

HEART-LUNG TRANSPLANTATION

Before the surgical technique for successful lung transplantation was developed, heart-lung transplantation was offered for end-stage pulmonary disease. Heart-lung transplantation involves a sternotomy and surgical anastomoses of the trachea, superior and inferior venae cavae, and aorta and is a technically less challenging operation compared with lung transplantation. With the ability to successfully transplant a single lung or two lungs, the use of heart-lung transplantation for pulmonary disease has dramatically decreased.[1,3] There are multiple reasons for this, including the following:

- The limited availability of satisfactory coupled heart-lung donations from single donors (governed in part by the distribution algorithm unique to each country)
- The practical advantage of using the heart-lung block for three separate donations (one heart and two single lungs)
- The decreased risk of cardiac rejection if isolated lung transplantation is performed
- The decreased risk of premature coronary artery disease
- The high demand for donor hearts by very ill heart transplant candidates with ventricular assist devices or artificial hearts in place

Despite concerns about the impact of right ventricular dysfunction commonly associated with chronic pulmonary disease or severe **pulmonary hypertension** in the immediate postoperative period, improvement in right ventricular function with lung transplantation leads to good outcomes after recovery from surgery.[3,14] For patients with congenital heart defects such as atrial septal defect, ventricular septal defect, or patent ductus arteriosus, as well as pulmonary hypertension from Eisenmenger syndrome, lung transplantation with repair of the congenital heart defect is generally the procedure of choice.[23]

LUNG TRANSPLANTATION

A common and severe complication of lung transplantation before 1983 was tracheal and bronchial anastomosis failure. When Cooper developed techniques to overcome this problem in the late 1980s,[2] single- and double-lung transplantation became the preferred options for adult patients with chronic pulmonary disease. Table 21-1 lists the diseases appropriate for bilateral lung transplantation. Table 21-3 list the contraindication to pediatric lung transplantation. Single-lung transplantation now is rarely performed in children.

Table 21-3 Contraindications to Pediatric Lung Transplantation

ABSOLUTE	RELATIVE
Active malignancy within 2 years	Pleurodesis
Sepsis	Renal insufficiency
Active tuberculosis	Markedly abnormal body mass index
Severe neuromuscular disease	Mechanical ventilation or extracorporeal membrane oxygenation
Documented refractory nonadherence	Scoliosis
Multiple-organ dysfunction	Poorly controlled diabetes
Acquired immunodeficiency syndrome	Osteoporosis
Hepatitis C with histologic liver disease	Chronic airway infection with multiple resistant organisms
Significant psychiatric illness in patient or primary caregiver	Fungal infection/colonization Atypical mycobacteria infection/colonization Hepatitis B

Data from Faro A, Mallory GB, Visner GA, et al.: American Society of Transplantation executive summary on pediatric lung transplantation. *Am J Transplant* 7(2)285–292, 2007.

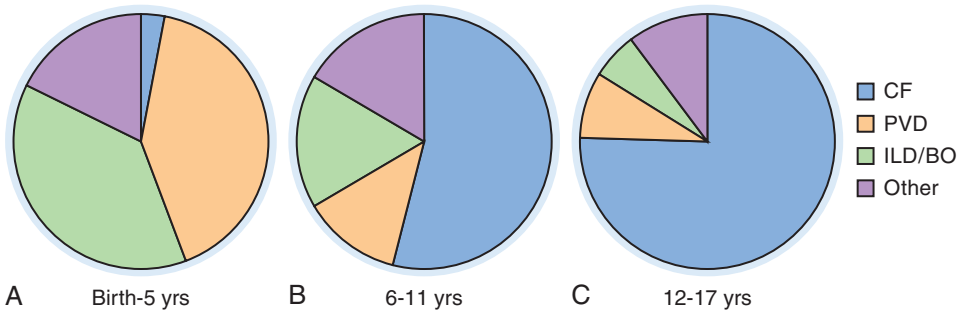


FIGURE 21-4 Frequency of primary diseases leading to lung transplantation in children by age. **A,** Diagnoses from birth through age 5 years. **B,** Diagnoses from birth through age 6 to 11 years. **C,** Diagnoses from age 12 through 17 years. *BO,* Bronchiolitis obliterans; *CF,* cystic fibrosis; *ILD,* interstitial lung disease; *PVD,* pulmonary vascular disease. (Data from http://optn.transplant.hrsa.gov; and Benden C, Edwards LB, Kucheryavaya AY, et al.: The registry of the International Society for Heart and Lung Transplantation: fifteenth pediatric lung and heart–lung transplantation report—2012. *J Heart Lung Transplant* 31:1087, 2012.)

Figure 21-4 shows the most common chronic lung diseases in children that lead to transplantation. **Cystic fibrosis** is the most common indication for bilateral lung transplantation, almost exclusively in children older than 6 years.[3]

Enthusiasm for lung transplantation has been tempered by a relatively low survival rate; the initial 1-year survival rate was only slightly more than 50%. This compares with early survival rates after heart-lung or double-lung transplants in patients with cystic fibrosis of 60% to 70% at 1 year in the 1990s.[24,25] As overall experience has increased, survival after lung transplantation has improved; the most recent actuarial survival at 1 year after transplant is approximately 85%.[3] Longer-term survival rates remain disappointing, however, with 5-year survival in the most recent era less than 50%. Post–lung transplant survival rates have a long way to go to be comparable with the success of kidney, heart, pancreas, and liver transplantation (Figure 21-5).[26]

Deaths within the first 90 days after lung transplantation (early deaths) result most commonly from graft failure caused by ischemia-reperfusion injury. Less common are surgical problems such as airway anastomotic dehiscence or massive hemorrhage. Even less common are overwhelming infection, either systemic or pulmonary; multiple organ failure; or acute graft rejection. Late deaths are generally related to infection or **bronchiolitis obliterans,** usually a manifestation of chronic rejection.[4,5]

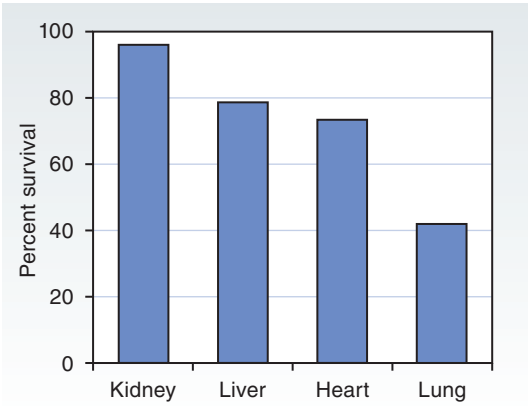


FIGURE 21-5 Five-year survival of patients younger than 18 years after kidney, liver, heart, and lung transplants in the United States. Because of the availability of renal dialysis, patient survival exceeds graft survival by more 20% at 5 years for kidney transplant recipients. (Data from http://optn.transplant.hrsa.gov.)

A particular concern in pediatric lung transplantation is the problem of donor–recipient size matching. In addition to the problems of donor availability among all transplantation candidates, the thoracic dimensions of infants and small children add another obstacle, so that size-appropriate donors are even less commonly available than for adolescents or adults.[27]

A potential solution to this problem is reduced-size transplantation, often from a living donor (e.g., transplanting an adult lower lobe to a pediatric patient to replace the entire lung[28]). Although initial attempts at living-related donation were disappointing, more recent experience suggests that LDLT can be successful, with 1-year survival of 60% to 80% with only minimal risk to the donor.[29] Therefore, LDLT might, in theory, help overcome the obstacles of donor waiting time, size limitation, and organ availability for an urgently ill transplant candidate. The lung allocation score system, which took effect in the United States in 2005, now lists patients according to a computed score of urgency, reducing the need for LDLT.[30]

IMMUNOSUPPRESSIVE REGIMENS

Although children commonly resume normal activity within weeks of transplantation, the medical regimen, including medications and testing, after thoracic transplantation is extensive, especially in the first year. In addition to an intense pharmacologic program, there are frequent office visits, multiple blood tests, repeated radiographs, serial echocardiograms in heart recipients, and, in most centers, surveillance biopsies. Even a minor illness can lead to hospitalization to rule out graft rejection or serious infection. With increasing

time after transplantation and successful graft function, there are fewer impositions on the lives of the child and family.

When children are referred to centers distant from their home communities, their families usually have to spend months before and often months after transplantation in the transplant center community. There are considerable financial and psychosocial costs to this dislocation of children and parents from their homes. The transplant patient trades one set of problems (the burdens of living with a terminal disease) for another (long-term immunosuppression and a lifelong risk of potential life-threatening complications). Because quality of life is dramatically better for most survivors, few families express regret after transplantation.

Most immunosuppressive regimens for organ transplantation (thoracic and other solid organs) include the combined use of cyclosporine or tacrolimus, azathioprine or mycophenolate mofetil, and prednisone.[3,18] Tacrolimus and mycophenolate mofetil are now the most commonly used immunosuppressants and are generally needed for the life time of the transplant recipient.[3] There has been an increasing trend to embrace a corticosteroid-free immunosuppressant program at pediatric heart transplant centers.[18] Many transplant cardiologists wean patients from or attempt to discontinue prednisone within weeks to months after transplantation. Because lung allografts are more susceptible to both acute and chronic rejection, immunosuppressant dosing is generally higher and more prolonged compared with that in heart transplant recipients. Few lung transplant pulmonologists attempt to wean patients from prednisone; at most, some patients can be weaned to alternate-day dosing.

COMPLICATIONS

The complications of thoracic organ transplantation can be grouped into the following categories:

- Respiratory failure and related problems
- Acute rejection
- Infection
- Chronic rejection or bronchiolitis obliterans
- Drug toxicity
- Other complications

RESPIRATORY PROBLEMS

All thoracic transplantation patients arrive in the intensive care unit after transplantation and receive mechanical ventilatory support via endotracheal tube. Most well-conditioned heart transplant patients with good myocardial contractility in the immediate postoperative period can be weaned from mechanical ventilation within the first hours to days. The surgical incision and thoracostomy tubes will result in reduced thoracic compliance, and both deep inspiration and cough will likely be compromised. With the judicious use of intravenous analgesics, chest physiotherapy, and, occasionally, regional nerve block or epidural anesthesia, most heart transplant patients, like their counterparts who undergo other cardiac surgical procedures, do well. With the increasingly common use of left ventricular assist devices, there is a growing number of severely deconditioned pediatric cardiac transplant recipients who may require longer periods of ventilator support. A subset of recipients experience severe myocardial failure postoperatively. Extracorporeal membrane oxygenation or a ventricular assist device may be required with or without mechanical ventilatory support for several days. With myocardial failure, some degree of pulmonary edema with reduced lung compliance occurs. These patients require aggressive intravenous cardiotonic and diuretic medications. Oxygen supplementation is almost always needed in these patients. Under some circumstances, a relatively large heart graft that is placed in a smaller child may compress the intrathoracic airways, with the left mainstem bronchus being particularly vulnerable to such compression. With compression, consolidation with absent breath sounds over the left lower lobe or low-pitched expiratory wheezing with a variable degree of dyspnea may result.

Heart-lung and lung transplant patients are more vulnerable to respiratory complications than are heart transplant patients. The thoracic incision is usually more extensive when lungs are transplanted. Allograft dysfunction after lung transplantation is common but highly variable. The delicate pulmonary capillary bed appears to be more susceptible to ischemic injury than is the myocardium, liver, or kidney in the context of transplantation. So-called *ischemia-reperfusion injury* in the lung is manifested as pulmonary capillary leak.

This reperfusion injury, which occurs in 10% to 20% of lung transplants, mimics acute respiratory distress syndrome clinically and radiographically. On chest radiography, pulmonary edema, either immediately after transplantation or within the first 72 hours, is usually a sign of ischemic injury or reperfusion injury (Figure 21-6).[33,34] Interruption of the pulmonary lymphatics, which are cut during surgery, also contribute to pleural, alveolar, and interstitial fluid accumulation. Reperfusion injury, now called *primary graft dysfunction,* affects 5% to 25% of adult and pediatric lung transplant recipients with varying severity.[35]

Subacute respiratory failure requiring ventilatory support for 1 to 2 weeks without severe parenchymal disease is seen in some patients who had significant preoperative hypercapnia. Respiratory control mechanisms may require many days to reset after lung or heart-lung transplantation.[36] Keys to management are to avoid oversedation and to provide adequate nutrition and ventilatory support until weaning can be achieved. Noninvasive ventilatory support with bilevel positive airway pressure may ease the transition from the pretransplant hypercarbic state to the posttransplant normocarbic state.

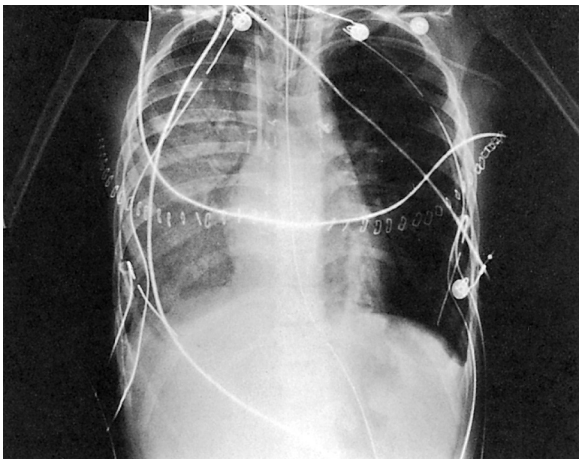


FIGURE 21-6 This chest radiograph demonstrates reperfusion injury to the right lung immediately after double-lung transplantation in an 11-year-old girl with cystic fibrosis. There is a ground-glass haziness with air bronchograms over the right lung field. The staples across the chest are external and used for surgical skin closure. There are surgical clips in each hilar region where the vascular anastomoses were performed. There is also an endotracheal tube, a nasogastric tube, a left subclavian vein catheter, a right internal jugular vein catheter, bilateral chest tubes, and surface electrodes. (From Moodie DS, Stillwell PC: Thoracic organ transplantation in children: the state of heart, heart-lung, and lung transplantation. *Clin Pediatr* 32:322–328, 1993.)

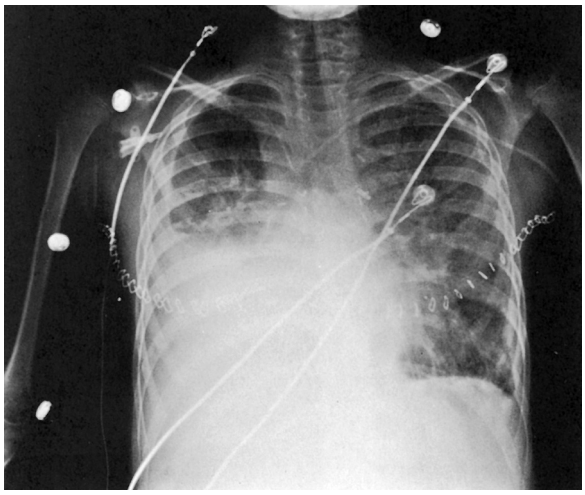


FIGURE 21-7 The same patient as in Figure 21-6, seen 3 weeks later during an episode of acute lung rejection. A large right pleural effusion obscures the right hemidiaphragm and the border of the right side of the heart. There is an extensive increase of peribronchial markings in both lungs and a blunted left costophrenic angle. All chest tubes and the endotracheal tube have been removed. A right subclavian vein catheter has been added. (From Moodie DS, Stillwell PC: Thoracic organ transplantation in children: the state of heart, heart-lung, and lung transplantation. *Clin Pediatr* 32: 322–328, 1993.)

Significant bronchial obstruction may develop after lung or heart-lung transplantation because of stricture or dehiscence at or just beyond the sites of bronchial anastomosis. Most airway complications will present within 3 months of transplantation, and although a few can be fatal if severe and early, most are treatable with bronchoscopic dilation, laser resection of granulation tissue, or the placement of airway stents.[37,38]

ORGAN REJECTION

The clinical signs and symptoms of organ rejection may be minimal or subtle. Acute rejection of the transplanted heart, if clinically apparent, results in decreased cardiac contractility with signs and symptoms of congestive heart failure. Tachycardia, tachypnea, and malaise may be noted. Echocardiography is the noninvasive diagnostic mode of choice to ascertain the physiologic signs of cardiac rejection. In a lung transplant patient, tachypnea, bibasilar inspiratory crackles on auscultation, increased interstitial infiltrates on chest radiography, and hypoxemia by pulse oximetry are often associated with acute rejection (Figure 21-7). For older patients who can perform spirometry, a drop in pulmonary function, either restrictive or obstructive, is often the most sensitive indicator of acute rejection.

Many transplant centers perform routine surveillance biopsies of the transplanted tissue in an effort to identify and treat early rejection before permanent organ damage occurs.[21,39] When clinically suspected, the diagnosis of rejection is also usually confirmed by biopsy.[4,21] Endomyocardial biopsy by means of biopsy forceps passed through a vascularly accessed catheter is the method of choice in heart transplant patients. For lung transplant patients, flexible bronchoscopy with transbronchial biopsy is used to obtain multiple pieces of tissue for histopathologic examination in children and adolescents. For infants and young children, rigid bronchoscopy or open-lung biopsy may be required, although tiny biopsy forceps may allow biopsy through the flexible bronchoscope even in very small children. Most transplantation physicians are uncomfortable augmenting immunosuppression without tissue confirmation of graft rejection.

INFECTION

It can be difficult to separate rejection from infection, especially on a clinical diagnostic basis, and in some cases they may coexist.[34] Although pulmonary infections are common because of the immunosuppression required with any solid organ transplant, the pulmonary infection rate for lung transplantation appears to be high.[39] This may be partially explained by the fact that the lung is the only solid organ that after transplantation is regularly in direct contact with the external environment and multiple potential pathogens. Many pulmonary bacterial infections are readily identified but often require bronchoalveolar lavage for accurate diagnosis and are easily treated with antibiotics. Pulmonary viral infections are less common but more often fatal, especially if cytomegalovirus is involved.[39] Fungal infections are particularly troublesome in terms of both accurate diagnosis and treatment. Because a transplant patient with cystic fibrosis

retains the native trachea and sinuses, there is a potential increase of infections from chronic colonization of the respiratory epithelia in the trachea and frank infection within the paranasal sinuses.[40] This can be particularly serious if the resident organisms have resistance to multiple antibiotics.[40,41] In fact, some centers consider infection with *Pseudomonas* species with no antibiotic sensitivity a contraindication to transplantation.[4] The highly antibiotic-resistant *Burkholderia cepacia* complex organisms have been associated with significant morbidity and mortality in patients with cystic fibrosis.[39,40] These resistant organisms are found most often in older patients with advanced lung disease, and these are the patients with cystic fibrosis who most likely need transplantation. Of concern is the report that *Burkholderia* species can be particularly lethal to transplant patients with cystic fibrosis who acquire it after transplantation.[40] The role of antibiotic prophylaxis in patients with cystic fibrosis who undergo lung transplantation remains to be clarified. A common and potentially effective prophylaxis for transplant patients with cystic fibrosis involves inhaled antibiotics, usually an aminoglycoside such as tobramycin.

BRONCHIOLITIS OBLITERANS

Bronchiolitis obliterans is unfortunately a common late complication in both heart-lung and lung transplant recipients.[4,5,31] The exact cause in an individual case is sometimes unknown, but it most likely represents the common pathway for different insults such as chronic rejection, infection, and aspiration. Bronchiolitis obliterans can be initially identified by a decrease in flow rates at low lung volumes during surveillance pulmonary function testing and can be confirmed sometimes by transbronchial biopsy but more definitively by open-lung biopsy. Because of the high frequency of false-negative transbronchial biopsies, most clinicians use the clinical definition of "bronchiolitis obliterans syndrome" for both diagnosis and treatment decisions.[44] In most patients, bronchiolitis obliterans is a progressive disease manifested by increasing dyspnea, increased coughing with sputum production, colonization or infection with *Pseudomonas* species, and eventual respiratory failure and death. A small minority of patients respond favorably to augmented immunosuppression, with reversal or stabilization of their airway dysfunction.[32] Bronchiolitis obliterans remains a major obstacle to the success of lung and heart-lung transplantation.

DRUG TOXICITY

All immunosuppressive regimens place the patient at risk for infection. In addition, each arm of the regimen may cause other complications from side effects or drug toxicity. Cyclosporine and tacrolimus have the highest potential toxicity. Hypertension and nephrotoxicity are most common, but fortunately are usually manageable. The major complication of both azathioprine and mycophenolate mofetil is a decreased white blood cell count caused by bone marrow suppression, which usually improves with temporary discontinuation of the medicine or a decrease in dose. There may be more symptoms of gastrointestinal disturbance with mycophenolate mofetil compared with azathioprine. Complications of prednisone are common in the immediate posttransplantation period, when high doses are used, but lessen with decreasing doses after several months. Prednisone is usually decreased to low daily doses (0.1 to 0.15 mg/kg/day) or to an alternate-day dosage schedule by 1 year after transplant. Because of the combined effects of tacrolimus and prednisone, some patients become glucose intolerant, particularly patients with cystic fibrosis, and may require long-term insulin therapy.

OTHER COMPLICATIONS

A broad spectrum of other complications occur less commonly after transplantation. For patients receiving heart or heart-lung transplants, accelerated coronary artery disease is a potentially serious problem.[18,19,21] Like bronchiolitis obliterans, it is a form of chronic graft rejection and is usually progressive. Other potential complications include obstructive sleep apnea, cerebrovascular accidents, and aspiration of gastric contents. Epstein-Barr virus–related lymphoproliferative disease is a neoplastic disorder that occurs in relation to the intensity and duration of immunosuppression. The incidence in pediatric thoracic transplantation varies from 1% to 10%.[16,45] It may regress with decreased levels of immunosuppression and/or chemotherapy but can occasionally progress to fatal malignancy. Other fairly common medical complications include generalized seizures, aggravated acne, and mild suppression of maximal exercise performance. Up to 25% of lung transplant recipients may experience unilateral vocal cord or hemidiaphragm paralysis, which may recover 3 to 6 months after transplant. Equally important are the psychosocial adjustments to the emotional "roller coaster" of thoracic organ transplantation.[46] Although almost all patients can benefit from extensive psychosocial support, occasionally some will require pharmacologic assistance to deal with either anxiety or depression.[46,47] These psychologic or psychiatric complications are quite common, and they are potentially serious. Nonadherence to the medical regimen is often fatal. The entire transplantation team must be alert for any psychologic or psychiatric complications in the hope of either their prevention or their early detection and treatment.

SURVIVAL AND QUALITY OF LIFE

Survival after pediatric heart transplantation in the most recent era exceeds 60% at 10 years and has

shown significant incremental improvement over time.[18] Survival after pediatric lung transplantation is less than 40% at 10 years in the most recent era, and there seems to be detectable but less impressive improvement in survival over time.[3] On the other hand, lung transplant recipients appear to have a higher functional status, with more than 85% of survivors having no limitations, in contrast to approximately 60% of heart transplant survivors.[3,18] Quality-of-life assessment in pediatric heart transplant recipients shows that overall health-related quality of life is lower than healthy peers but comparable to other chronic disease groups.[48] Furthermore, a significant minority of these children have cognitive or behavioral issues.[49] There is less published information on quality of life in pediatric lung transplant recipients. The authors' experience is that significant disability and neurodevelopmental deficits are uncommon. There is ongoing research in our own center, which will be published in the near future.

ROLE OF THE RESPIRATORY THERAPIST

There are multiple areas of interaction between the respiratory therapist (RT) and the transplant patient. Care of a patient who undergoes thoracic transplantation always involves teamwork by a variety of health care professionals. A child who receives a lung or heart-lung transplant is especially likely to require an RT on the team. Familiarity with the diseases leading to transplantation, as well as the transplantation process, will help the practitioner provide more comprehensive care to the patient as well as improve interactions with the health care team. The RT may already be familiar with the transplant candidate because of his/her role in providing routine care for the primary disease process, particularly for chronic pulmonary diseases such as cystic fibrosis. The RT may become a key contact with the transplant candidate in the initial evaluation process or during pulmonary function testing. After the patient has been accepted to the transplantation list, the RT may be involved in providing an exercise evaluation and rehabilitation program to optimize the patient's condition while he or she is awaiting transplantation. Immediately after the transplantation procedure, the RT will be involved with the patient in the intensive care unit, primarily providing mechanical ventilatory support and maintenance of the artificial airway. Because of the temporary interruption of ciliary function, the RT may be asked to provide aerosolized bronchodilators, mechanical aids to assist full inflation and cough, and bronchopulmonary hygiene. For most patients, this therapy is not required on a long-term basis. Shortly after the patient is taken off mechanical ventilation, the RT may be involved in additional mucus clearance measures. Exercise and rehabilitation should be resumed as soon as possible after extubation.

REHABILITATION

There is limited literature to guide decision-making regarding rehabilitation during the immediate posttransplant period. However, deconditioning from a prolonged illness is likely. Therefore, postoperative interventions like lower limb resistance and early active muscle training are likely to be of benefit.[50] One study involving children found improvements in 6-minute walking at 3 months and 1 year in heart and lung transplant recipients who participated in an exercise program 3 times a week after transplant.[51]

Over the intermediate and long-term posttransplant period, patients and families often forget the importance of bronchial denervation in masking symptoms of significant lower respiratory tract disease. Lung transplant recipients can develop airway obstruction related to purulent bronchitis with surprisingly little cough. We have emphasized the importance of monitoring lung function at home as the single most sensitive indicator of lung health. Patients are provided with a hand-held home spirometry unit and pulse oximetry that they need training on to help monitor their trajectory. Airway clearance devices such as positive expiratory pressure (PEP) or oscillatory PEP are offered as a tool to aid in cough with mucus clearance. Refresher sessions are important during the extended period of follow-up. Lastly, the RT may be involved in the transplant patient's care by assisting with follow-up pulmonary function tests, instructing the patient in the use of home spirometry, and assisting with bronchoscopies.

Case Study 1

An 18-month-old infant with a dilated cardiomyopathy undergoes heart transplantation, receiving a heart from a 3-year-old child twice his weight. The early posttransplant recovery goes well, and he weans from cardiac pressor agents and is extubated. He has a mediastinal drainage tube in place. As the respiratory therapist, you are called because the chest radiograph shows left lower lobe consolidation, and auscultation reveals a monophonic expiratory wheeze. Sa_{O_2} is 95% on 1 L/minute oxygen supplementation. There is a mild increase in work of breathing.

Which intervention would you recommend?

1. Reintubation with positive pressure breathing
2. Nebulized albuterol
3. Trial of nasal continuous positive airway pressure
4. Urgent flexible bronchoscopy
5. Chest computed tomography (CT) scan

See Evolve Resources for answers.

Case Study 2

A 16-year-old girl with cystic fibrosis and advanced lung disease undergoes a successful bilateral lung transplant. She is transferred out of the intensive care unit on the fourth postoperative day with two chest tubes, with Sa_{O_2} 96% on room air. You are called into her room by her nurse because she is complaining of dyspnea and her Sa_{O_2} is 79%. You note a significant air leak in one of the atria connected to the left chest tube.

Which of the following is the correct action after calling for a physician?

1. Clamp the chest tube.
2. Administer oxygen by nonrebreather mask.
3. Order an urgent chest radiograph.
4. Urgently return to the operating room.
5. Order a chest CT scan.

See Evolve Resources for answers.

Key Points

- Pediatric heart transplantation dates to the early 1980s, whereas pediatric lung transplantation really began in the 1990s.
- Heart-lung transplantations have dramatically decreased over the past 2 decades.
- Survival after transplantation is significantly longer with heart transplantation compared with lung transplantation, which is related to the increased susceptibility of lung transplant recipients to both infection and allograft rejection.
- Lung transplant recipients require higher doses of immunosuppressant medications and have more frequent complications than heart transplant recipients.
- The most common immunosuppressive agents in the current era are tacrolimus and mycophenolate.
- Respiratory complications are common in thoracic organ transplant recipients and often require the input of an informed, well-trained respiratory care practitioner.

Assessment Questions

See Evolve Resources for the answers.

1. What is the frequency of transplantations performed in the pediatric age group, in order from most to least?
   - **A.** Lung >heart-lung >heart
   - **B.** Heart >heart-lung >lung
   - **C.** Lung >heart >heart-lung
   - **D.** Heart >lung >heart-lung
2. What is the major reason why fewer lungs are transplanted per donor compared with heart transplants in childhood?
   - **A.** There are fewer lung transplant candidates than heart transplant candidates in childhood.
   - **B.** There are fewer lung transplant programs than heart transplant programs.
   - **C.** The lungs are more likely than the heart to be injured or infected in a brain-dead donor.
   - **D.** The size of lungs is less adaptable to children of different ages than the size of the heart.
3. What is the major medical problem in the immediate posttransplantation period for pediatric heart transplant patients?
   - **A.** Graft failure
   - **B.** Weaning from mechanical ventilatory support
   - **C.** Cardiac arrhythmias
   - **D.** Graft rejection
4. What is the most common serious medical problem in the immediate posttransplantation period for pediatric lung transplant recipients?
   - **A.** Graft failure
   - **B.** Weaning patients from ventilator support
   - **C.** Pneumonia from the donor
   - **D.** Graft rejection
5. For what condition is heart-lung transplant surgery most commonly performed in pediatric patients?
   - **A.** Cystic fibrosis
   - **B.** Pulmonary hypertension
   - **C.** Infants with lung disease as a result of technical difficulties in isolated lung transplantation
   - **D.** Pulmonary hypertension with congenital heart disease
6. Donation after cardiac death most commonly has provided organs for:
   - **A.** Heart transplantation
   - **B.** Heart-lung transplantation
   - **C.** Lung transplantation
   - **D.** All of the above
7. How long is immunosuppression used in lung, heart, and heart-lung transplantation?
   - **A.** Only during the critical 6 months after transplantation; the patient is then weaned.
   - **B.** Lifelong immunosuppression is needed.
   - **C.** Lifelong only in lung and heart-lung transplantation because of the higher incidence of graft rejection.
   - **D.** Lifelong only in heart and heart-lung transplantation because lung infections become a greater risk to survival after the first year because of immunosuppression.
8. Among the most important risks for pulmonary complications after lung transplantation in children are all of the following *except:*
   - **A.** Dangers of childhood vaccines
   - **B.** Absence of cough reflex because of interruption of the nerve supply to the transplanted lungs
   - **C.** Immunosuppression
   - **D.** Frequency of inevitable exposure to community respiratory viruses and other pathogens

9. Organ rejection is:
- **A.** A problem only in lung and heart-lung transplantation
- **B.** A problem only in the critical first 6 months after thoracic transplant
- **C.** The most common cause of late death in heart and lung transplantation
- **D.** Receding as a common problem because of advances in early detection and better immunosuppression

10. What is the role of the respiratory therapist in transplantation?
- **A.** Unimportant after isolated heart transplantation because the native lungs are, by definition, healthy
- **B.** Important only in the postoperative period in heart, heart-lung, and lung transplantation, during the variable period of weaning from mechanical ventilatory support
- **C.** Needed with many intercurrent respiratory infections after lung or heart-lung transplantation because of blunting of the cough reflex
- **D.** Critical in evaluating oxygen saturation trends for cardiologists who are unfamiliar with this technology

REFERENCES

1. Hosenpud JD, Bennett LE, Keck BM, Boucek MM, Novick RJ. The registry of the International Society for Heart and Lung Transplantation: eighteenth official report—2001. *J Heart Lung Transplant*. 2001;20:805.
2. Cooper JD. The evolution of techniques and indications for lung transplantation. *Ann Surg*. 1990;212:249.
3. Goldfarb SB, Benden C, Edwards LB, Kucheryavaya AY, Dipchand AI, Levvey BJ, et al. The registry of the International Society for Heart and Lung Transplantation: eighteenth official pediatric lung and heart-lung transplantation report—2015; focus theme: early graft failure. *J Heart Lung Transplant*. 2015;34(10):1255-1263.
4. Trulock EP. Lung transplantation. *Am J Respir Crit Care Med*. 1997;155:789.
5. Yusen RD, Edwards LB, Dipchand AI, et al. The registry of the International Society for Heart and Lung Transplantation: thirty-second annual pediatric lung and heart–lung transplantation report—2016. *J Heart Lung Transplant*. 2016;35(10):1170-1184.
6. Marks WH, Wagner D, Pearson TC, et al. Organ donation and utilization, 1995-2004: entering the collaborative era. *Am J Transplant*. 2006;6:1101.
7. de Perrot M, Snell GI, Babcock WD, et al. Strategies to optimize the use of current available lung donors. *J Heart Lung Transplant*. 2004;23:1127.
8. Kutsogiannis DJ, Pagliarello G, Doig C, Ross H, Shemie SD. Medical management to optimize donor organ potential: review of the literature. *Can J Anesth*. 2006;53:820.
9. Cooper DK, Keogh AM, Brink J, et al. Report of the Xenotransplantation Advisory Committee of the International Society for Heart and Lung Transplantation: the present status of xenotransplantation and its potential role in the treatment of end-stage cardiac and pulmonary diseases. *J Heart Lung Transplant*. 2000;19:1125.
10. Starnes VA, Barr ML, Cohen RG, et al. Living-donor lobar lung transplantation experience: intermediate results. *J Thorac Cardiovasc Surg*. 1996;112:1284.
11. Morrissey PE, Monaco AP. Donation after circulatory death: current practices, ongoing challenges, and potential implications. *Transplantation*. 2014;97(3):258-264.
12. Based on OPTN data as of February 1, 2013. Available at: https://optn.transplant.hrsa.gov/data/citing-data/.
13. Boucek MM, Mashburn C, Dunn SM, et al. Pediatric heart transplantation after declaration of cardiocirculatory death. *N Engl J Med*. 2008;359:709.
14. Sweet SC, Spray TL, Huddleston CB, et al. Pediatric lung transplantation at St. Louis Children's Hospital, 1990-1995. *Am J Respir Crit Care Med*. 1997;155:1027.
15. Noyes BE, Kurland G, Orenstein DM. Lung and heart–lung transplantation in children. *Pediatr Pulmonol*. 1997;23:39.
16. Baum D, Bernstein D, Starnes VA, et al. Pediatric heart transplantation at Stanford: results of a 15-year experience. *Pediatrics*. 1991;88:203.
17. Cohen AH, Mallory Jr GB, Ross K, et al. Growth of lungs after transplantation in infants and in children younger than 3 years of age. *Am J Respir Crit Care Med*. 1999;159:1747.
18. Kirk R, Dipchand AI, Edwards LB, et al. The registry of the International Society of Heart and Lung Transplantation: fifteenth pediatric heart transplantation report—2012. *J Heart Lung Transplant*. 2012;31:1065.
19. Pahl E, Fricker FJ, Armitage J, et al. Coronary arteriosclerosis in pediatric heart transplant survivors: limitation of long-term survival. *J Pediatr*. 1990;116:177.
20. Boucek MM, Kanakriyeh MS, Mathis CM, Trimm RF 3rd, Bailey LL. Cardiac transplantation in infancy: donors and recipients. Loma Linda University Pediatric Heart Transplant Group. *J Pediatr*. 1990;116:171.
21. Ross M, Kouretas P, Gamberg P, et al. Ten- and 20-year survivors of pediatric orthotopic heart transplantation. *J Heart Lung Transplant*. 2006;25:261.
22. Shewmon DA, Capron AM, Peacock WJ, Schulman BL. The use of anencephalic infants as organ sources: a critique. *JAMA*. 1989;261:1773-1781.
23. Spray TL, Mallory GB, Canter CE, Huddleston CB, Kaiser LR. Pediatric lung transplantation for pulmonary hypertension and congenital heart disease. *Ann Thorac Surg*. 1992; 54:216.
24. Ramirez JC, Patterson GA, Winton TL, de Hoyos AL, Miller JD, Maurer JR. Bilateral lung transplantation for cystic fibrosis. *J Thorac Cardiovasc Surg*. 1991;103:287.
25. Mendeloff EM, Huddleston CB, Mallory GB, et al. Pediatric and adult lung transplantation for cystic fibrosis. *J Thorac Cardiovasc Surg*. 1998;115:404.
26. *U.S. Organ Procurement and Transplantation Network and The Scientific Registry of Transplant Recipients*. Available at: http://www.optn.org. Accessed October 2008.
27. Noirclerc M, Shennib H, Giudicelli R, et al. Size matching in lung transplantation. *J Heart Lung Transplant*. 1992;11: S203.
28. Starnes VA, Lewiston NJ, Luikart H, Theodore J, Stinson EB, Shumway NE. Current trends in lung transplantation. Lobar transplantation and expanded use of single lungs. *J Thorac Cardiovasc Surg*. 1992;104:1060.
29. Starnes VA, Woo MS, MacLaughlin EF, et al. Comparison of outcomes between living donor and cadaveric lung transplantation in children. *Ann Thorac Surg*. 1999;68:2279.

30. Egan T, Murray S, Bustami RT, et al. Development of the new lung allocation system in the United States. *Am J Transplant*. 2006;6:1212.
31. Boehler A, Kesten S, Weder W, Speich R. Bronchiolitis obliterans after lung transplantation: a review. *Chest*. 1998; 114:1411.
32. Date H, Lynch JP, Sundaresan S, Patterson GA, Trulock EP. The impact of cytolytic therapy on bronchiolitis obliterans syndrome. *J Heart Lung Transplant*. 1998;17:869.
33. Jurmann MJ, Dammenhayn L, Schaefers HJ, Haverich A. Pulmonary reperfusion injury: evidence for oxygen-derived free radical mediated damage and effects of different free radical scavengers. *Eur J Cardiothorac Surg*. 1990;4:665.
34. Paradis IL, Duncan SR, Dauber JH, Yousem S, Hardesty R, Griffith B. Distinguishing between infection, rejection, and the adult respiratory distress syndrome after human lung transplantation. *J Heart Lung Transplant*. 1992;11:S232.
35. Meyers BF, de la Morena M, Sweet SC, et al. Primary graft dysfunction and other selected complications of lung transplantation: a single-center experience of 983 patients. *J Thorac Cardiovasc Surg*. 2005;129:1421.
36. Trachiotis GD, Knight SR, Hann M, et al. Carbon dioxide response in lung transplant recipients [abstract]. *Am Rev Respir Dis*. 1992;145:A702.
37. Patterson GA, Todd TR, Cooper JD, Pearson FG, Winton TL, Maurer J. Airway complications after double lung transplantation. Toronto Lung Transplant Group. *J Thorac Cardiovasc Surg*. 1990;99:14.
38. Kaditis AG, Gondor M, Nixon PA, et al. Airway complications following pediatric lung and heart-lung transplantation. *Am J Respir Crit Care Med*. 2000;162:301.
39. Trulock EP, Ettinger NA, Brunt EM, Pasque MK, Kaiser LR, Cooper JD. The role of transbronchial lung biopsy in the treatment of lung transplant recipients. An analysis of 200 consecutive procedures. *Chest*. 1992;102:1049.
40. Maurer JR, Tullis DE, Grossman RF, Vellend H, Winton TL, Patterson GA. Infectious complications following isolated lung transplantation. *Chest*. 1992;101:1056.
41. Nunley DR, Grgurich W, Iacono AT, et al. Allograft colonization and infections with Pseudomonas in cystic fibrosis lung transplant recipients. *Chest*. 1998;113:1235.
42. Chaparro C, Maurer J, Gutierrez C, et al. Infection with Burkholderia cepacia in cystic fibrosis: outcome following lung transplantation. *Am J Respir Crit Care Med*. 2001; 163:43.
43. Snell GI, de Hoyos A, Krajden M, Winton T, Maurer JR. Pseudomonas cepacia in lung transplant recipients with cystic fibrosis. *Chest*. 1993;103:466.
44. Cooper JD, Billingham M, Egan T, et al. A working formulation for the standardization of nomenclature and for clinical staging of chronic dysfunction in lung allografts. International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 1993;12:713.
45. Cohen AH, Sweet SC, Mendeloff E, et al. High incidence of posttransplant lymphoproliferative disease in pediatric patients with cystic fibrosis. *Am J Respir Crit Care Med*. 2000; 161:1252.
46. Kurland G, Orenstein DM. Lung transplantation and cystic fibrosis: the psychosocial toll. *Pediatrics*. 2001;107:1419.
47. Craven JL, Bright J, Dear CL. Psychiatric, psychosocial and rehabilitative aspects of lung transplantation. *Clin Chest Med*. 1990;11:247.
48. Uzark K, Griffin L, Rodriguez R, et al. Quality of life in pediatric heart transplant recipients: a comparison with children with and without heart disease. *J Heart Lung Transplant*. 2012; 31:571.
49. Wray J, Radley-Smith R. Beyond the first year after pediatric heart or heart-lung transplantation: changes in cognitive function and behavior. *Pediatr Transplant*. 2005;9:170.
50. Mitchell MJ, Baz MA, Fulton MN, Lisor CF, Braith RW. Resistance training prevents vertebral osteoporosis in lung transplant recipients. *Transplantation*. 2003;76(3):557-562.
51. Deliva RD, Hassall A, Manlhiot C, Solomon M, McCrindle BW, Dipchand AI. Effects of an acute, outpatient physiotherapy exercise program following pediatric heart or lung transplantation. *Pediatr Transplant*. 2012;16(8):879-886.

Neonatal Pulmonary Disorders

22

Anne Hansen, Jonathan Levin

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. Identify and differentiate the causes of neonatal respiratory distress and understand the underlying pathophysiology of each one.
2. Discuss the factors in prenatal and postnatal life that may increase the risks for developing respiratory distress.
3. Recognize the clinical features of common pulmonary disorders in neonates, differentiate among various diagnostic entities, and identify those that are life threatening.
4. Describe the preventive and therapeutic approach for various forms of neonatal pulmonary diseases to optimize outcome and minimize morbidity.

Key Terms

acute life-threatening event
amnioinfusion
apnea
apnea of infancy
apnea of prematurity
brief resolved unexplained event (BRUE)
extremely low-birth-weight infant
gentle ventilation
low-birth-weight infant
meconium
oxygenation index
periodic breathing
permissive hypercapnia
pneumomediastinum
pneumopericardium
pneumoperitoneum
pneumoretroperitoneum
pneumothorax
postductal
precipitous delivery
preductal
pulmonary interstitial emphysema
reduced alveolar recruitment
subcutaneous emphysema
sudden infant death syndrome
systemic air embolism
tension pneumothorax
very-low-birth-weight infant
volutrauma

Disorders that result in respiratory distress remain a major reason for morbidity and mortality among neonates. The more premature the neonate is, the more likely that respiratory complications will develop. However, term and postterm infants can also experience respiratory difficulty resulting from pulmonary or nonpulmonary conditions (Table 22-1). The most common neonatal pulmonary disorders are addressed in this chapter.

RESPIRATORY DISTRESS SYNDROME

INCIDENCE

Respiratory distress syndrome (RDS), formerly known as *hyaline membrane disease,* is estimated to affect 1% of births in the United States. Its incidence and severity are inversely related to gestational age and birth weight. A large cohort study from the National Institute of Child Health and Human Development (NICHD) had a 93% incidence of RDS in infants younger than 28 weeks gestation born between 2002 and 2007.[1] In a report from the NICHD Neonatal Research Network, the incidence of RDS was 44% in infants weighing 501 to 1500 g (Box 22-1).[2] RDS may occur in late preterm and term infants, albeit with much less frequency; in one large cohort of US births between 2002 and 2008, RDS was diagnosed in 10.5% of infants born at 34 weeks gestation but only 0.3% of infants born at 38 weeks gestation.[3]

In 1979, RDS was the second-ranking cause of death in infants, but because of the progress made in prenatal care, it dropped to eighth place in 2014, when RDS accounted for only 10.5 deaths per 100,000 live births.[4]

Although the greatest risk factor for RDS is prematurity, other risk factors include maternal diabetes, multiple births, cesarean delivery, **precipitous delivery**, fetal asphyxia, cold stress, and a maternal history of previously affected infants, suggesting a genetic component. Incidence is higher in male and white infants.

ETIOLOGY AND PATHOPHYSIOLOGY

In 1959, Avery and Mead reported that RDS was associated with a deficiency of pulmonary surfactant and abnormal lung surface tension properties.[5] Since that time, it has been widely accepted that the pathophysiology of RDS is the result of an insufficient amount of surfactant and immature cellular and vascular development of the lungs.

Normal fetal lung development occurs in stages, starting with the embryonic stage (four to five weeks gestation), followed by the pseudoglandular stage (5 to 16 weeks), the canalicular stage (16 to 24 weeks), the saccular stage (24 to 32 weeks), and the alveolar stage (after 32 weeks). Primitive alveoli develop between 27 and 35 weeks of gestation, and true alveoli develop after 32 weeks of gestation, increasing in number for at least 2 years after term equivalence.

At approximately 20 weeks of gestation, alveolar type II cells begin to differentiate, which synthesize and store surfactant as lamellar bodies. Increasing amounts are produced as the fetus approaches term. Between 28 and 38 weeks of gestation, surfactant is secreted into the alveoli and eventually migrates into the amniotic fluid through the trachea. Surfactant is composed of 90% lipids (primarily phospholipids) and 10% protein (SP-A, SP-B, SP-C, and SP-D). With its release into the alveoli, surfactant reduces the surface tension and helps maintain alveolar stability when the lung transitions to a gas-filled organ at birth. Infants born before 28 weeks of gestation have structural underdevelopment of the terminal air spaces with deficiency in both the quantity and quality (related to differences in composition) of surfactant, leading to a high risk of RDS.

Deficient surfactant production or deficient release of surfactant into the immature respiratory alveoli results in an increase in surface forces and lung elastic recoil. Coupled with the extremely compliant chest wall of the preterm infant, this leads to **reduced alveolar recruitment** (atelectasis). This condition is characterized by decreased functional residual capacity (FRC), decreased pulmonary compliance, increased pulmonary resistance, and ventilation–perfusion mismatch.

The resulting hypoxia, hypercapnia, and respiratory acidosis constrict the pulmonary arteries and reduce

Table 22-1 Neonatal Disorders That May Present as Respiratory Distress

CONDITION	GESTATIONAL AGE	HISTORY	EXAMINATION	GASES	PRESENTATION		CHEST RADIOGRAPH	COMMENTS
					LESS THAN 6 HOURS	6 HOURS		
Respiratory distress syndrome	PT	No or incomplete maternal steroid administration	Prematurity, decreased aeration	Respiratory acidosis with hypoxemia	Typical	Rare	Low lung volume "Ground glass" Air bronchograms	Working diagnosis in all preterm neonates unless chest radiograph suggests alternative. Always consider infection.
Pneumonia/ infection	Any	Risk factors for chorioamnionitis	Signs and symptoms of sepsis	Respiratory acidosis with hypoxemia	Any age	Any age	Often nonspecific	Difficult to exclude; working diagnosis pending clinical course and laboratory testing (CBC, +/− CRP, culture of blood +/−, tracheal aspirate, CXR).
Aspiration pneumonia	Any	May have history of feeding discoordination	May have observed aspiration event	Respiratory acidosis with hypoxemia	Rare	Typical	Unchanged immediately after event	Warrants feeding evaluation, modified swallow study.
Meconium aspiration	FT	Meconium-stained amniotic fluid at delivery Postmaturity	Meconium-stained skin +/− nails and cord	Respiratory acidosis with hypoxemia	Typical	Rare	Overinflated with streaky, patchy infiltrates	Diagnosis based on history of meconium-stained amniotic fluid. Infection may coexist.
Persistent pulmonary hypertension	FT more than PT	May have had meconium aspiration or mild asphyxia	Preductal and postductal saturation differential, may hear soft murmur of tricuspid insufficiency	Marked hypoxemia, +/− preductal–postductal saturation differential; may have relatively normal P_{CO_2}	Typical	Rare	May see decreased pulmonary blood flow; often accompanies meconium aspiration	Echocardiogram shows right-to-left shunting through PFO or PDA. Differential includes cyanotic heart disease.
Pneumothorax or pneumomediastinum	Any	May have required PPV at birth	Asymmetric breath sounds, hypotension, + transillumination	Respiratory acidosis with hypoxemia	Any age	Any age	Extrapleural air with atelectasis +/− mediastinal shift	Most typical in setting of positive pressure ventilation.
Transient tachypnea	FT more than PT	Often cesarean section delivery without labor	Peaceful tachypnea	Mild respiratory acidosis and hypoxemia	Typical	Rare	Fluid in fissure with hyperinflation	Most common cause of mild respiratory distress in term newborns.

Continued

Table 22-1 Neonatal Disorders That May Present as Respiratory Distress—cont'd

CONDITION	GESTATIONAL AGE	HISTORY	EXAMINATION	GASES	PRESENTATION		CHEST RADIOGRAPH	COMMENTS
					LESS THAN 6 HOURS	6 HOURS		
Pulmonary hemorrhage	PT more than FT	PDA or other cause of excess pulmonary blood flow coagulopathy, bleeding tendency, after administration of exogenous surfactant	Blood in larynx or suctioned from endotracheal tube	Respiratory acidosis with hypoxemia	Rare	More common	Unhelpful; usually a white-out	Diagnosis based on clinical findings.
Pulmonary hypoplasia	Any	Oligohydramnios, prolonged rupture of membranes	Potter's features	Profound hypoxemia and hypercapnia	Typical	Rare	Small lungs, bell-shaped chest, often develop pnemothorax (PTX)	Often fatal
Congenital pulmonary malformations	FT more than PT	Depends on malformation May have been detected on antenatal ultrasound	Depends on malformation	Depends on malformation	Typical	If mild symptoms	Usually diagnostic	Diaphragmatic hernia or eventration, congenital pulmonary adenomatous malformation, TEF/EA, lobar agenesis
Upper airway obstruction	FT more than PT	Typically no prenatal concern If severe, can cause polyhydramnios	Stridor, respiratory distress; if choanal atresia, unable to pass nasogastric tube via nare(s) Symptoms resolve with intubation	Hypercapnia and hypoxia, gases normal when intubated	Typical if congenital	If congenital and symptoms are mild, or if acquired	Usually normal	Recommend ORL consult laryngoscopy be diagnostic.
Primary neurologic or muscle disease	FT more than PT	May be positive FH or history of unexplained neonatal death May have history of Polyhydramnios	Marked hypotonia Areflexia, abnormal facial expression No evidence of lung disease	May have mild hypercapnia	If symptoms are severe	Typical	Usually normal	Recommend neurology consultation. May need electromyography or muscle biopsy.
Congenital heart disease	FT more than PT	May have been detected on antenatal ultrasound	Murmurs, signs of heart failure, diminished pulses	Often cyanotic with normal to low CO_2	If right to left shunt	If duct dependent	Abnormal pulmonary blood flow, heart size or shape	Echocardiogram usually diagnostic.
After severe asphyxia	FT	Nonreassuring fetal heart tracing (NRF HRT), low Apgar scores	Other features of asphyxia including low tone	Marked metabolic acidosis	Typical	Rare	Normal	Tachypnea driven by metabolic acidosis.
Inborn errors of metabolism	FT more than PT	State screen may be positive. May have FH or history of unexplained neonatal death.	No evidence of lung disease Tachypnea driven by metabolic acidosis	Severe metabolic acidosis with normal to low $PaCO_2$	Rare	Typical	Usually normal	Diagnosis based on laboratory testing, metabolism consultation.

CBC, Complete blood count; *CRP,* C-reactive protein; *CXR,* chest x-ray; *FT,* full term; *PDA,* patent ductus arteriosus; *PT,* preterm.

Box 22-1 Incidence of Respiratory Distress Syndrome by Birth Weight

BIRTH WEIGHT (g)	INCIDENCE OF RESPIRATORY DISTRESS SYNDROME
501-750	71%
751-1000	55%
1001-1250	37%
1251-1500	23%

(From Fanaroff AA, Stoll BJ, Wright LL, et al: Trends in neonatal morbidity and mortality for very low birth weight infants. *Am J Obst Gynecol* 196:147.e1, 2007.)

pulmonary blood flow. This results in damage to the cells lining the alveoli and pulmonary hypertension. The elevated pulmonary blood pressures can in turn lead to increased right-to-left shunting through the patent ductus arteriosus (PDA) and foramen ovale (extrapulmonary), as well as within the lung itself (intrapulmonary). Other pathophysiologic processes that contribute to the clinical picture include poor gas exchange secondary to inadequate surface area, compliant chest wall that reduces effectiveness of ventilation, thickened alveolar–capillary membrane, insufficient vascularization, inflammation and lung injury, and resulting pulmonary edema.

Other clinical scenarios may present with similar pathophysiology. Meconium aspiration syndrome (described later in this chapter) or pulmonary hemorrhage may inactivate surfactant. Though rare, genetic disorders of surfactant proteins, including abnormalities in surfactant protein B and C genes, as well as a gene responsible for transporting surfactant across membranes (ABC transporter 3 [*ABCA3*]), present with severe and often lethal familial neonatal respiratory disease.[6]

Chronic stress seems to protect infants at risk for the development of RDS by stimulating surfactant synthesis, likely via endogenous production of steroids. Conditions associated with chronic stress include maternal toxemia, prolonged rupture of membranes, and chorioamnionitis. Histologic chorioamnionitis is associated with a decreased incidence of RDS, and in experimental models, bacterial endotoxin or the proinflammatory cytokine interleukin 1 (IL-1) induces lung maturation when given by intraamniotic injection.[7]

CLINICAL PRESENTATION AND DIAGNOSIS

Clinical Presentation

Although many premature infants will have a brief "honeymoon" period shortly after delivery, many will present with signs and symptoms within the first 6 hours after birth. Infants with RDS exhibit tachypnea and labored breathing, including subcostal retractions and nasal flaring. A characteristic grunt during expiration, an attempt to maintain the FRC, may also be present. Intercostal and subcostal retractions are apparent and occur when the negative intrathoracic inspiratory pressures distort the chest wall instead of inflating the stiff lungs. The retractions may have a "see-saw" appearance, with the abdomen protruding as the chest pulls in. Infants often look distressed, and the very premature infant may be hypotonic with decreased responsivity. Chest auscultation reveals diminished aeration despite the increased work of breathing.

Without stabilization of the alveoli, infants with RDS have increasing cyanosis that is relatively unresponsive to oxygen therapy. Larger infants may need minimal oxygen initially but require more as atelectasis becomes progressively worse. Without exogenous surfactant administration, the disease will typically progress over 48 to 72 hours, with subsequent improvement as endogenous surfactant production is increased and marked diuresis occurs, with improvement in pulmonary function usually by 1 week of age.

Investigations

1. Blood gas analysis: Reveals moderate to severe hypoxemia, varying degrees of hypercapnia, and respiratory acidosis.
2. Chest x-ray (CXR): Typically reveals air bronchograms and diffuse, fine, granular (reticulogranular) densities, described as a "ground-glass" appearance (Figure 22-1). The heart may be slightly enlarged.
3. Hyponatremia is often present because of water retention; this improves with fluid restriction.
4. Assessments of fetal lung maturity before delivery are rarely used before 32 weeks of gestation because of the high prevalence of fetal lung immaturity at this gestational age. Even at gestational ages between 32 and 38 weeks, assessments of lung maturity are often omitted in favor of clinical judgment (i.e., need for urgent delivery because of fetal or maternal indications, or safe delay of delivery regardless of fetal lung maturity). When assessment of fetal lung maturity is used to help decide the need for a semielective preterm delivery, the following may be used:
   a. Lecithin-to-sphingomyelin (L:S) ratio: Lecithin, also known as *dipalmitoylphosphatidylcholine,* is the most abundant phospholipid found in surfactant. RDS is unlikely if the L:S ratio is 2.0 or greater. The L:S ratio is unreliable in pregnancies complicated by diabetes and Rh isoimmunization. Additionally, the test may take several hours to perform.
   b. Phosphatidylglycerol (PG) level: PG is the second most abundant phospholipid in surfactant, and levels increase toward term. The presence of PG in amniotic fluid indicates a low risk for RDS. A patient with an L:S ratio above 2 and a lack of PG has a more than 80% risk of RDS.

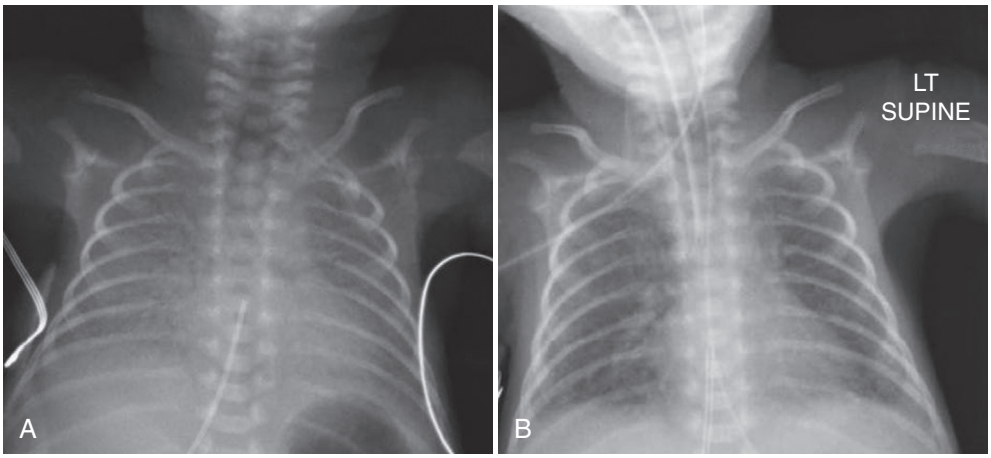


FIGURE 22-1 These images were obtained from a 27-week infant (birth weight 670 g) with respiratory distress syndrome. **(A)** Preintubation and surfactant, with fine granular "ground glass" opacification bilaterally and air bronchograms present. **(B)** Postintubation and administration of exogenous surfactant, with endotracheal tube in place and improved aeration bilaterally. The umbilical venous catheter is in high position in the right atrium on the film. This infant went on to have severe bronchopulmonary dysplasia.

c. Foam stability test (shake test): This is performed by mixing amniotic fluid with different volumes of 95% ethanol. When this mixture is shaken with air, a foam develops that can be seen for several hours at room temperature. If no surfactant is present, the foam will not appear or will appear only briefly, indicating a high likelihood of immature lungs. This test is not as specific as a low L:S ratio.

PREVENTION

1. Prevention of prematurity: Because RDS is associated with incomplete development of the lung at birth, prevention of prematurity will largely prevent RDS. Avoiding unnecessary or poorly timed elective cesarean section, appropriate management of high-risk pregnancy and labor, and prediction of pulmonary immaturity with possible *in utero* acceleration of maturation with antenatal steroids are important preventive strategies.
2. Antenatal steroid therapy: Clinical trials have shown that maternal corticosteroid treatments decrease the incidence of RDS by about 50%, and infants who do develop RDS tend to have less severe disease.[8] Antenatal steroids also reduce (1) neonatal mortality; (2) the need for and duration of ventilatory support; and (3) the incidence of severe intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), early-onset sepsis, and developmental delay. Postnatal growth is not adversely affected. Antenatal steroids do not increase the risk of maternal death, chorioamnionitis, or puerperal sepsis.

Guidelines for antenatal steroid usage have been produced by multiple organizations, including the American Congress of Obstetricians and Gynecologists[9] and the Royal College of Obstetricians and Gynaecologists.[10] Their recommendations include the following:

- Antenatal treatment with corticosteroids should be considered for all women at risk of preterm labor between 24 and 34 weeks and for women at risk of delivering within 7 days between 34 and 36 weeks of gestation. Steroids may also be considered in the periviable period (23 to 24 weeks) for women at risk of delivering within 7 days.
- Treatment should consist of two doses of betamethasone given intramuscularly 24 hours apart or four doses of dexamethasone given 12 hours apart. Betamethasone is often preferred because it was associated with a lower risk of IVH in a Cochrane review compared with dexamethasone; however, rates of *severe* IVH and periventricular leukomalacia (PVL) were similar.[11]
- Treatment for less than 24 hours is still associated with significant improvement in outcome; thus corticosteroids should be given unless immediate delivery is anticipated.

TREATMENT

Keys to the general management of infants with RDS are as follows:

1. Prevent hypoxemia and acidosis (this allows normal tissue metabolism, optimizes surfactant production, and prevents right-to-left shunting related to relatively high pulmonary pressures).
2. Prevent worsening atelectasis and pulmonary edema.
3. Minimize oxidant lung injury.
4. Minimize lung injury caused by mechanical ventilation.
5. Optimize fluid management (avoiding hypovolemia and shock, on the one hand, and edema, particularly pulmonary edema, on the other).
6. Reduce metabolic demands, largely by providing a neutral thermal environment.

Surfactant Replacement

The efficacy of exogenous surfactant administration is well established in reducing mortality and morbidity (including pneumothorax and pulmonary interstitial emphysema) in premature infants.[12,13] However, more recent data recognized that the benefits of surfactant administration must be weighed against the risks of intubation and mechanical ventilation. This change in practice is reflected in the most recent American Academy of Pediatrics (AAP) guideline regarding respiratory care of preterm infants.[14]

Types of surfactants. Several types of surfactant preparations are licensed for use in babies with RDS (Table 22-2). Exogenous lung surfactant can be either natural or synthetic; early synthetic forms lacked protein B and C analogues. Both forms of surfactants are effective at reducing the severity of RDS; however, comparative trials demonstrate a lower requirement for early ventilatory support and fewer pneumothoraces with natural surfactant extracts.[15] A 2015 Cochrane metaanalysis suggested improved outcomes with porcine-derived extract (poractant alfa) versus bovine minced extract (beractant), including a lower risk of mortality or oxygen requirement at 36 weeks, PDA needing treatment, and repeat administration of surfactant. However, the effect may have been related to higher doses of poractant than beractant.[16] In 2012, a peptide-containing synthetic surfactant was made that mimicked protein B activity (lucinactant), but it is not currently available because of a voluntary discontinuation by the manufacturer.

Timing of administration. In the era of noninvasive respiratory support, every effort is made to minimize exposure to sustained mechanical ventilation and supplemental oxygen. Two basic strategies for surfactant replacement have emerged: prophylactic (or preventive) treatment, in which surfactant is administered at the time of birth or shortly thereafter to infants who are at high risk for developing RDS, and rescue (or therapeutic) treatment, in which surfactant is administered after the initiation of mechanical ventilation in infants with clinically confirmed RDS. Although prophylactic administration in mechanically ventilated patients has been shown to be superior compared with rescue therapy, many of these studies were performed before the routine use of continuous positive airway pressure (CPAP) in the delivery room to establish FRC and prevent atelectasis.[17] Selective analysis of more recent studies, conducted with more consistent use of antenatal steroids and an initial trial of CPAP in the delivery room, supports a decreased risk of chronic lung disease or death when using early stabilization on CPAP and selective surfactant administration.[18]

An alternative approach is intubation and surfactant administration followed by immediate extubation (INSURE), which has been used commonly worldwide. Early clinical trials supported this approach versus prophylactic administration of surfactant and mechanical ventilation with regard to mechanical ventilation or oxygen requirement at 28 days. However, in the 2011 Vermont Oxford Network Delivery Room Management Trial, the INSURE approach resulted in a similar risk reduction for death and bronchopulmonary dysplasia (BPD) as the early trial of CPAP approach.[19]

Thus current guidelines recommend early stabilization with nasal CPAP (see Continuous Positive Airway Pressure) and selective intubation with surfactant administration for infants with apnea, respiratory failure, or persistent hypoxemia on CPAP (forced inspiratory oxygen [FiO_2] of 0.30-0.40 or more to maintain oxygen saturation of at least 90%). When surfactant is administered, it is most effective when given early (first 2 hours of life), with an attempt to rapidly wean toward extubation. An additional dose of surfactant may be considered for infants who remain intubated at 12 hours of life with an Fio_2 requirement above 0.30.[20]

Methods of administration. The surfactant preparation is delivered over a period of a few seconds via the endotracheal tube (ETT), usually through a feeding tube that has been cut to an appropriate length to be at a level just above the carina. The peripheral dispersion of surfactant into the terminal airways is facilitated by intermittent positive-pressure ventilation (IPPV), either manually or using the ventilator. Oxygen saturation should be closely monitored during administration, and tidal volumes or peak inspiratory pressures should be monitored closely

Table 22-2 Currently Available Surfactants

	TRADE NAME	SOURCE	MANUFACTURER	INITIAL DOSE	REPEAT DOSING
Poractant alfa	Curosurf	Porcine	Chiesi Farmaceutici	200 mg/kg/dose (2.5 mL/kg)	1.25 mL/kg every 12 hours for up to 2 total doses
Calfactant	Infasurf	Bovine	Ony	105 mg/kg/dose (3 mL/kg)	3 mL/kg every 12 hours for up to 3 total doses
Beractant	Survanta	Bovine	Abbott Laboratories	100 mg/kg/dose (4 mL/kg)	4 mL/kg every 6 hours for up to 4 total doses

afterward because of the potential for rapidly changing lung compliance.

Other methods of surfactant administration without intubation have been used with varying success. These include antenatal intraamniotic instillation, pharyngeal instillation, laryngeal mask instillation, direct tracheal instillation without intubation through a thin catheter, and surfactant nebulization. A 2016 systematic review of available evidence suggested promising results for less-invasive surfactant administration into the trachea through a thin catheter with regard to a combined outcome of death and BPD.[21] However, the findings were limited by the overall low quality of evidence related to potential for bias, thus these methods have not yet been widely adopted until they are proven in well-designed randomized controlled trials.

Complications. Procedural complications resulting from the administration of surfactant include plugging of the ETT by surfactant, desaturation and increased need for supplemental oxygen, bradycardia from hypoxia, tachycardia caused by agitation, pharyngeal or esophageal deposition of surfactant, administration of surfactant to only one lung (i.e., right mainstem intubation), and administration of a suboptimal dose.

Physiologic complications of surfactant replacement therapy include apnea, pulmonary hemorrhage, increased necessity for treatment of PDA, and **volutrauma** or pneumothorax resulting from an increase in lung compliance after surfactant replacement with failure to wean ventilator settings.

Oxygen Therapy

During the initial assessment phase, or in mild cases of RDS (particularly in term or near-term infants), oxygen can be provided via an oxygen hood or cannula. With an oxygen hood, the oxygen is warmed, humidified, and delivered through an air–oxygen blender that allows precise control over the oxygen concentration.

Oxygenation is assessed by means of either pulse oximetry or blood gas analysis until the appropriate oxygen level is obtained. Pulse oximetry is a reliable, noninvasive method to monitor oxygenation and in most infants is preferred over frequent blood gas analysis.

When providing oxygen therapy, care should be taken to minimize the Fio_2 to no more than necessary, particularly for preterm infants. Hyperoxemia may contribute to lung damage and BPD via free radical toxicity and retinopathy of prematurity (ROP) through abnormal vascularization. Multiple trials that have enrolled thousands of preterm infants have sought to identify optimal oxygen saturation targets, comparing low (85%-89%) versus high (91%-95%) target ranges.[22] These include the Canadian Oxygen Trial,[23] the Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (SUPPORT) study,[24] and the Benefits of Oxygen Saturation Targeting II (BOOST-II) trial.[25] In summary, the studies showed an increased risk of mortality at hospital discharge and increased risk of necrotizing enterocolitis, but lower risk of severe retinopathy among survivors in the low-saturation target group. Thus many units institute a saturation target range of approximately 90% to 95% in premature infants receiving supplemental oxygen based on these data.

Continuous Positive Airway Pressure

If oxygen saturation cannot be kept in an acceptable range by hood or cannula oxygen, or if the patient develops excessive carbon dioxide (CO_2) retention or work of breathing, the next step in the escalation of respiratory support is CPAP. CPAP may be administered via various facial interfaces, with a continuous-flow ventilator or tubing submerged in sterile water to deliver the desired peak-end expiratory pressure. The oscillations provided by "bubble" CPAP may have some benefits over a continuous-flow ventilator, including improved lung recruitment, work of breathing, and gas exchange.[26]

A CPAP of 5 to 6 cm H_2O is the usual starting point for these infants. The pressure can then be adjusted in increments of 1 to 2 cm H_2O to a maximum of about 8 cm H_2O while observing the baby's respiratory rate and effort as well as monitoring oxygen saturation. An orogastric tube is placed to decompress gastric air. As the infant improves, weaning begins by gradually reducing the FiO_2 to maintain the target oxygen saturation. Generally, when FiO_2 is less than 0.30, CPAP can be reduced to 5 cm H_2O. Physical examination will provide evidence of respiratory effect during weaning, and CXR may help estimate lung volume. Lowering of the distending pressure should be attempted with caution if the lung volumes appear low and alveolar atelectasis persists. CPAP generally can be discontinued if there is no distress, the infant has few or no apneic spells, and the Fio_2 remains less than 0.30.

As mentioned previously, the early application of CPAP in preterm newborns can reduce the need for intubation, thereby improving mortality and respiratory outcomes. Early alveolar expansion in the delivery room may establish an FRC and may stimulate intrinsic surfactant production without further intervention. During this time, if the infant requires an Fio_2 of more than 0.30 to 0.40 on CPAP, consider intubation and exogenous surfactant treatment.

The safety and efficacy of early CPAP were established in the landmark SUPPORT trial. In this study, infants born between 24 and 27 weeks of gestation were randomized to receive prophylactic surfactant administration with a limited ventilation strategy or

early application of CPAP with strict criteria for intubation and surfactant administration. Rates of death and BPD were similar, with similar rates of adverse events and air leaks. However, the most immature infants, born at 24 to 25 weeks of gestation, benefited most from the early CPAP, with improved mortality.[27] Follow-up data among the entire cohort at 18 to 22 months demonstrated improved respiratory symptoms and morbidity and no difference in neurodevelopmental outcomes.[28,29] Early application of CPAP may be considered in preterm infants for the treatment of RDS, because subsequent systematic reviews and guidelines have supported this approach to improve respiratory morbidities and prevent development of chronic lung disease.[14,18,20,30,31,32]

CPAP is also used as a step-down mode from mechanical ventilation in infants, particularly preterm infants, with RDS. Nasal intermittent positive pressure ventilation (NIPPV) is sometimes used as an alternative noninvasive means of support in RDS, particularly after extubation to avoid the need for reintubation, though current data have not shown NIPPV to be superior to CPAP with regard to development of chronic lung disease or mortality.[33,34] Novel methods such as noninvasive neurally adjusted ventilatory assist (NIV-NAVA), which detects diaphragm electrical activity (Edi) to coordinate noninvasive breaths, may offer improvements to noninvasive ventilation, with better patient synchrony and tolerance.[35] A humidified, heated high-flow nasal cannula, with or without oxygen, has also not been shown to be equivalent or superior to CPAP as initial therapy for RDS in preterm infants.[36] Options for noninvasive ventilation are a topic of active research.

Mechanical Ventilation

Typical indications for endotracheal intubation and mechanical ventilation are infants with respiratory failure or persistent apnea. Reasonable measures of respiratory failure are (1) arterial blood pH less than 7.20 to 7.25, (2) $PaCO_2$ of 60 mm Hg or higher, (3) oxygen saturation less than 85% at FiO_2 of 40% or more on CPAP, and (4) persistent apnea.

Generally, once the infant is stabilized in the neonatal intensive care unit (NICU), a pressure-limited ventilator using a sinusoidal flow pattern is used. Peak inspiratory pressures (PIPs) are generally adjusted to 15 to 25 cm H_2O, depending on the size of the infant and the severity of the disease, to establish a tidal volume (V_T) between 4 and 5 mL/kg. Positive end-expiratory pressure (PEEP) levels of 4 to 6 cm H_2O are used to prevent further alveolar collapse, and rates of 20 to 40 breaths per minute are used to treat hypercapnia. Inspiratory time (Ti) should be initiated at 0.3 to 0.4 second. If a longer Ti is required before surfactant administration, it should be lowered to 0.3 second after surfactant is administered. After surfactant administration, pulmonary compliance may improve rapidly, requiring lower PIPs to attain a similar V_T.

Most modern ventilators use pressure and flow measurements to produce real-time pulmonary function data. These numeric data and graphical displays can be used to correct V_T to optimize ventilation parameters and pulmonary mechanical parameters. Ventilator modes such as synchronized intermittent mandatory ventilation (SIMV), pressure support, and assist-control modes can reduce work of breathing and blood pressure fluctuations if sensitivities are set properly. Modes that maintain a consistent V_T, known as *volume-targeted ventilation*, reduce the risk of volutrauma (damage to the lung caused by overdistention by a mechanical ventilator set for an excessively high V_T), particularly after the administration of surfactant.[37] High-frequency ventilation (HFV) may be indicated in infants who cannot be ventilated with the usually effective Fio_2 levels, ventilator pressures, and rates; this includes high-frequency oscillatory ventilation (HFOV) and high-frequency jet ventilation (HFJV). Despite their use as rescue therapy, current evidence does not yet support their use as initial therapy in RDS over conventional ventilation.[38]

Caffeine citrate (bolus followed by maintenance dosing) should be considered before extubation to prevent apnea of prematurity. Many centers start caffeine within the first 24 to 72 hours of birth, given evidence of its role in improving rates of bronchopulmonary dysplasia (see Apnea).

Supportive Care and Monitoring

The general principles for supportive care of any premature infant should be followed. Treatment of acidosis, hypoxia, hypotension, and hypothermia may decrease the severity of RDS.

Use of an incubator is preferable to a radiant warmer in **very-low-birth-weight** (VLBW) **infants** because of the high insensible water losses associated with radiant heat. Calories and fluids should initially be provided intravenously, with enteral feeds initiated and advanced as tolerated. Excessive fluids might contribute to the development of PDA, pulmonary edema, and BPD.

Optimal care requires careful and frequent monitoring of heart and respiratory rates, oxygen saturation, blood pressure, temperature, blood gas status, serum electrolytes, glucose, and hematocrit. In addition to cardiopulmonary monitors and pulse oximetry, transcutaneous oxygen and CO_2 monitors and end-tidal CO_2 can be used as noninvasive tools to monitor the infant's progress.

Chest radiography is useful in managing VLBW infants who are mechanically ventilated, particularly in the setting of acute changes or decompensation. Malposition of the ETT can occur with slight repositioning

of the infant, and an air leak syndrome such as pneumothorax or pulmonary interstitial emphysema can develop.

COMPLICATIONS AND PROGNOSIS

In milder cases, signs and symptoms of RDS reach a peak within 72 hours, followed by gradual improvement. Spontaneous diuresis and an increased ability to oxygenate the infant are the first signs of improvement.

Severely affected infants may die, usually in the first week, with death most often associated with pulmonary interstitial emphysema, pneumothorax, or IVH. Extremely premature infants (22-25 weeks of gestation) may have an initial "honeymoon" period in which the patient has stable ventilator settings but will exhibit increased oxygen and ventilator demands as time progresses. Not only do these **extremely-low-birth-weight** (ELBW) **infants** have immature lungs, but their extreme prematurity also presents challenges because metabolic and cardiac functions are affected.

Changes in perinatal care, such as the use of antenatal steroids, exogenous surfactant administration, early CPAP, and lung-protective strategies of mechanical ventilation (patient-triggered modalities, volume-controlled modes, and high-frequency oscillatory ventilation [HFOV]), have led to improvements in survival and outcomes of infants with RDS over the past 30 years.[39]

The clinical outcome in preterm infants surviving RDS is often associated with lung disease in the form of BPD, reactive airway disease, and an increase in and vulnerability to respiratory disorders. Other complications encountered include IVH, ROP, infection, and NEC.

BRONCHOPULMONARY DYSPLASIA

DEFINITIONS

Bronchopulmonary dysplasia (BPD), sometimes referred to as neonatal chronic lung disease (CLD), was first described by Northway et al. in 1967 as a severe chronic lung injury in premature infants who survived hyaline membrane disease after treatment with mechanical ventilation and oxygen.[40] It is the most common long-term complication of prematurity and results in significant morbidity and mortality.

In 2001, a workshop conducted by the National Institutes of Child Health and Human Development (NICHD) proposed a definition for BPD diagnosis and severity based on oxygen requirement at 28 postnatal days for infants born <32 weeks, and at 29-55 postnatal days or discharge to home (whichever comes first) for infants born ≥32 weeks (Table 22-3).[41] Since the criteria for administering supplemental oxygen can greatly affect the reported incidence of BPD, a physiologic room air trial to standardize the need for supplemental oxygen has been proposed as a way of reducing the variability in diagnostic criteria, with arterial oxygen saturation (SaO_2) less than 90% in room air considered as the cutoff at which supplemental O_2 is required.[42] Since the 2001 definition was published, there have been attempts to redefine the above criteria, because current definitions, while useful at time points in the NICU, do not necessarily predict long-term respiratory outcomes and do not account for changing practices (for example, use of high-flow nasal cannula [HFNC]).[40,43]

Table 22-3 Definition of Bronchopulmonary Dysplasia: Diagnostic Criteria

	GESTATIONAL AGE	
	LESS THAN 32 WEEKS	**32 WEEKS OR OLDER**
Time point of assessment	36 weeks PMA or discharge to home, whichever comes first Treatment with oxygen comes first	>28 days but <56 days postnatal age or discharge to home, whichever comes first
Mild BPD	Breathing room air at 36 weeks PMA or discharge, whichever comes first	Breathing room air by 56 days postnatal age or discharge, whichever comes first
Moderate BPD	Need* for >30% oxygen and/or positive pressure (PPV or NCPAP) at 36 weeks PMA or discharge, whichever comes first	Need* for <30% oxygen without positive pressure age or discharge, whichever comes first
Severe BPD	Need* for 30% oxygen and/or positive pressure (PPV or NCPAP) at 36 weeks PMA or discharge, whichever comes first	Need* for 30% oxygen and/or positive pressure (PPV or NCPAP) at 56 days postnatal age or discharge, whichever comes first

*A physiologic test confirming the oxygen requirement at the assessment time point remains to be defined. This assessment may include a pulse oximetry saturation range. BPD usually develops in neonates being treated with oxygen and positive-pressure ventilation for respiratory failure, most commonly respiratory distress syndrome. Persistence of clinical features of respiratory disease (tachypnea, retractions, rales) is considered common in the broad description of BPD and has not been included in the diagnostic criteria describing the severity of BPD. Infants treated with oxygen >21% and/or positive pressure for non-respiratory disease (e.g., central apnea or diaphragmatic paralysis) do not have BPD unless they also develop parenchymal lung disease and exhibit clinical features of respiratory distress. A day of treatment with oxygen >21% means that the infant received oxygen >21% for more than 12 hours on that day. Treatment with oxygen >21% and/or positive pressure at 36 weeks PMA or 56 days postnatal age or discharge should not reflect an "acute" event but rather the infant's usual daily therapy for several days preceding and following 36 weeks PMA, 56 days postnatal age, or discharge.

BPD, Bronchopulmonary dysplasia; *NCPAP,* nasal continuous positive airway pressure; *PMA,* postmenstrual age; *PPV,* positive-pressure ventilation.

(From Jobe AH, Bancalari E: Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 163(7):1723-1729, 2001.)

In current practice, the classic progressive stages of disease first described by Northway et al. are less commonly seen. Thus, this form of BPD—characterized by volutrauma, barotrauma, and oxygen toxicity to the lungs during mechanical ventilation for RDS—is referred to as "old BPD." The lungs of patients with "old BPD" were characterized by airway injury, bronchial smooth muscle hypertrophy and peribronchial inflammation, and parenchymal fibrosis. In contrast, "new BPD" often develops in preterm newborns who may have required minimal or even no ventilator support and relatively low F_IO_2 during the early postnatal days. The lungs of patients with "new BPD" are characterized by alveolar hypoplasia, decreased septation, reduction of areas for gas exchange, and abnormal vascular development.[44]

Some very prematurely born babies without significant initial respiratory disease go on to develop chronic lung disease. In 1960, Wilson and Mikity described five preterm infants with diffuse lung infiltrates appearing at 10 to 30 days. These preterm infants had respiratory distress in the first days of life, which appeared to resolve, but had recurrence of cyanosis and distress 1 to 5 weeks later. Radiologically, there were diffuse pulmonary infiltrates that in some infants changed to a cystic emphysematous pattern. It is unclear if this condition, referred to as Wilson-Mikity syndrome or chronic pulmonary insufficiency of prematurity (CPIP), is part of the spectrum of "new BPD" or a distinct entity.[45]

INCIDENCE

The incidence of BPD varies widely among different centers. This is due not only to differences in patient susceptibility and management but also to discrepancies in the way BPD is defined. According to the Vermont Oxford Network, the incidence of BPD in 2009 was 30.4% for very-low-birth-weight (<1500g) infants, an increase from 26.2% in 2000.[46] Although surfactant treatment has improved overall survival of extremely premature infants, the incidence of BPD using the NICHD consensus definition was 68% for infants born <28 weeks of gestation, with 42% requiring supplemental oxygen at 36 weeks.[47] Incidence decreases with increasing gestational age, and is rare in infants born after 32 weeks gestational age. It is unclear if the incidence is stable or increasing.[48]

PATHOGENESIS

Northway et al. proposed four major factors in BPD pathogenesis: (1) lung immaturity, (2) respiratory failure, (3) oxygen supplementation, and (4) positive-pressure mechanical ventilation. Beyond these factors, new knowledge suggests additional complex processes involved in the pathogenesis of BPD, including inflammation, aberrations in lung growth and lung signaling pathways, derangements in transcription factors and growth factors, new evidence related to oxidant lung injury, and a broader understanding of the genetics of BPD (Figure 22-2).

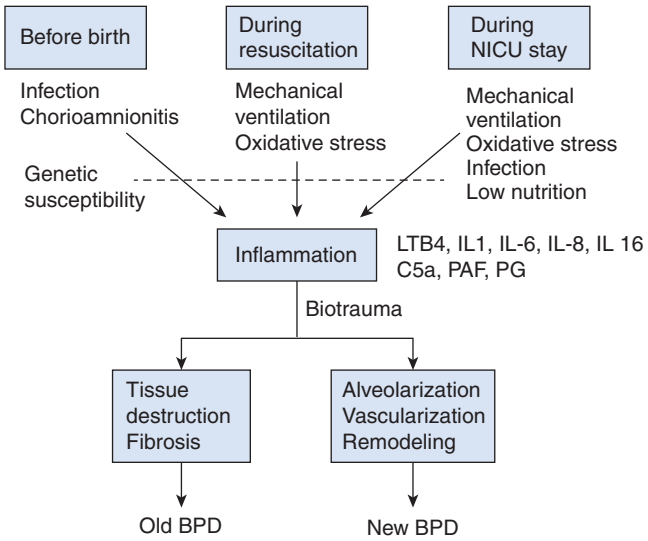


FIGURE 22-2 Pathogenesis of bronchopulmonary dysplasia. (From Shou-Y Wu, et al: Budenoside therapy in preterm infants to prevent bronchopulmonary dysplasia. *NeoReviews* 13[8]:467-475, 2012.)

Prematurity

The incidence of BPD is inversely related to gestational age and birth weight, strongly suggesting that incomplete development of the lungs plays an important role in the pathogenesis of BPD.[49]

Ventilation-Induced Lung Injury

Barotrauma and volutrauma from positive pressure ventilation can damage immature airways. Volutrauma due to large tidal volumes seems to play a more important role than barotrauma caused by increased airway pressures. Injury may occur at resuscitation if newborns are subject to aggressive positive ventilation. Prematurely born lambs given six manual inflations of 35 to 40 ml/kg immediately after birth, compared with those not given positive pressure breaths, had worse lung function at 4 hours of age, as indicated by lower inspiratory capacity.[50] Ventilation-induced lung injury contributes to a cascade of inflammation and cytokine release, further amplifying the lung injury process.

Hypoxia/hyperoxia–induced lung injury. Northway et al. originally proposed that oxygen exposure may deleteriously affect the lung via production of toxic free-radical oxygen metabolites and inflammatory pathways. New clinical and experimental data suggest that, although hyperoxia alone plays an important role in BPD pathogenesis, intermittent hypoxia occurring during exposure to hyperoxia may exacerbate BPD through worsening of oxidative lung injury.[51] Most premature infants requiring supplemental oxygen and/or mechanical ventilation have intermittent episodes of hypoxia during their acute course, but

infants who develop BPD have more frequent episodes of hypoxia than those who do not.[52]

To resist the detrimental effects of oxygen, the body has evolved a number of compensatory antioxidant systems. Antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase seem to play an important role in preventing the toxic effects of oxygen. Other elements, such as vitamin E, glutathione, and selenium, are also part of the endogenous antioxidant mechanisms. However, preterm infants have lower concentrations of antioxidant enzymes than full-term infants.

Inflammation. Evidence suggests that exposure to antenatal inflammation may have a protective effect of reducing the incidence of RDS in premature infants while paradoxically increasing the risk of lung damage and BPD.[53] Neonatal sepsis has also been associated with development of BPD.[54]

The increase in expression of pulmonary proinflammatory cytokines, chemokines, adhesion molecules, proteases, and angiogenic factors in concert with a decreased capacity to downregulate this response in premature infants suggest that persistent endogenous generation of these factors might contribute to chronic lung injury and inflammation.[55]

Several studies have suggested an association between *Ureaplasma urealyticum* and the development of severe respiratory failure and BPD in VLBW infants. In 1988, three independent groups published single-center cohort studies linking respiratory tract *Ureaplasma* colonization with development of BPD.[56] Colonization occurred inversely proportional to gestational age at birth. An updated 2014 meta analysis of the literature continues to support an association between pulmonary *Ureaplasma* colonization in preterm infants and development of BPD.[57] It has been suggested that macrolide prophylaxis in premature infants could prevent development of BPD. A 2011 randomized control led trial of azithromycin prophylaxis in all premature infants <1250 g failed to show improvement in BPD or mortality, but a subgroup analysis of infants known to be colonized with *Ureaplasma* did show a significant reduction in rates of BPD.[58] This link was supported in a 2014 meta analysis; however, widespread prophylaxis with azithromycin has not been adopted at this time due to a lack of safety and pharmacokinetic data.[59]

Nutrition. In preterm infants, the presence of fetal growth restriction independently raises the risk for BPD.[60] Data from experimental animal studies have shown that the ability to handle oxidative lung injury is negatively affected by malnutrition, especially protein malnutrition. Undernourishment causes alveolar loss and simplification, similar to what is seen in infants with BPD. Slow postnatal growth rates in preterm sheep also result in fewer numbers of alveoli and reduced surface area for gas exchange in relation to lung or body weight. Additionally, in preterm neonates, trace element deficiency, especially zinc, copper, selenium, chromium, molybdenum, manganese, iodine, and iron, may predispose the infant to lung injury, and supplementation may provide protection. Vitamins A and E are nutritional antioxidants that may help prevent lipid peroxidation and maintain cell integrity; levels are often low in premature infants. While vitamin E supplementation has not been shown to prevent BPD, studies have shown that vitamin A supplementation has a modest effect in reducing BPD.[61,62] However, due to cost concerns, the need to administer vitamin A by intramuscular injection, and national drug shortages, routine use of vitamin A has decreased in recent years. Nonetheless, a large study comparing a historical cohort has not shown a significant change in BPD rates despite the fall in vitamin A usage, though this may be confounded by other changing practices over this time.[63]

Patent ductus arteriosus. A clinically significant PDA may contribute to pulmonary edema through excess left-to-right shunting and subsequent bronchopulmonary dysplasia. However, infants with PDA are exposed to multiple factors that increase the risk of lung injury, and these factors become important confounders in the reported association between PDA and increased risk for BPD. For example, excess fluid intake and less weight loss in the first 10 days of life may contribute to both a clinically significant PDA and bronchopulmonary dysplasia.

In fact, there has been a movement away from aggressive therapy for PDA (either medical or surgical) given the lack of evidence showing long-term benefit.[64] In fact, prophylactic treatment with indomethacin, though decreasing the incidence of PDA, did not reduce the risk of BPD among infants with PDA and increased the risk of BPD among infants who did not have a PDA, an effect that seemed to be explained by increased oxygen requirements and decreased weight loss in the first week in indomethacin-treated infants.[65] Further, there was an independent association between surgical ligation and the development of BPD among infants who subsequently received treatment for PDA.[66]

Genetics. Bhandari et al. reported that, based on twin analyses, genetic factors account for 53% of the susceptibility to BPD.[67] Several specific genetic loci linked to the development of BPD include genes involved in surfactant function, alveologenesis and vascular growth and remodeling, and factors affecting the response to oxidative stress. Though initial genome-wide association studies were largely unrevealing in finding single-nucleotide polymorphisms associated with BPD, more recent analyses demonstrate polymorphisms in nitric oxide pathways and in lung development and repair associated with BPD.[68]

Vascular hypothesis. Thébaud and Abman have proposed a "vascular hypothesis" for the pathogenesis of BPD: whereas normal alveolar development progresses in response to the secretion of angiogenic growth factors, such as vascular endothelial growth factor (VEGF) and nitric oxide (NO), lung angiogenic growth factor expression has been found to be decreased in BPD, a finding that may explain the arrest of vascular growth and impairment of alveolar growth.[69] These vascular changes may contribute to pulmonary hypertension associated with particularly severe cases of BPD.

CLINICAL PRESENTATION AND DIAGNOSIS

BPD, with rare exceptions, follows the use of mechanical ventilation with intermittent positive pressure during the first weeks of life. The development of BPD is often suspected when mechanical ventilation and oxygen dependence extend beyond 10 to 14 days, and the risk of bronchopulmonary dysplasia can be determined using a web-based calculator by the NICHD.[70]

As mentioned earlier, the classic BPD described by Northway et al. is now extremely rare with the advent of antenatal steroids, postnatal surfactant, and ventilator strategies better suited for preterm newborn infants. Instead, the typical picture of "new BPD" is the one affecting smaller and more immature infants (birth weight 400 to 1000 g) than the original studied population (birth weight more than 1000 g) with milder functional and radiographic changes, revealing more diffuse haziness without the marked changes observed in the severe forms of BPD.[41]

These infants may have varying degrees of RDS in the first weeks of life, and in fact some may receive minimal ventilatory support during this time. However, within a few days or weeks after birth, these infants display deteriorating lung function and increased ventilator or oxygen requirements (Figure 22-3). This

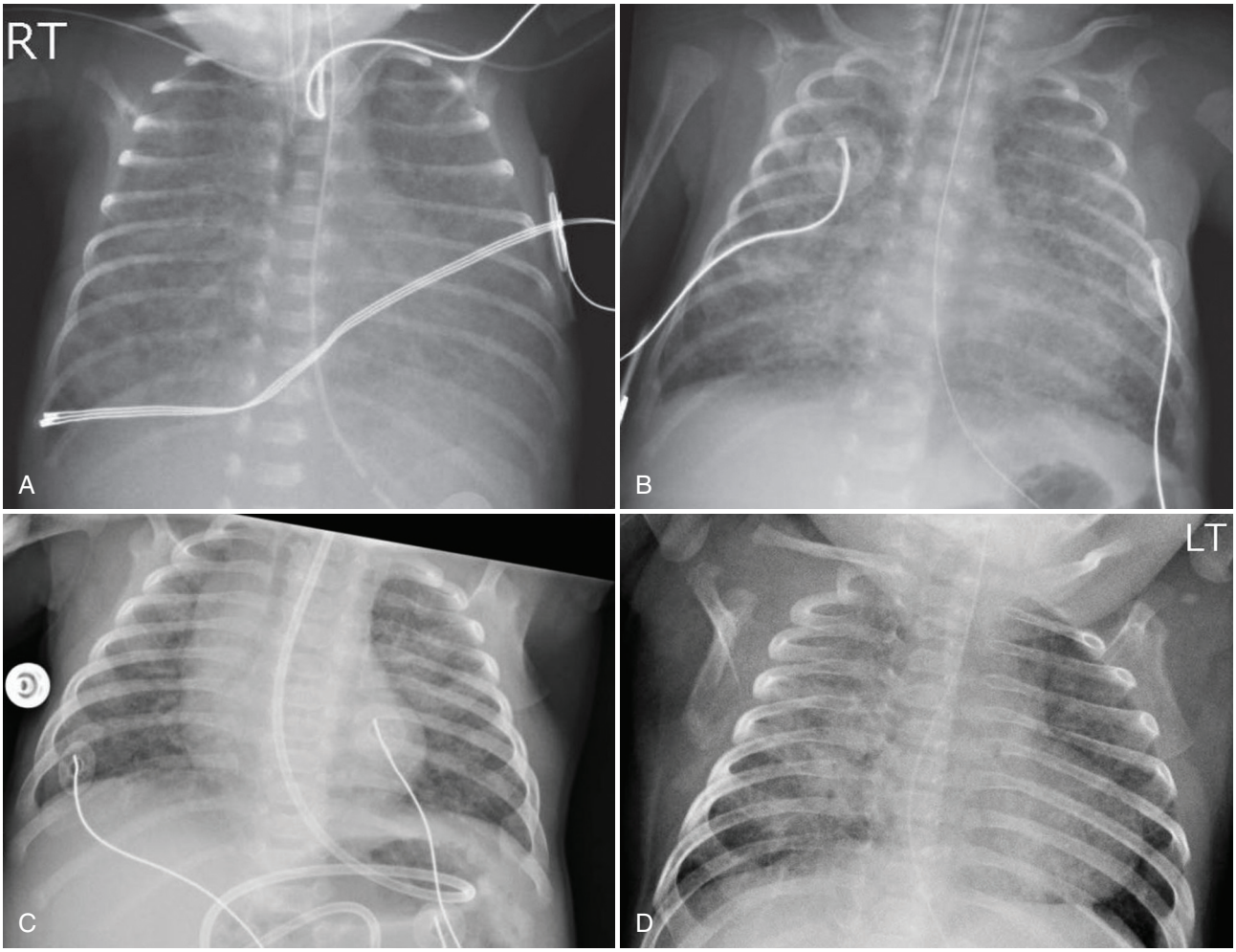


FIGURE 22-3 These images are from the same patient as Figure 22-1, an infant born at 27 weeks of gestation with respiratory distress syndrome. They represent progression of lung disease into "new" bronchopulmonary dysplasia over time. These images differ from "old" BPD, in which radiographs showed developing cystic changes and hyperinflation. The images are taken at **(A)** 2 weeks of age, with developing coarseness to lung disease (also note endotracheal tube in upper trachea); **(B)** 1 month of age, with increasing heterogeneity and differential areas of atelectasis and edema (again, patient remains intubated); **(C)** 3 months of age, with coarseness and low lung volumes (also note post pyloric feeding tube, which is partially visualized); and **(D)** 5 months of age, with edema and some small cystic changes noted.

deterioration in respiratory status may be related to a hemodynamically significant PDA, inflammation caused by bacterial infection or colonization, or inflammatory processes triggered by oxygen or mechanical ventilation; all are risk factors associated with the development of BPD.

Although infants with "new BPD" may require mechanical ventilation and oxygen for a prolonged period, many will require minimal or no additional respiratory support by the time of NICU discharge. There remains a small minority of infants with "new BPD" who have more severe lung dysfunction, characterized by progressive respiratory failure that may even be associated with pulmonary hypertension and cor pulmonale, severe airway damage, bronchomalacia, airway obstruction, and death.[43] If infants with this more severe form of BPD acquire acute bacterial or viral pulmonary infections, their lung damage may be further exacerbated.

The diagnosis of BPD is based on the clinical and radiographic manifestations, but these are not specific. For this reason, other etiologies that could lead or contribute to the lung injury should be considered, particularly in atypical or abnormally severe cases. Among these, one must rule out congenital heart disease, pulmonary lymphangiectasia, chemical pneumonitis resulting from recurrent aspiration, cystic fibrosis, and inherited surfactant protein deficiencies (see section on RDS).

PREVENTION

The cornerstone of management of BPD is prevention by avoiding factors that predispose to injury.

Lung-Protective Ventilator Strategies

Because of lung immaturity from preterm birth, many premature infants require respiratory assistance to sustain life. As discussed previously, positive pressure ventilation can be damaging to the preterm lung, so the therapeutic goal is to provide this lifesaving respiratory support without further compromising the already vulnerable lung.

Gentle ventilation is a descriptive term for respiratory support for preterm infants using a low V_T strategy to decrease lung injury, with acceptance of higher values of $PaCO_2$ (50 to 55 mmHg), called permissive hypercapnia.

In an attempt to avoid mechanical ventilation via an ETT, most recent practice favors early application of NCPAP in the delivery room in an attempt to establish FRC and stabilize respiratory status without prophylactically intubating and providing surfactant.[14,27,30] Nasal intermittent positive-pressure ventilation (NIPPV) has been explored as the primary modality of respiratory support but has not been shown to have an advantage over NCPAP.[33] When mechanical ventilation is needed, volume-controlled or volume-guaranteed ventilation can provide a more consistent V_T than pressure-targeted ventilation and may therefore result in less lung injury. More centers are using this mode of ventilation in premature infants, although it requires ventilators than can detect the small expired tidal volumes in premature infants. High frequency ventilation, another approach to potentially limit volutrauma, was not found to be consistently protective in preventing or decreasing BPD.[37]

Oxygen Therapy

Studies have shown that NICUs that set goals of lower oxygen saturation levels (85 to 89%) for premature infants requiring oxygen therapy had fewer cases of BPD, along with fewer cases of ROP, but higher mortality rates, than those using higher oxygen saturation goals (91-95%).[22,71] This is discussed further in the RDS section. Many NICUs use target saturation range of 90 to 95% based on these data.

Nutrition and Fluid Management

Early and rigorous provision of adequate calories and protein to premature infants might potentially improve antioxidant capacity and decrease risk for BPD. Additionally, the nutritional requirements of infants with BPD are higher, and adequate growth is an important therapy for BPD (discussed in Treatment section).

However, excess fluid intake and a lack of postnatal weight loss in the first week of life have been shown to predispose infants to BPD. Fluid restriction may reduce pulmonary edema and minimize lung injury that contributes to BPD, as well as reduce the likelihood of developing a symptomatic PDA. Thus, fluid restriction must be balanced with nutritional needs, and evidence has been lacking regarding the effectiveness of restriction in preventing BPD. Thus, the practice in many units is to advance to routine total fluid levels of 140 to 150mL/kg/day over the course of the first week, avoiding higher targets in the absence of signs of dehydration.[72]

Corticosteroids

The efficacy of antenatal steroids to accelerate fetal lung maturation, reduce neonatal mortality, and improve early respiratory distress is well established. However, this practice has not had an impact on rates of BPD; this may be due to increased survival of sicker infants. The antiinflammatory properties of steroids include inhibition of prostaglandins, leukotrienes, and cyclooxygenase I and II; decrease of neutrophil recruitment in the lung; reduction in vascular permeability; and improvement of pulmonary edema. These properties make their use an enticing postnatal strategy to reduce the risk and severity of BPD. However, there are concerns regarding detrimental neurodevelopmental outcomes when premature infants are exposed to postnatal steroids.

Early, standard-dose dexamethasone is effective at improving short-term lung function, moving toward

extubation, and reducing the incidence of BPD. However, early administration (≤7 days) was associated with increased risk of cerebral palsy (CP) and abnormal neurologic exams at long-term follow-up.[73] Additionally, short-term adverse effects include hyperglycemia, hypertension, intestinal perforations, and infection. Late administration (> 7 days) was associated with decreased mortality but also showed a trend toward increased CP and abnormal neurologic exams.[74] It may be that late administration of dexamethasone improved survival in infants most at risk of neurologic impairment rather than directly cause the impairment. However, there are documented changes in brain anatomy by MRI seen in preterm infants after dexamethasone administration.[75] Because of these concerns, the AAP recommends against the use of high-dose dexamethasone for BPD prevention in premature infants.

Other steroid formulations have also been studied, and there may be a role for systemic steroids for BPD prevention, particularly in higher-risk patients. In the DART protocol, low-dose dexamethasone (0.89mg/kg total dose over 10 days) given after 1 week of life (median 23 days) facilitated extubation without adverse neurological effects at 2 years of age but had no effect on mortality or incidence of BPD at 36 weeks of age.[76, 77]

Hydrocortisone, which has different potency, binding affinity to brain receptor sites, and mineralocorticoid activity, has been suggested to have less of a long-term neurologic impact than dexamethasone, though there are mixed reports of outcomes.[78,79,80] Importantly, early administration (≤7 days) of hydrocortisone has been associated with spontaneous intestinal perforation.[81] A recent French multicenter study suggested improved rates of BPD with **early** prophylactic hydrocortisone (first 10 days of life), though the study stopped enrollment early due to lack of funding.[82] An ongoing study by the NICHD is looking at the efficacy of a 10-day hydrocortisone course in intubated premature infants at 14 to 28 days of life. Overall, evidence of consistent longer-term pulmonary benefit with prophylactic hydrocortisone is currently lacking.

Some centers favor prednisolone, given the wealth of experience in other pediatric respiratory diseases, such as asthma, as well as its lower potency than dexamethasone. Additionally, there is supporting data from the oncologic literature regarding the long-term neurologic safety of methylprednisolone over dexamethasone.[83] However, there has been a paucity of trials supporting the use of methylprednisolone in prevention of BPD, currently limited to a single observational study;[84] a more recent retrospective study showed that a 5-to-10-day oral prednisolone course was effective in weaning premature infants of >36 weeks postmenstrual age off oxygen therapy.[85]

In summary, current AAP guidelines do not recommend **routine** use of corticosteroids to prevent BPD. Standard-dose dexamethasone is not recommended, and data are insufficient at this time to make a recommendation on low-dose dexamethasone, early low-dose hydrocortisone (acknowledging that there may be a subpopulation who could benefit from this therapy), or higher-dose hydrocortisone after the first week of life.[86]

Inhaled steroids, such as budesonide, have been suggested as a safer route to prevent BPD due to limited systemic toxicity. Early trials failed to show effectiveness; a large trial in 2015 demonstrated a small but significant decrease in BPD risk with administration of early (within 24 hours after birth) prophylactic inhaled budesonide (27.8 versus 38 percent) but a nonsignificant trend toward increased mortality (16.9% versus 13.6%). Inhaled steroids are not routinely used by most units in preventing BPD.[87]

Methylxanthines

Methylxanthines work as phosphodiesterase inhibitors and play an important role in regulating intracellular levels of the second messengers cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), and they may have antiinflammatory properties as well.

The Caffeine for Apnea of Prematurity (CAP) trial revealed a significant decrease of BPD in infants who received caffeine; this was attributed to a shorter period of positive pressure support (about 1 week) for infants receiving caffeine in the trial.[88]

Ineffective therapies

Inhaled nitric oxide, since its original use in persistent pulmonary hypertension of term infants, has been extensively investigated in animal models of lung immaturity and lung injury; it has been found to diminish lung inflammation, reduce lung neutrophil infiltration, and enhance lung growth and alveolar development. However, multiple trials have found no benefit in the prevention of BPD in preterm infants.[89]

Antioxidants have been investigated in prevention of BPD due to inadequate defense systems in the lungs of preterm infants. While initially supported in observational studies, randomized trials did not show benefit to the administration of the antioxidant superoxide dismutase for the prevention of BPD.[90]

Future Therapies

Mesenchymal stem cells. Bone marrow–derived and umbilical cord blood (UCB)–derived multipotent mesenchymal stem cells (MSCs) have been found to be efficacious in experimental models of lung injury. A phase I trial assessing the safety and feasibility of transplanting allogeneic UCB-dervied MSCs into premature infants at very high risk of developing BPD has been completed and phase II trials are under way.[91]

TREATMENT

The goals of treatment during the NICU course are to minimize further lung injury (e.g., barotrauma and volutrauma, oxygen toxicity, inflammation), diminish oxygen consumption, and maximize nutrition. The challenge is that the mechanical ventilation and supplemental oxygen needed to maintain gas exchange are the same factors implicated in the pathogenesis of lung damage.

Optimal care of infants with BPD should be provided by a multidisciplinary team, including representatives from neonatology, pulmonology, respiratory therapy, nutrition, pharmacy, occupational therapy, speech therapy, physical therapy, social work, and discharge planning.

Oxygenation

Supplemental oxygen remains a mainstay of therapy for infants with BPD. The goal oxygen saturation ranges remain controversial; the SUPPORT trial and others suggest that a saturation goal of 90% to 95% prior to development of retinal vascular maturity should be considered to reduce risk of mortality and minimize further risk of ROP and BPD.[28] Once retinal vascular maturity is achieved, usually around 36 weeks postmenstrual age, most pulmonologists recommend maintaining infants with established BPD at oxygen saturations around 92%, with slightly higher levels (92% to 95%) for infants with BPD and growth failure, recurrent respiratory exacerbations, or PPHN.[92]

Mechanical Ventilation

CPAP or high-flow nasal cannula therapy is used when possible to maintain adequate oxygenation and ventilation while avoiding the need for prolonged ventilation or reintubation for ventilator support.

Initial management of premature infants requiring mechanical ventilation is described in the RDS section and focuses on lung-protective strategies—low peak pressures with goal tidal volumes of 4 to 6 cc/kg, short inspiratory times (0.3-0.4 seconds), and permissive hypercapnia. At some point during an infant's course, lung mechanics change and the focus becomes adequate ventilation rather than prevention of developing lung disease. In this stage, shorter Ti and higher flow rates can exaggerate the maldistribution of the inspired gas, and lower tidal volumes can result in atelectasis. In severe BPD, the ventilator strategy should focus on obstructive airway disease with higher tidal volumes (8-12 cc/kg) and longer Ti (0.5 to 0.6 seconds) delivered at slower rates. Higher PEEP (between 6 and 8 cm H_2O) may be required to avoid atelectasis, and to avoid airway obstruction in infants with bronchomalacia.[92] This strategy is directly related to the striking differences in lung physiology that characterize newborns with acute respiratory failure compared with infants with severe BPD. Dramatic heterogeneity of lung disease, characterized by marked regional variability in time constants, provides the physiologic rationale for this strategy in severe BPD, to improve the distribution of ventilation, minimize physiologic dead space and gas trapping, and improve gas exchange. It is unclear exactly when this strategy change should occur, but recent guidelines suggest at about 1 month of age (Table 22-4).

The duration of mechanical ventilation must be limited as much as possible to reduce the risk of mechanical trauma and infection. Weaning from the ventilator is difficult and should be accomplished gradually. When the patient can maintain an acceptable PaO_2 and $PaCO_2$ with low PIP (< 15 to 18 cm H_2O) and FIO_2 (< 0.3 to 0.4), the ventilator rate is gradually reduced to allow the infant to perform an increasing proportion of the respiratory work. During the process of weaning, it may be necessary to increase the FIO_2. Concurrently, the $Paco_2$ can rise to values in the 50s to 60s mm Hg, as long as the pH is within acceptable limits (>7.28). In small infants, caffeine can be used as a respiratory stimulant, as discussed in the RDS section. When the patient is able to maintain

Table 22-4 Ventilator Strategies in Bronchopulmonary Dysplasia

Early (prevention)	Strategies to prevent acute lung injury: 1. Low V_T (4-6 mL/kg) 2. Short inspiratory times (0.2-0.3 seconds) 3. Increased PEEP as needed for lung recruitment without overdistention (as reflected by high peak airway pressures) 4. Adjust Fio_2 to target Spo_2 (range: 90-95%) 5. **Permissive hypercapnia**
Late (established BPD)	Strategies for effective gas exchange: 1. Marked regional heterogeneity: • Larger V_T (10-12 mL/kg) • Longer inspiratory time (≥0.6 sec) 2. Airway obstruction: • Slower rates (10-20 bpm) allow better emptying, especially with larger V_T • Complex role for PEEP with dynamic airway collapse 3. Interactive effects of vent strategies: • Changes in rate, V_T, inspiratory and expiratory times, and pressure support are highly interdependent • Overdistention can increase agitation and paradoxically worsen ventilation 4. Permissive hypercapnia to facilitate weaning

BPD, Bronchopulmonary dysplasia; *PEEP,* positive end-expiratory pressure; V_T, tidal volume.
(From Abman SH, Nelin LD: Management of infants with severe bronchopulmonary dysplasia. In Bancalari E, eds.: *The Newborn Lung: Neonatology Questions and Controversies,* 2nd ed, Philadelphia, 2012, Elsevier Saunders.)

acceptable blood gas levels for several hours on low ventilator rates (15 to 20 breaths per minute), extubation should be attempted. An extubation readiness test for 2 hours (tolerance of straight pressure support of 10 with a PEEP of 5) can typically provide functional information regarding the likelihood of successful intubation.

After extubation, atelectasis may develop, which can present with respiratory distress, worsening blood gases, and oxygen requirement. In smaller infants, the immediate use of nasal CPAP, NIPPV, or high-flow nasal cannula after extubation can stabilize respiratory function and reduce the need to reinstitute mechanical ventilation; NIPPV may be more successful at avoiding reintubation but does not affect overall outcomes with regard to lung disease and mortality.[93]

Tracheostomy may be required in those infants who require prolonged mechanical ventilation (still requiring substantial positive pressure support a few weeks beyond their due dates), or who develop other airway complications such as sublglottic stenosis. Advantages include the benefit of clinical stability with prolonged ventilation while optimizing neurodevelopmental and growth-related outcomes.

Fluid, Nutritional, and Feeding Management

Fluid management. Infants with BPD generally do not tolerate excessive or even normal amounts of fluid intake and have a marked tendency to accumulate excessive pulmonary interstitial fluid. This excess can lead to a deterioration of pulmonary function with exaggeration of hypoxemia, prolonging ventilator dependency.

To reduce lung fluid in infants with BPD, water and salt intake should be limited to the minimum required to provide the calories necessary for metabolic needs and growth. Most infants can be managed with 130 to 140 ml/kg/day. Human milk with fortification is recommended. In severely affected infants, further restriction (with a necessary increase in caloric density) may be considered. When pulmonary edema persists despite fluid restriction, diuretic therapy can be considered. Because the increased metabolic demand of severe BPD can be associated with a low PaO_2, it is important to maintain adequate oxygenation and a relatively normal blood hemoglobin concentration.

Nutritional management. Optimizing both enteral and parenteral nutrition is essential to growth and recovery of preterm infants with BPD. Beginning parenteral nutrition as soon as possible and then introducing and advancing enteral feeds meticulously is crucial to overall health of these infants.

High-calorie milk and supplements of protein, calcium, phosphorus, and zinc can be used to maximize the intake of calories while restricting fluid intake to prevent pulmonary edema and congestive heart failure. If enteral nutrition is precluded for more than 3 or 4 days, parenteral nutrition with glucose, amino acids, and fat should be substituted until the gastrointestinal tract again becomes functional.

Adequacy of nutrition should be closely monitored, along with growth charts for weight, head circumference, and length. Other means of assessment include arm anthropometry to determine muscle mass and fat deposits, measurement of serum levels of albumin, and air displacement plethysmography to determine body fat–free mass and adiposity, though their clinical relevance remains to be determined.[94] Fractures of ribs or long bones noted on routine x-rays together with generalized bone demineralization are often observed in infants with BPD and are usually a manifestation of osteopenia of prematurity.

Anti-reflux and anti-aspiration measures. The contribution of gastroesophageal reflux (GER) to severe BPD remains controversial. GER may present as "spells" after feeds in premature infants with BPD. Therapeutic positioning may be employed, though it is important to establish safe supine sleep positioning for prevention of sudden infant death syndrome prior to discharge. Pharmacologic acid blockade is not routinely used in premature infants with uncomplicated GER given the lack of clear benefit as well as the associated risks, including increased rates of necrotizing enterocolitis and pneumonia.[95] There may be some infants with severe GER and lung disease where acid suppression has a role. Starting an antacid trial and then discontinuing the antacid if there is no improvement prevents long-term use of an ineffective therapy with potential risk.

Aspiration is also a concern in premature infants, particularly those with BPD. This may occur from above in infants who have begun to orally feed, or from below via GER. The infant should be monitored for symptoms of aspiration with feeds, including coughing, choking, wheezing, or "spells' with feeds. Silent aspiration may occur in a significant number of premature infants, and should be suspected with ongoing lung disease, chronic cough, or recurrent respiratory infections. A multidisciplinary approach with feeding specialists is recommended.

Transpyloric feeds are considered in the setting of severe BPD with a clinical suspicion for GER and/or recurrent aspiration; though this has not yet been validated in the literature, it is being evaluated in ongoing clinical trials. Surgical correction via fundoplication is reserved for unique circumstances given a lack of clear benefit and the risks of the surgery.

Drug Therapies

Diuretics. Diuretics improve short-term pulmonary compliance and airway resistance by reducing lung edema.[96,97] Therefore short courses may be considered for exacerbations or to wean off positive pressure support or supplemental oxygen. Though evidence of

the efficacy of long-term diuretic use is lacking, it is frequently prescribed. The two most commonly used diuretic classes are loop diuretics and thiazides, which act on the distal renal tubule. Diuretics can cause significant electrolyte imbalances, including hypochloremic alkalosis and hypokalemia, particularly when used in younger preterm infants. Additionally, longer-term use of loop diuretics is associated with ototoxicity and nephrocalcinosis. Some centers use spironolactone (a potassium-sparing diuretic) concomitantly with loop or thiazide diuretics to avoid electrolyte imbalances, but evidence to support this practice is lacking.

In an effort to only treat diuretic responders, a short trial of furosemide can be considered for infants with BPD and persistent pulmonary edema despite moderate fluid restriction, with consideration of a longer course of either furosemide or thiazide diuretics for those who demonstrate a positive response and tolerate the shorter course well. If committing to a longer course, serum electrolytes should be followed and potassium chloride supplementation used as needed to treat the resulting hypochloremia that may impair growth. Infants with a history of long-term furosemide use should be screened for nephrocalcinosis with renal ultrasound.[98]

Bronchodilators. Infants with BPD have airway smooth muscle hypertrophy and often have signs of bronchial hyperreactivity that acutely improves with bronchodilator therapy, but response rates are variable. Data do not support a role for inhaled bronchodilators, such as β2-agonists (albuterol), in the prevention of BPD, and limited data exist regarding the use of inhaled bronchodilators for the treatment of acute exacerbations of BPD. Adverse effects include tachycardia and arrhythmias.[99,100] Nonetheless, a trial of β2-agonists can be considered for acute episodes of bronchospasm in older infants with severe BPD.

Methylxanthines. Methylxanthines, including aminophylline, theophylline, and caffeine, are stimulants that act to increase respiratory drive, improve diaphragmatic contractility, and decrease apnea. They also have bronchodilatory and diuretic properties, which all work to improve pulmonary mechanics. However, theophylline has significant cardiac toxicity and levels must be closely monitored. Caffeine may be a safer alternative, and its use can be considered in older infants with severe BPD (even after resolution of apnea of prematurity).

Steroids. As discussed earlier, controversy exists over the role of prophylactic steroids in BPD prevention given their significant toxicity. In older infants with BPD, a short course of oral prednisolone or IV methylprednisolone may be helpful in the management of persistent oxygen requirements or acute deterioration of lung function not due to intercurrent respiratory infection.[85]

Pulmonary vasodilators. Patients with severe BPD are at high risk for development of pulmonary hypertension and cor pulmonale. Pulmonary hypertension is an important risk factor for mortality in infants with BPD.[101] Therefore screening echocardiograms should be performed in patients with severe BPD. The mainstay of therapy for pulmonary hypertension in BPD is appropriate oxygenation and avoidance of hypoxia (with goal saturations 92-95%); current pharmacologic therapies for pulmonary hypertension in infants with BPD generally include iNO, sildenafil, and endothelin receptor antagonists.[102] A report of increased mortality rates when using sildenafil to treat pulmonary hypertension in children led to an FDA black-box warning; however, it continues to be used in selected infants, with limited evidence of efficacy and safety.[103]

Social Issues

Dealing with a chronic childhood illness can be difficult for any parent. Support should focus on the adjustment process of caring for a chronically ill child in the hospital and at home, including the potential of home medical equipment, time needed for multiple medical appointments, communication with multiple health care teams, and issues of social isolation.

OUTCOME

Long-Term Morbidity

Pulmonary complications. Tachypnea, retractions, dyspnea, cough, and wheezing can be seen for months to years in seriously affected children.

In infancy, reactive airway disease occurs more often, and infants with BPD are at increased risk for bronchiolitis and pneumonia. The rehospitalization rate for respiratory illness during the first 2 years of life is approximately twice that for premature infants without BPD.[104] Respiratory syncytial virus (RSV) prophylaxis with palivizumab is vital in this population and is recommended by the AAP during viral season in the first year of life for all infants with BPD and in the second year of life for those who remain on oxygen, systemic steroids, or diuretics.[105]

Although complete clinical recovery into childhood can occur, underlying pulmonary function, gas exchange, and radiographic abnormalities may persist beyond adolescence. Obstructive patterns in pulmonary function (decreased FEV_1 and FEV/FVC ratio) can be seen throughout childhood into adolescence.[106] The impact of persistent minor abnormalities of function and growth on long-term morbidity and mortality is not known, though studies suggest that abnormal function persists into adulthood.[107] Understanding the long-term pulmonary outcomes of infants with BPD is complicated by the ongoing evolution of care of

premature infants, including antenatal steroids and RDS management (including changing delivery room management with CPAP), and the evolving nature of BPD such that current studies the evaluating adult survivors of BPD may not reflect the outcomes of their contemporary infant counterparts.

Recurrent wheezing episodes and asthma-like symptoms are common in childhood and adolescent survivors of BPD.[108] The mechanism is not clear and these patients may be less responsive to bronchodilators than typical children with asthma.

Airway problems, such as tonsillar and adenoidal hypertrophy, vocal cord paralysis, subglottic stenosis, and tracheomalacia, are common. Subglottic stenosis may require tracheotomy to relieve upper airway obstruction.

Cardiac complications. Cardiac complications include pulmonary hypertension, cor pulmonale, systemic hypertension, left ventricular hypertrophy, and the development of aortopulmonary collateral vessels, which, if large, may cause heart failure. As discussed earlier, pulmonary hypertension significantly increases the risk of mortality; thus infants with severe BPD should undergo screening with echocardiography.

Neurodevelopmental delays and neurologic deficits. BPD is an independent risk factor for neurodevelopmental impairment, with poor developmental outcome correlating with prolonged hospitalization and requirement for prolonged oxygen in infants with severe BPD.[109] Both motor and cognitive delays are seen, and can persist into school-age years.

Other complications. Growth failure is common, due to increased metabolic demands, poor oxygenation, and side effects of therapy (steroids). Other complications include sequelae of therapy such as nephrolithiasis, osteopenia, and electrolyte imbalances.

Mortality

Postdischarge mortality among all infants with BPD in the first 2 years is about 2.5%, and up to 5% in children with severe BPD.[110] Infants who are discharged from the hospital on home ventilation have a mortality rate as high as 21%, and mortality may be as high as 38% among infants with BPD and pulmonary hypertension.[92]

TRANSIENT TACHYPNEA OF THE NEWBORN

INCIDENCE

Transient tachypnea of the newborn (TTN) is a relatively benign, self-limited condition, first described by Avery and colleagues in 1966.[111] It is rarely described in infants born prematurely, but it occurs in approximately 5 per 1000 infants delivered between 37 and 42 weeks of gestation. It is most common after elective cesarean section delivery without labor.

PATHOPHYSIOLOGY AND RISK FACTORS

Early theories of lung fluid clearance focused on the role of thoracic compression during vaginal delivery and were supported by the observation that TTN is more common among babies born by elective cesarean section. Current attention has focused on the roles of catecholamines, glucocorticoids, and thyroid hormones in bringing about a permanent change in the lung epithelium phenotype and causing the fetal lung epithelia to switch from lung fluid secretion to absorption. There is evidence that genetic polymorphisms in β-adrenergic receptor encoding genes are more common in babies with TTN.

Cesarean delivery without labor is a risk factor for the development of TTN, because the process of lung reabsorption of alveolar fluid has not yet commenced. Additional risk factors for TTN include male gender and a mother with asthma. The mechanism underlying the gender-associated risk and the increase associated with maternal asthma are unclear, although there is speculation that these infants have an altered sensitivity to catecholamines that may play a role in the delayed clearance of lung fluid. Macrosomia and multiple gestations also increase the risk of TTN. The associations between TTN and other obstetric factors, such as excessive sedation and large amounts of intravenous fluids given to the mother, have been less consistent. It has been postulated that delayed cord clamping might increase the risk of TTN because of placental-fetal transfusion; however, this has not been shown to be true.

CLINICAL PRESENTATION AND DIAGNOSIS

A term or near-term infant with TTN typically presents with tachypnea and cyanosis within the first few hours after birth. Often the tachypnea is described as "comfortable," though it can be accompanied by grunting, retractions, and nasal flaring. Arterial blood gas (ABG) analysis reveals mild to moderate hypoxemia, hypercapnia, and respiratory acidosis. CXR may show pulmonary vascular congestion, prominent perihilar streaking, fluid in the interlobular fissures, hyperexpansion, and a flat diaphragm (Figure 22-4). Mild cardiomegaly and pleural effusions may also be present.

DIFFERENTIAL DIAGNOSIS

TTN is a clinical diagnosis. Because TTN is similar in its initial presentation to conditions such as RDS, sepsis or pneumonia, and persistent pulmonary hypertension of the newborn (PPHN), it is often a diagnosis of exclusion; unless symptoms are mild and rapidly improving, alternative diagnoses should be considered.

TTN also must be distinguished from hyperventilation as respiratory compensation for a metabolic acidosis. This is most commonly seen in term infants with birth asphyxia. These infants are tachypneic without

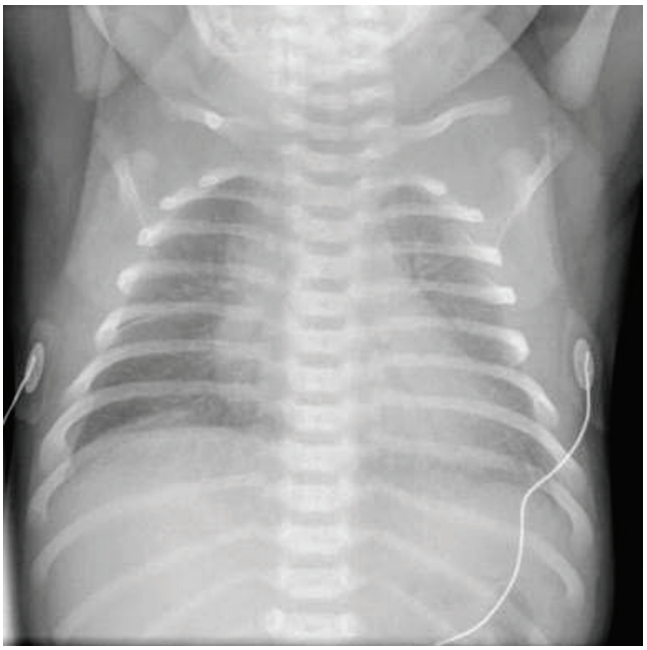


FIGURE 22-4 Transient tachypnea of the newborn with overinflated lungs, increased interstitial streaky markings, and fluid in the intralobar fissure. (Courtesy of Anne Hansen.)

radiographic changes apart from occasional asphyxia-related cardiomegaly.

TREATMENT

Treatment is largely supportive. The objectives of treatment of TTN are to maintain adequate oxygenation and ventilation. Supplemental oxygen can be administered via oxygen hood to maintain saturations above 90%. CPAP levels of approximately 5 cm H_2O may be needed when higher FiO_2 levels are required or for more severe respiratory distress.

Infants with sustained respiratory rates greater than 60 breaths per minute should not be fed orally; therefore these infants should be maintained either with gavage feedings for respiratory rates between 60 and 80 or nothing by mouth (NPO) with intravenous fluids. It has been suggested that fluid restriction may improve the course of TTN.[112] However, furosemide administration to accelerate clearance of lung fluid has shown no benefit in attenuating the course of TTN.[113]

Some infants are initially treated with broad-spectrum antibiotics until the diagnosis of sepsis or pneumonia is excluded.

Given that *in utero* alveolar fluid clearance occurs through β-adrenergic receptors, inhaled racemic epinephrine has been studied as a possible intervention for TTN; a single small randomized trial failed to show a clinical benefit but did not demonstrate any adverse effects.[114]

PROGNOSIS AND COMPLICATIONS

The condition is self-limited. The distress, hypoxemia, and mild respiratory acidosis usually resolve within 48 hours. Complications are rare, though air leaks may occur, particularly if the baby has required support with positive pressure ventilation.

NEONATAL PNEUMONIA

INCIDENCE

Neonatal pneumonia contributes to an estimated 750,000 to 1.2 million deaths of newborn infants worldwide and likely contributes to even more stillbirths.[115] In developed countries, pneumonia only affects about 1% of full-term infants, but it may occur in more than 10% of infants in NICUs, with premature infants at particular risk. At autopsy, findings consistent with neonatal pneumonia range as high as 30%, although inflammatory findings may be nonspecific. Risk factors include mothers of lower socioeconomic status and teenage mothers who may be at higher risk for sexually transmitted infections.

Although this section focuses on neonatal pneumonia, relevant aspects of systemic infections in newborns are included in the discussion of etiology, prevention, and treatment.

ETIOLOGY AND PATHOPHYSIOLOGY

Causative Organisms

Organisms responsible for infectious pneumonia typically mirror those responsible for early-onset neonatal sepsis. Group B *Streptococcus* (GBS) was the most common bacterial isolate in most locales from the late 1960s to the late 1990s, when the use of intrapartum chemoprophylaxis began reducing neonatal and maternal infection by this organism. Despite the decreased frequency, GBS remains a common isolate in early-onset (age younger than 3 days) infections in term and near-term infants. *Escherichia coli* has become and continues to be the most common bacterial isolate among premature infants.[116] Early-onset pneumonia from GBS may progress rapidly to shock or death, and mortality is high (20-50%) regardless of treatment. When the onset of GBS disease is later (2-3 weeks after birth), the infant may present with meningitis rather than pneumonia, the pathogen is usually a different strain of the organism, and there is a better prognosis.

Other bacteria that should be considered when pneumonia is acquired *in utero* or in the immediate perinatal period include *Klebsiella* spp, group D streptococci, *Listeria monocytogenes,* and pneumococci. In the developing world or in HIV-affected mothers, *Mycobacterium tuberculosis* may be acquired transplacentally. Late-onset neonatal pneumonia develops more than 3 days up to several weeks after birth. In addition to these organisms, it can be caused by infections from *Staphylococcus* and *Pseudomonas* organisms and fungi. Although infection with *Chlamydia trachomatis* does appear to be acquired during parturition, pneumonia caused by this organism typically has a gradual onset of respiratory symptoms beyond 3 weeks of postnatal life.

Ureaplasma urealyticum has been linked to maternal chorioamnionitis. It has been isolated from the upper and lower respiratory tracts of infants with acute respiratory failure and has been associated with the development of BPD.[117]

Viral pneumonia can be acquired by the fetus from transplacental passage of organisms, as may be the case in congenital intrauterine infections (TORCH syndrome: *T*oxoplasmosis, *R*ubella, *C*ytomegalovirus, *H*erpes simplex virus). Viruses are the etiologic agent for some postnatally acquired pneumonias. Viral pneumonia may go undiagnosed in the neonate, although epidemics resulting from respiratory syncytial virus infection and adenovirus have been associated with significant morbidity and mortality.

Modes of Transmission

Intrauterine (Transplacental). Intrauterine infection is a result of clinical or subclinical maternal infection with a variety of agents (*Listeria, Mycobacterium,* cytomegalovirus [CMV], *Treponema pallidum, Toxoplasma gondii,* rubella virus, varicella virus, parvovirus B19) and hematogenous transplacental transmission to the fetus. Transplacental infection may occur at any time during gestation, with signs and symptoms present at birth, or may be delayed.

Ascending vertical transmission. Most early-onset bacterial neonatal pneumonia, typically from GBS and *E. coli,* is a result of ascending infection from the genital tract before or during labor. The infant can contract pneumonia through aspiration of contaminated amniotic fluid or by extended exposure to bacteria that may be in the vaginal tract. This type of transmission of bacteria is a result of heavy colonization of the maternal genitourinary tract. Prolonged rupture of membranes longer than 18 hours before delivery creates a significant chance of the infant's contracting bacteria and is thought to be one of the greatest predisposing factors to neonatal pneumonia. It is also possible that bacteria such as GBS could gain access to the fetus by ascent through intact membranes.

Postnatal (nosocomial or community acquired). After birth, neonates are exposed to infectious agents in the hospital or in the community. Postnatal infections, also known as *horizontal transmission,* may be passed to the newborn by direct contact with hospital personnel, the mother, or other family members; from breast milk (HIV, CMV); or from inanimate sources such as contaminated equipment. Some of the organisms responsible for postnatal pneumonia are airborne, whereas others are spread by contact.

The most common source of postnatal infections in hospitalized newborns is hand contamination by health care personnel. In the treatment of neonates, certain invasive lines (e.g., umbilical catheters, central venous lines) as well as ETTs and respiratory equipment can be avenues for late-onset nosocomial infections.

Risk Factors

The most important neonatal factors predisposing to infection are prematurity and **low birth weight** (LBW; less than 2500 g). Preterm LBW infants have a 3- to 10-fold higher incidence of infection than full-term, normal-birth-weight infants.

Other risk factors include the following:

- Prolonged rupture of membranes (longer than 18 hours)
- Maternal peripartum fever (38° C/100.4° F), chorioamnionitis, urinary tract infection (UTI), previous delivery with GBS disease
- Perineal colonization with GBS or *E. coli*
- Meconium-stained or foul-smelling, cloudy amniotic fluid
- Resuscitation at birth—infants who had fetal distress or were severely depressed at birth and required intubation and resuscitation
- Multiple gestations
- Invasive procedures, invasive monitoring, and respiratory or metabolic support
- Infants with neurologic abnormalities who are at risk for aspiration
- Infants with airway or pulmonary anomalies
- Infants with galactosemia (predisposition to *E. coli* infection), immune defects, or asplenia

CLINICAL PRESENTATION AND DIAGNOSIS

Early-onset infections are acquired before or during delivery and present before the first week of life, usually before 72 hours. The age at onset depends on the timing of exposure and virulence of the infecting organism. The infant may have a history of fetal tachycardia with low Apgar scores and often required some type of supplemental oxygen or even resuscitation at birth. Late-onset infections develop after the first week of life from organisms acquired in the hospital or the community, particularly in VLBW preterm infants or in term infants requiring prolonged neonatal intensive care.

The nonspecific nature of the clinical signs that are characteristic of neonatal infections makes a high index of suspicion the key to timely diagnosis. Early signs and symptoms of pneumonia may be nonspecific; they include poor feeding, lethargy, irritability, cyanosis, temperature instability, and unwell appearance. Respiratory symptoms include grunting, tachypnea, retractions, flaring of the alae nasi, cyanosis, tachypnea, apnea, and progressive respiratory failure. If the infant is premature, signs of progressive respiratory distress may be superimposed on RDS. For infants on mechanical ventilation, a need for increased ventilatory support may indicate infection. Signs of pneumonia on physical examination in older children, such as dullness to percussion, change in breath sounds, and the presence of rales or rhonchi, are very difficult to appreciate in a neonate.

Several factors should alert the health care provider to the possibility of neonatal pneumonia— a history of

maternal infection or fever, premature labor, prolonged rupture of membranes, malodorous or stained amniotic fluid, chorioamnionitis, or findings suggesting infection on placental pathology.

Anytime neonatal pneumonia is suspected, appropriate laboratory diagnostic tests should be performed, such as complete blood cell count (CBC), C-reactive protein (CRP), and blood cultures. Gram stain and cultures of tracheal aspirates may be performed if the patient is intubated. Urine and cerebrospinal fluid cultures may also be performed to assess for other sites of infection.

Blood gas values reveal hypoxemia and hypercapnia, and metabolic acidosis may develop in the setting of sepsis.

CXR may be nonspecific or may show a diffuse granular pattern with widespread bilateral involvement, especially if the infant acquired the infection *in utero.* This may be difficult to distinguish from the radiographic findings in RDS. The presence of pleural effusions may help distinguish neonatal pneumonia from RDS, which rarely presents with effusions. If aspiration of contaminated amniotic fluid has occurred, CXR may appear as an aspiration pneumonitis with patchy infiltrates. When an infection is acquired postnatally, the radiographic findings often change from normal to severely abnormal over the first few days. Depending on the severity of the disease process and the causative organism, pleural effusions, pulmonary edema, and pneumatoceles may develop (Figure 22-5).

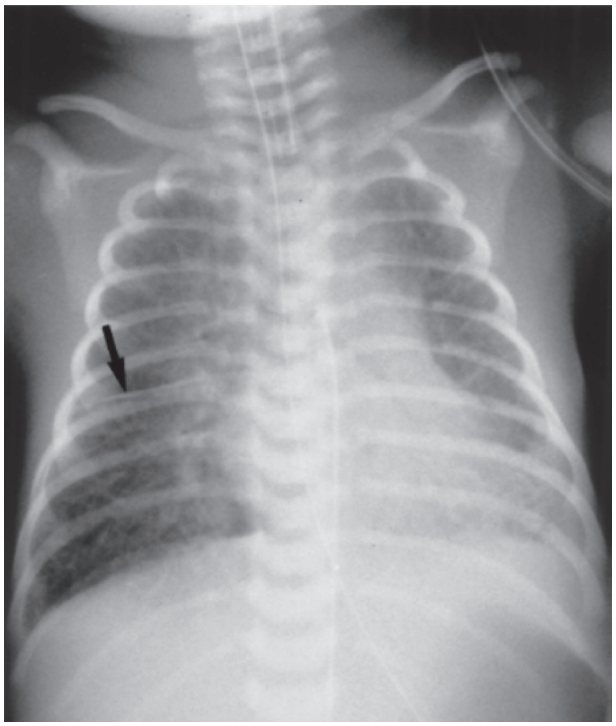


FIGURE 22-5 Group B streptococcal pneumonia with widespread interstitial shadowing with more confluent alveolar consolidation at the left bases and fluid in the horizontal fissure *(arrow).* (From Arthur R: The neonatal chest x-ray. *Paediatr Respir Rev* 2:311, 2001.)

PREVENTION

Aggressive management of suspected maternal chorioamnionitis with antibiotic therapy during labor, along with rapid delivery of the infant, reduces the risk of early-onset neonatal sepsis and pneumonia. Vertical transmission of GBS is significantly reduced by selective intrapartum chemoprophylaxis.[118]

Maternal immunization protects the mother against vaccine-preventable diseases that can cause intrauterine infections (rubella, hepatitis B, varicella) and may also protect the infant via passive transfer of protective maternal antibodies (tetanus). Toxoplasmosis is preventable with appropriate diet and avoidance of exposure to cat feces.

Neonatal infection with *Chlamydia* can be prevented by identification and treatment of infected pregnant women. Mother-to-child transmission of HIV is significantly reduced by maternal antiretroviral therapy during pregnancy, labor, and delivery; cesarean section delivery before rupture of membranes; and antiretroviral treatment of the infant after birth.

Prevention of Nosocomial Infection

Principles for the prevention of nosocomial infection include adherence to universal precautions with all patient contact, avoiding nursery crowding and limiting nurse-to-patient ratios, strict compliance with handwashing, meticulous neonatal skin care, minimizing the risk of contamination of all indwelling catheters, decreasing the number of blood draws, reducing the duration of all indwelling catheters and mechanical ventilation days, encouraging appropriate advancement of enteral feedings, providing education and feedback to nursery personnel, and ongoing monitoring and surveillance of nosocomial infection rates in the NICU.

TREATMENT

The normal course of treatment in neonatal pneumonia is multifaceted and includes appropriate antibiotic or antiviral therapy, oxygenation, and adequate ventilation. To prevent rapid deterioration, early intervention, aggressive management, and continuous monitoring are required, especially for infants with early-onset GBS disease.

Pharmacotherapy

Suspected early-onset pneumonia should be treated with intravenous broad-spectrum antibiotics, most commonly ampicillin and gentamicin. Ampicillin provides coverage for common bacterial pathogens, including GBS, *E. coli,* and, more rarely, *Listeria monocytogenes.* Gentamicin provides synergistic coverage. Third-generation cephalosporins such as cefotaxime, used with ampicillin, can be considered as an alternative to gentamicin but have been shown to be associated with increased mortality.[119] Whenever neonatal pneumonia is suspected, broad-spectrum antibiotics are given for

at least 48 hours, or until definitive culture results are obtained. If results prove that infection is present, or if clinical suspicion is high, antibiotics are continued for at least 7 days, and up to 21 days in the setting of suspected gram-negative meningitis. Treatment of late-onset pneumonia is based on local organism patterns but often includes antibiotics effective against methicillin-sensitive *Staphylococcus aureus* (MSSA) (such as nafcillin) or methicillin-resistant *S. aureus* (MRSA) (such as vancomycin) and a synergistic aminoglycoside for gram-negative coverage.

Antiviral agents may be administered to infants with pneumonia of viral origin, such as acyclovir for herpes simplex virus infection. In the case of some viral pathogens that are congenitally transmitted, such as CMV and rubella, irreversible damage to the central nervous system (CNS) has already occurred, and postnatal therapy cannot reverse it.

Respiratory Support

Ensuring airway patency may be more challenging in neonates with pneumonia because of the often profuse, potentially obstructive secretions and mucopurulent exudates. Chest physiotherapy and judicious suctioning are warranted. Deep suctioning should be avoided, because it can cause airway trauma and swelling, which in turn may cause large airway obstruction. The infant with cyanosis, hypoxemia, and hypercapnia may require mechanical ventilation. Adequate gas exchange depends not only on alveolar ventilation but also on perfusion and gas transport capacity. Preservation of pulmonary and systemic perfusion is essential, using volume expanders, inotropes, afterload reduction, blood products, and nitric oxide as needed. Near-term and term infants who are unresponsive to conventional ventilation and other supportive measures may benefit from extracorporeal membrane oxygenation (ECMO). Improved rates of survival have been reported in this group.[120]

Complications and Prognosis

Morbidity and mortality associated with neonatal pneumonia depend on the causative organism and responsiveness to antimicrobial therapy. Management includes frequent assessment for complications of prematurity and sepsis as well as their treatment: air leaks, PPHN, IVH, and the eventual development of BPD if mechanical ventilation is required for extended periods.

The progression of neonatal pneumonia can be variable. Fulminant infection is most commonly associated with pyogenic organisms such as GBS. Onset may occur during the first hours or days of life, with the infant often manifesting rapidly progressive circulatory collapse and respiratory failure. Outcome is generally good in full-term infants but is worse in infants with risk factors, including premature infants or those with underlying lung disease.

MECONIUM ASPIRATION SYNDROME

DEFINITION

Meconium is the thick, black-green–tinged bowel contents of a newborn, which is usually passed within 48 hours after delivery. The term was coined by Aristotle from the Greek words *meconium arion*, meaning "opium-like," because he believed that the substance induced fetal sleep.[121] Meconium is a sterile substance composed of swallowed amniotic fluid, salts, mucus, bile, and other cellular debris. Meconium is sterile, but when aspirated into the lung may cause a release of cytokines, serious airway obstruction, air trapping, and enhanced growth of bacteria. Furthermore, contents of meconium can compete with surfactant components for adsorption to the alveolar surface, and enzymes in meconium can break down certain surfactant components.

INCIDENCE

Meconium staining of the amniotic fluid (MSAF) occurs in approximately 10% to 15% of deliveries. Meconium aspiration syndrome (MAS) develops in approximately 4% to 10% of infants born through MSAF. Of these neonates who develop MAS, one-third require ventilatory support, 10% develop air leaks, and, despite appropriate management strategies, there is a 5% to 10% mortality rate. Of newborns with PPHN, about 5% of cases are related to MAS.[122]

Meconium passage into the amniotic fluid occurs in the first trimester and ceases at approximately 20 weeks, at which point the anal sphincter is innervated. MSAF is uncommon in preterm infants, because meconium passage requires strong peristalsis and anal sphincter tone. Therefore MAS rarely occurs in infants of less than 36 weeks gestational age. The longer a pregnancy is allowed to continue past term, the greater the chances of passage of meconium, possibly related to rising motilin levels. Changing obstetric practice by delivering babies before 41 weeks' gestation has significantly decreased the risk of MSAF and MAS.[123]

ETIOLOGY AND PATHOPHYSIOLOGY

Fetal passage of meconium has long been accepted as a sign of intrauterine stress or hypoxia. Theoretically, the infant becomes hypoxic *in utero* (possibly because of cord or head compression or exhausted oxygen reserves during prolonged labor), causing a vagal response, relaxed anal sphincter tone, and passage of meconium into the amniotic fluid. The normal intrauterine activity of the fetus involves the movement of small amounts (1-5 mL) of amniotic fluid into and out of the upper airways. If meconium is present in the amniotic fluid, the potential to aspirate it is always present, but chances are increased with hypoxia or stress because of greater respiratory effort and possibly gasping respirations *in utero.* Aspiration may also occur after delivery when expansion of the chest allows the fluid or meconium, or both, to be dispersed even deeper into the infant's lungs.

After delivery, the normal pulmonary mechanisms are hindered in the setting of MAS. Aspirated meconium causes a ball-valve effect because of partial obstruction of the airways (Figure 22-6). Inflammation of the airways and secretion production (a normal response to a foreign substance within the lungs) occurs, and a chemical pneumonitis often develops. Meconium also inactivates surfactant, which may lead to atelectasis and decreased pulmonary compliance.

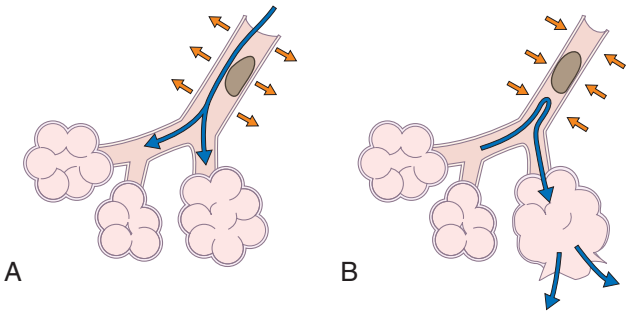


FIGURE 22-6 Air trapping behind particulate matter (i.e., meconium) in an airway, which leads to alveolar overexpansion and rupture. Tidal gas passes the meconium on inspiration when the airway dilates **(A)** but does not exit on expiration when the airway constricts **(B)**. (From Harris TR, Herrick BR: *Pneumothorax in the Newborn.* Biomedical Communications, Tucson: Arizona Health Sciences Center, 1978.)

It has been suggested that intrauterine hypoxia not only stimulates the passage of meconium but also causes restructuring of the pulmonary vascular bed. The hypoxia may result in pulmonary vasoconstriction, which causes many infants with MAS to then develop PPHN. Figure 22-7 summarizes the pathophysiologic events that occur with the passage of meconium and MAS.

CLINICAL PRESENTATION AND DIAGNOSIS

Clinical Presentation

An infant with MAS is usually term or postterm, has been delivered through MSAF, and has already experienced significant intrauterine stress or hypoxia. The history may include prolonged labor or nonreassuring fetal heart tracings, such as late decelerations or lack of variability.

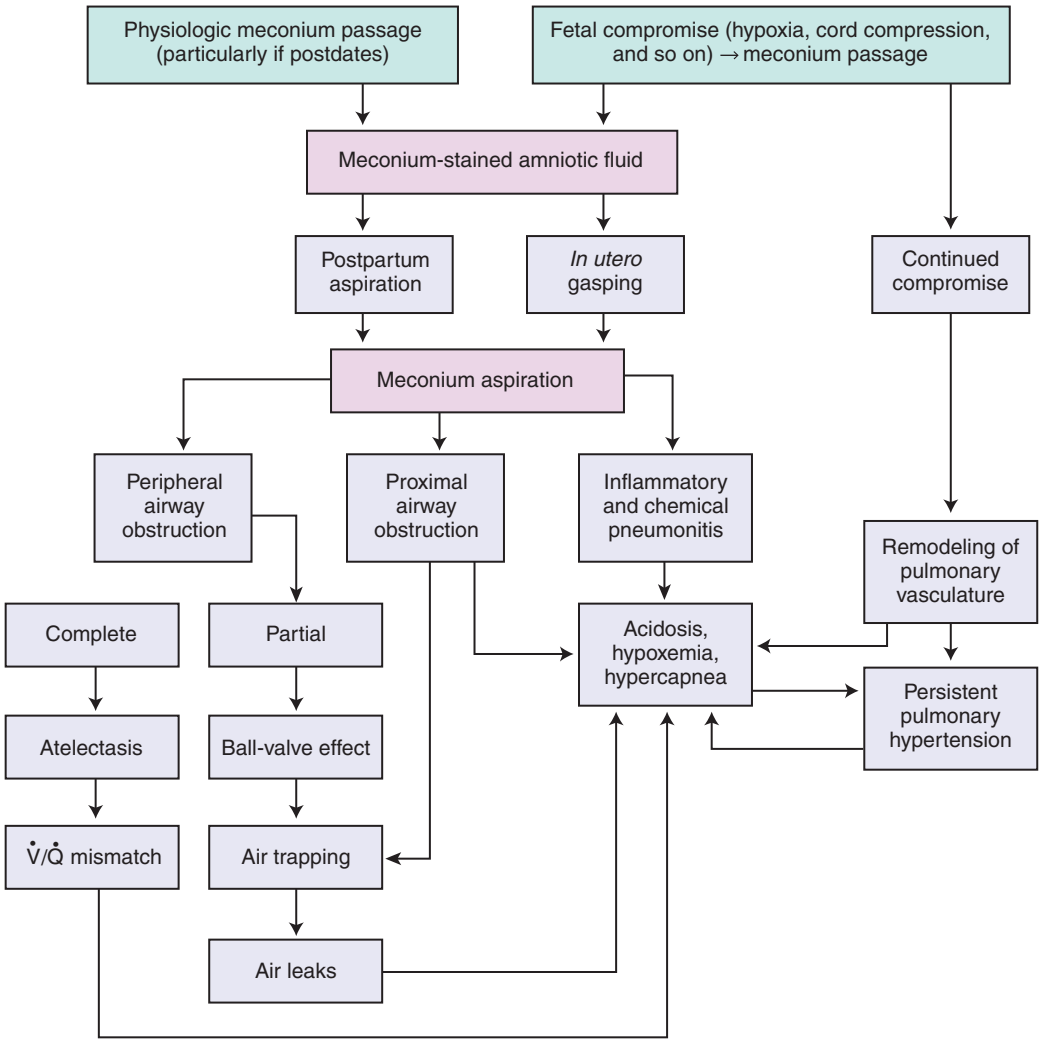


FIGURE 22-7 Pathophysiology of meconium aspiration syndrome (MAS). (Redrawn from Wiswell TE, Bent RC: Meconium staining and the meconium aspiration syndrome. *Pediatr Clin North Am* 40:957, 1993. Modified from Bacsik RD: Meconium aspiration system. *Pediatr Clin North Am* 24:467, 1977.)

Physical examination often reveals an infant with yellow-stained skin, nails, and cord and the postmature signs of peeling skin and long fingernails. Depending on the extent of stress or hypoxia, the infant may be depressed at birth and then quickly develop cyanosis and respiratory distress, including gasping respirations, grunting, retractions, nasal flaring, and tachypnea. Auscultation of the chest reveals rales as well as areas of significantly diminished aeration, with the anteroposterior diameter of the chest often increased because of hyperexpansion and overinflation.

Investigations

Arterial access is preferred for frequent ABG monitoring. ABG analysis indicates hypoxemia and respiratory acidosis. The infant may also have significant metabolic acidosis, depending on the severity of the hypoxia before birth.

The classic chest radiograph shows widespread patchy areas of atelectasis caused by obstruction, as well as hyperexpansion with flattening of the diaphragm secondary to air trapping (Figure 22-8). Pulmonary air leaks, including pneumothorax and pneumomediastinum, may also be found. Echocardiography may be helpful to detect pulmonary hypertension and right-to-left shunt.

PREVENTION

Prevention of postmature delivery by induction of labor at 41 weeks and close intrapartum monitoring for fetal hypoxia and distress are important in the prevention of MAS. The evidence (or lack of evidence) for other strategies is listed in the following sections.

Amnioinfusion (Injection of Normal Saline Into the Amniotic Sac)

In the past it was believed that by infusing fluid into the mother's uterus, the uterine fluid volume would either dilute the meconium or alleviate compression of the cord and prevent gasping. However, current evidence proves that amnioinfusion does not reduce the risk of MAS.[124]

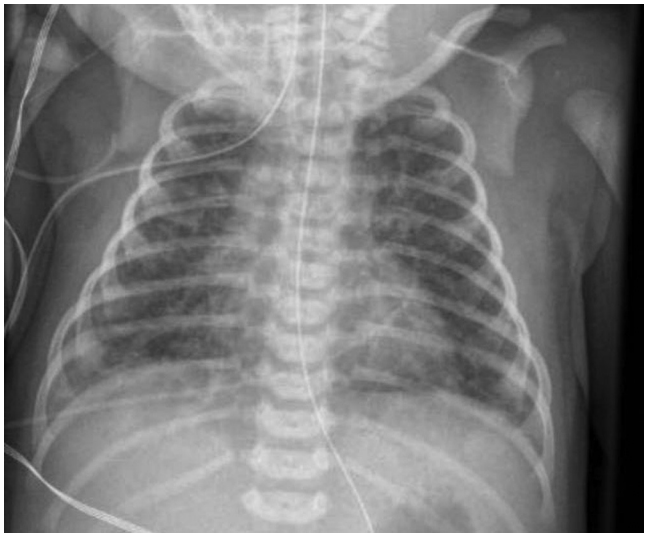


FIGURE 22-8 Meconium aspiration syndrome with heterogeneous, patchy pulmonary infiltrates in association with hyperinflated lungs.

Intrapartum Nasopharyngeal and Oropharyngeal Suctioning

Large international randomized controlled trials showed that intrapartum nasopharyngeal and oropharyngeal suctioning by obstetric providers does not reduce the incidence of MAS.[125]

Endotracheal Intubation and Intratracheal Suctioning in the Delivery Room

The AAP Neonatal Resuscitation Program Steering Committee and the American Heart Association (AHA) have updated guidelines for management of babies exposed to meconium in the 2015 Neonatal Resuscitation Program (NRP). One of the significant changes in the current guidelines is removal of the recommendation to suction the trachea of nonvigorous infants born through MSAF. Performing elective endotracheal suctioning of meconium does not offer benefit in preventing MAS, based on a lack of evidence demonstrating benefit and aiming to avoid harm.[126] The AAP and AHA no longer recommend routine immediate endotracheal intubation and suctioning for nonvigorous infants. Care of these infants is guided by the same principles as outlined in the NRP, in which intubation is indicated for inadequate respiratory effort (apnea, gasping, or poor oxygenation) or bradycardia despite bag–mask ventilation, or when chest compressions are required.

Gastric Suctioning

Theoretically, postnatal suctioning of the gastric contents in meconium-stained infants could prevent postnatal reflux or emesis and frank aspiration of MSAF; however, routine gastric lavage before feeding has not been shown to decrease the incidence of MAS in babies born through MSAF.[127]

Potentially Dangerous Maneuvers of No Proven Benefit

Cricoid pressure, epiglottal blockage, and thoracic compression are examples of unsafe and ineffective historical maneuvers that should not be used.

TREATMENT

Supplemental Oxygen Therapy

The goal is to maintain acceptable systemic oxygenation. Generally, this consists of sustaining peripheral oxygen saturation between 95% and 99% or Pao_2 between 60 and 80 mm Hg. Oxygen is also a pulmonary vasodilator; therefore hypoxia should be avoided. CPAP may be considered in infants who require Fio_2 of more than 0.4.

Mechanical Ventilation

As many as 30% of infants with MAS require intubation and mechanical ventilation.[128] Indications include hypercarbia ($Paco_2 > 60$ mmHg) or persistent hypoxemia ($Pao_2 < 50$ mm Hg). Conventional ventilation may require high peak inspiratory pressures (30-35 cm H_2O) and longer inspiratory times (0.4-0.5 seconds) at lower rates (20-25 breaths per minute) than in premature infants with respiratory distress syndrome.

High-Frequency Ventilation

HFV has been used in MAS in the hope that the lower pressures and higher frequencies will prove advantageous. Theoretical benefits include less barotrauma, increased mobilization of secretions, and improved ability to achieve goal blood gas ranges. HFOV, particularly when used with inhaled nitrous oxide (iNO), may improve oxygenation and outcome, in infants with PPHN and MAS.[129]

Surfactant Therapy

Because surfactant within the lung may be inactivated by the presence of meconium, surfactant replacement therapy can be considered as a treatment for MAS. Surfactant administration seems to reduce the severity of respiratory symptoms and may reduce the disease progression and the need for ECMO.[20,130] An alternative approach is the use of dilute surfactant to lavage the lungs of infants with MAS. Three randomized controlled trials have assessed lung lavage with dilute surfactant. Infants receiving this therapy had more favorable composite outcomes in terms of mortality and need for ECMO, but the studies were small, and the practice is not well established and can have significant complications.[131,132]

Inhaled Nitric Oxide

iNO should be considered in infants with concomitant PPHN who are not responding to conventional therapy (see Persistent Pulmonary Hypertension of the Newborn).

Extracorporeal Membrane Oxygenation

ECMO is the therapy of last resort in infants with refractory respiratory failure on HFV and iNO.

Cardiovascular Support

Infants should be managed with a goal of normal blood pressure. In the setting of PPHN, a systemic blood pressure greater than pulmonary blood pressure will decrease right-to-left shunting. Circulatory support with normal saline, packed red cells, and vasopressors (typically dopamine) may be required.

Steroid Therapy

Corticosteroids are not recommended for treatment of MAS; evidence supporting the use of steroids for this indication is insufficient.[133]

Other Therapies

Infants being treated for MAS should have minimal tactile stimulation. Discomfort can increase catecholamine release and pulmonary vasoconstriction, resulting in worse right-to-left shunting. Thus adequate sedation is of paramount importance, and in severe cases, neuromuscular blockade is necessary to prevent dyssynchrony with the ventilator. Chest physiotherapy should be used sparingly to prevent agitation and PPHN.

Antibiotics are routinely administered initially, because pneumonia may be difficult to differentiate from MAS. Infants in the acute phase of illness are typically maintained NPO with parenteral nutrition and close attention to ensuring normal blood sugar and electrolytes, including calcium.

COMPLICATIONS AND PROGNOSIS

Complications of MAS are widespread and depend on the severity of the disease and the level of treatment necessary. Barotrauma or air leak syndrome is always a risk with positive-pressure ventilation (PPV), especially in an infant with MAS in whom the ball-valve effect produces air trapping. The patient should be closely monitored for sudden deterioration, which could be indicative of tension pneumothorax. Immediate needle aspiration of the air, insertion of a chest tube, or both may be indicated.

Another serious complication in MAS is increased intracranial pressure. Because the cranium is a fixed cavity, volume capacity is limited. Venous drainage is inhibited by increased intrathoracic pressure, creating a potential for elevated intracranial pressure. The neonate with unstable vasculature who is already compromised may be predisposed to a higher incidence of IVH.

PPHN is associated with MAS in approximately one-third of cases and contributes to the mortality associated with this syndrome. If a patient develops PPHN, echocardiography should be performed to ascertain the degree of right-to-left shunt, assess cardiac function, and exclude congenital heart disease as the cause.

The mortality rate of meconium-stained infants is considerably higher than that of unstained infants. The decline in neonatal deaths caused by MAS during the last decades is related to improvements in obstetric and neonatal care. Residual lung problems are rare but include cough, wheezing, and persistent hyperinflation for up to 5 to 10 years.[134] The ultimate prognosis depends on the extent of CNS injury from asphyxia and the presence of associated problems, such as PPHN.[135]

PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

DEFINITION

PPHN is a clinical syndrome that occurs as a result of disruption in the normal perinatal fetal–neonatal

Box 22-2 Factors Associated with Persistent Pulmonary Hypertension of the Newborn

Structural Lung and Heart Disease
- Congenital diaphragmatic hernia
- Congenital cystic adenomatous malformation
- Alveolar capillary dysplasia
- Pulmonary hypoplasia
- Congenital heart defects
- *In utero* ductus arteriosus closure

Perinatal Clinical Predictors
- Late prematurity (34 to <37 weeks)
- Postmaturity (>41 weeks)
- Cesarean section
- Nulliparity
- Oligohydramnios
- Chorioamnionitis
- Fetal distress
- Asphyxia
- Small for gestational age
- Large for gestational age

Postnatal Factors
- Meconium aspiration syndrome
- Respiratory distress syndrome
- Sepsis

Maternal Health
- Advanced maternal age (>34 years)
- Asthma
- Diabetes mellitus
- Urinary tract infection
- Preeclampsia
- Antenatal illicit drug exposure
- Aspirin and/or nonsteroidal antiinflammatory drug use
- Selective serotonin reuptake inhibitor use
- Cigarette smoking

Race and Gender
- Black
- Male

(Adapted from Delaney C, Cornfield DN: Risk factors for persistent pulmonary hypertension of the newborn. *Pulm Circ* 2(1):15, 2012; with additional information from Steurer MA, et al: Persistent pulmonary hypertension of the newborn in late preterm and term infants in California. *Pediatrics* 139(1), 2017.)

circulatory transition. It is characterized by sustained elevated pulmonary vascular resistance (PVR) and alterations in pulmonary vasoreactivity, resulting in right-to-left shunting of blood across the foramen ovale or the PDA.

PPHN is present when an infant with an echocardiographically confirmed structurally normal heart has the following conditions: (1) hypoxemia disproportionate to the degree of suspected lung disease, and (2) evidence of a right-to-left ductal shunt (Pao_2 gradient between a **pre-** and **postductal** site of blood sampling of more than 20 mm Hg or difference in Spo_2 from the preductal right hand to the postductal lower extremities of more than 10%). Of note, if the shunt occurs at the level of the foramen ovale and not the PDA, PPHN will not cause a preductal–postductal differential.[136]

INCIDENCE

PPHN occurs in 1 to 2 per 1000 live births and is associated with a high risk of mortality, reported at 7.6% in a recent study. Risk factors include late preterm infants (34-37 weeks); black maternal race; large-for-gestational-age (LGA) or small-for-gestational-age (SGA) status; and mothers with diabetes, obesity, or advanced maternal age.[137]

ETIOLOGY AND PATHOPHYSIOLOGY

PPHN can be idiopathic or secondary to different conditions, including intrapartum asphyxia, infection, pulmonary hypoplasia, congenital heart disease, MAS, RDS, or drug therapy.[138] Box 22-2 lists factors commonly associated with PPHN.

In fetal life, the placenta functions as the organ for gas exchange. This function is facilitated by both shunting of blood through the foramen ovale and hypoxic pulmonary arteriole vasoconstriction, which causes approximately 90% of pulmonary blood flow to be shunted from right to left toward the placenta. At birth, the umbilical cord is cut and the lungs transition to become the organ for gas exchange. With the first postnatal breaths, PVR decreases dramatically. By 24 hours of life, 80% of the total decrease in PVR has occurred, with the remaining reduction taking place over the next 2 weeks of life. The decrease in PVR occurs in response to (1) increases in Pao_2 and pH, (2) air expanding the lung, and (3) release of vasoactive substances, including prostaglandins, bradykinin, and endogenous nitric oxide.

The fetus prepares for this transition late in gestation by increasing pulmonary vascular expression of nitric oxide synthases and soluble guanylate cyclase. The prostacyclin pathway is also important for vasodilation. Prostacyclin stimulates adenylate cyclase to increase intracellular cyclic adenosine monophosphate (cAMP) levels, which, as with cyclic guanosine monophosphate (cGMP), leads to vasorelaxation through a decrease in intracellular calcium concentration (Figure 22-9).

In infants with PPHN, this decrease in PVR either fails to occur adequately or is reversed by pulmonary vascular hyperreactivity to irritating stimuli. PPHN is often characterized as one of three types:[139]

1. Maladaptation: Structurally normal but abnormally constricted pulmonary vasculature caused by lung parenchymal diseases such as MAS, RDS, or pneumonia.
2. Excessive muscularization: Lung with normal parenchyma but remodeled pulmonary vasculature characterized by increased smooth muscle cell thickness and distal extension of muscle to vessels that are usually nonmuscular. Many factors promote vascular remodeling in PPHN, such as an increase in

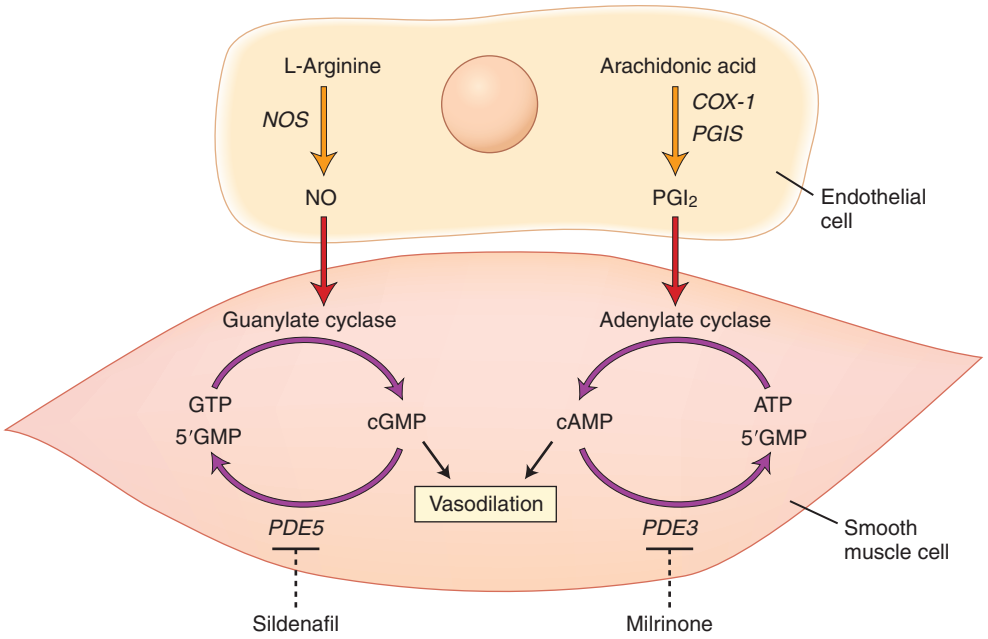


FIGURE 22-9 Nitric oxide (*NO*) and prostacyclin (i.e., prostaglandin I2 [PGI_2]) signaling pathways that regulate pulmonary vascular tone in the developing lung. (From Steinhorn RH, Abman SH: Persistent pulmonary hypertension. In Gleason CA, Devaskar SU, eds.: *Avery's Disease of the Newborn,* 9th ed, Philadelphia, 2012, Saunders.)

pulmonary blood flow *in utero;* hypoxia; hyperoxia; and various mediators, including endothelin type 1 (ET-1), platelet activating factor (PAF), reactive oxygen species (ROS), platelet-derived growth factor (PDGF), transforming growth factor β (TGF-β), and other growth factors. On the other hand, some mediators may inhibit vascular remodeling, such as the nitric oxide/cGMP pathway and vascular endothelial growth factor (VEGF). Thus stimuli suppressing these inhibitory signaling mechanisms may also contribute to pulmonary vascular remodeling.

3. Hypoplastic vasculature: Associated with underdevelopment of the pulmonary vasculature, as seen in congenital diaphragmatic hernia.

These designations are imprecise, however, and high PVR in most patients likely involves overlapping changes among these categories.

CLINICAL PRESENTATION AND DIAGNOSIS

Clinical Presentation

PPHN should be suspected in all term infants who are cyanotic despite adequate ventilation. The recognition of risk factors for PPHN, such as MAS, is one of the major diagnostic tools to differentiate babies with PPHN from those with structural heart disease, keeping in mind that idiopathic PPHN can present without signs of acute perinatal distress. Many infants will have a history of perinatal depression with low Apgar scores. Marked lability in oxygenation is often part of the clinical history.[140]

An infant with PPHN usually presents within the first 12 hours of life with cyanosis, tachypnea, and hypoxia that are refractory to oxygen therapy and signs of respiratory distress, including retractions, grunting, and nasal flaring.

Investigations

CXR appearance varies depending on the associated disorder. Early CXR is often clear, with minimal evidence of respiratory involvement relative to the cyanosis and respiratory distress the infant exhibits. Idiopathic and asphyxic PPHN may show well-expanded or hyperexpanded lungs with diminished vascularity, whereas PPHN resulting from pulmonary disorders (e.g., MAS, RDS, TTN) reveals abnormal pulmonary findings characteristic of the particular disorder. Cardiomegaly may be evident and develops as a result of the increased right ventricular afterload caused by the pulmonary hypertension.

ABG assessment reveals hypoxemia. Infants may hyperventilate because of the persistent hypoxemia. Hypocalcemia and hypoglycemia may develop as well, particularly in asphyxic infants.

Echocardiography should be performed in infants with suspected PPHN. Real-time echocardiography combined with Doppler flow imaging studies demonstrates right-to-left or bidirectional shunting across a patent foramen ovale and/or a ductus arteriosus. Deviation of the intraatrial or intraventricular septum into the left atrium or ventricle is seen in severe PPHN. Tricuspid or mitral insufficiency may be visualized echocardiographically together with poor contractility when PPHN is associated with myocardial ischemia. The degree of tricuspid regurgitation can be used to estimate pulmonary artery pressure. Echocardiography

should also be used to evaluate ventricular function and exclude structural heart disease.

DIFFERENTIAL DIAGNOSIS

A number of disorders, some of which are associated with secondary pulmonary hypertension, are misdiagnosed as PPHN. Therefore an important aspect of the evaluation of an infant with presumed PPHN is an effort to rule out other conditions, including the following:

1. Structural cardiovascular abnormalities associated with right-to-left ductal or atrial shunting, including the following:
   a. Obstruction of pulmonary venous return: Infradiaphragmatic total anomalous pulmonary venous return, hypoplastic left heart syndrome, cor triatriatum, congenital mitral stenosis
   b. Myopathic left ventricular (LV) disease: Endocardial fibroelastosis, Pompe disease
   c. Obstruction of LV outflow: Critical aortic stenosis, supravalvular aortic stenosis, interrupted aortic arch, coarctation of the aorta
   d. Complete mixing lesions with elevated pulmonary vascular resistance: Endocardial cushion defect, hemitruncus
   e. Arteriovenous malformation, coronary arteriovenous fistula
   f. Miscellaneous disorders: Ebstein anomaly, transposition of the great arteries
2. LV or right ventricular (RV) dysfunction associated with right-to-left hemodynamic shunting: LV dysfunction as a result of ischemia or obstruction caused by myopathic LV disease or obstruction of LV outflow might present with a right-to-left ductus arteriosus shunt. RV dysfunction may be associated with right-to-left atrial shunting as a result of decreased diastolic compliance and elevated end-diastolic pressure.

These diagnoses must be differentiated from idiopathic PPHN caused by pulmonary vascular remodeling or vasoconstriction. Signs favoring cyanotic congenital cardiac disease over PPHN include cardiomegaly, weak pulses, active precordium, pulse differential between upper and lower extremities, pulmonary edema, grade 3 or higher murmur, and persistent preductal and postductal Pao_2 at 40 mm Hg or less.[136]

TREATMENT

PPHN constitutes a medical emergency in which immediate appropriate intervention is critical to reverse hypoxemia, improve pulmonary and systemic perfusion, and minimize hypoxic-ischemic end-organ injury.

The goal of respiratory support is to achieve normoxia and a neutral or slightly alkalotic acid-base balance that facilitate the normal perinatal circulatory transition. Once stability is achieved, weaning should be undertaken conservatively, with careful attention to the infant's tolerance of each step in tapering cardiorespiratory support.[136]

1. General management: Includes maintenance of normal temperature, electrolytes (particularly calcium), glucose, hemoglobin, and intravascular volume. Acidosis, which worsens PVR, should be corrected by normalizing gas exchange and using sodium acetate in intravenous fluids to improve metabolic acid-base derangements.
2. Minimal handling: Because infants with PPHN are extremely labile, with significant deterioration after seemingly "minor" stimuli, this aspect of care deserves special mention. ETT suctioning in particular should be performed only if indicated and not as a matter of routine. Noise level and physical manipulation should be kept to a minimum.
3. Supplemental oxygen: Because hypoxia is a potent pulmonary vasoconstrictor, oxygen therapy to achieve normoxia is the most important therapy to reduce PVR. However, excess oxygen exposure may release free radicals that worsen pulmonary hypertension. Typically, preductal Spo_2 is maintained between 90% and 99%. Preductal (right arm) and postductal (lower extremity) oxygen saturations should be continuously monitored.[136]
4. Mechanical ventilation: Mechanical ventilation may be required to improve oxygenation and achieve goal blood gases. The goal of mechanical ventilation should be to maintain normal FRC by recruiting areas of atelectasis, as well as to avoid overexpansion. Ventilators should be adjusted to maintain adequate oxygenation and normal ventilation until stability is achieved for 12 to 24 hours. Although specific strategies may differ by center, reasonable targets may be maintaining oxygen saturation between 90% and 99%, $Paco_2$ at 40 to 50 mm Hg, and arterial pH at approximately 7.35 to 7.40. These targets should be adjusted based on underlying lung disease, if present.[136]

HFV is an important modality if a newborn has underlying parenchymal lung disease with low lung volumes. Oscillatory ventilation (HFOV) has shown to be more effective than conventional ventilation when delivering nitric oxide. Jet ventilation (HFJV) may be useful in infants with air leak.[141]

Patients with PPHN should be cared for at a center with experience in the multiple subtleties of its management.

Pharmacotherapy

Pulmonary vasodilator agents. Guidelines for treatment with vasodilators are as follows:

1. iNO: Nitric oxide is an endothelial-derived gas-signaling molecule that relaxes vascular smooth muscle and can be delivered to the lung by means of an inhalation device. It works through cGMP intracellular signaling pathways to relax the vascular smooth muscle, thereby causing pulmonary

vasodilation. It is quickly bound by hemoglobin in circulation and inactivated, resulting in minimal systemic vasodilation and hypotension. iNO has been shown to decrease the need for ECMO among term infants with severe respiratory failure related to pulmonary hypertension.[142,143]

The **oxygenation index** (OI; calculated as [mean airway pressure × Fio_2 × 100]/Pao_2) is often used to gauge the severity of disease. Treatment with iNO is indicated for newborns with an OI of 25 or more. Toxicity from methemoglobinemia should be monitored. iNO is most effective when administered by HFOV compared with conventional ventilation.[141] The typical starting dose is 20 ppm. The patient should be weaned when FiO_2 is less than 60% to maintain Spo_2 above 90%, done gradually to avoid rebound hypoxemia.

2. Phosphodiesterase inhibitors (e.g., sildenafil) have been shown to improve OI in case series data.[144] However, the US Food and Drug Administration (FDA) has issued a warning that sildenafil may increase mortality in children with pulmonary arterial hypertension; thus more data is needed before making a routine recommendation regarding its use in neonates.
3. Other agents still considered investigational include prostacyclin analogs (epoprostenol, treprostinil, beraprost, and iloprost) and endothelin receptor antagonists (bosentan and ambrisentan).[145,146]

Sedation and analgesia. Because catecholamine release activates pulmonary α-adrenergic receptors, thereby potentially raising PVR, a narcotic analgesic that blocks the stress response, such as a fentanyl infusion (1 to 4 µg/kg/hr) or, when the infant is not hypotensive, morphine infusion (0.05 to 0.1 mg/kg/hr), is a useful adjunct therapy. Neuromuscular blocking agents can be used to prevent dyssynchrony with the ventilator.

Maintenance of adequate cardiac output and systemic blood pressure. The degree of right-to-left shunting depends on the pulmonary-to-systemic gradient. Avoiding systemic hypotension is critical. Monitoring is ideally performed with arterial access to closely follow blood pressure, acid-base balance, and lactic acidosis. Urine output is also a valuable indicator of organ perfusion. When PVR is near systemic blood pressure, the infant may require mean arterial blood pressure of 45 to 55 mm Hg to decrease right-to-left shunting; lower pressure may be targeted as PVR improves. Strategies to provide hemodynamic support include the following:

- Hypovolemia can be corrected by administering volume expanders.
- Cardiotonic/vascular agents, such as dopamine and epinephrine, can be used. These increase cardiac output and may improve systemic blood pressure through peripheral vasoconstriction but can have the side effect of increasing PVR through adrenergic effects. Milrinone may be effective in the setting of ventricular dysfunction, because it decreases PVR.[147]

Extracorporeal Membrane Oxygenation

ECMO is a lifesaving therapy for infants who have failed conventional management or iNO treatment. ECMO is generally considered for infants with OI greater than 40 and in some centers is used when OI is greater than 60 when the infant is on HFOV. Approximately 80% of infants started on ECMO for PPHN survive[148] (see Chapter 20).

COMPLICATIONS AND PROGNOSIS

As recently as the late 20th century, the mortality rate for PPHN was nearly 40%. The introduction of high-frequency ventilation, nitric oxide, and ECMO has significantly improved survival rates, though mortality rates may remain as high as 10%, and infants who do survive are still at significant risk of neurodevelopmental delays.[149]

NEONATAL APNEA

DEFINITIONS

Apnea is defined as an unexplained episode of cessation of breathing for 20 seconds or longer, or a shorter respiratory pause associated with bradycardia, cyanosis, pallor, or hypotonia.

Apnea of prematurity (AOP) is defined as sudden cessation of breathing that lasts for at least 20 seconds or is accompanied by bradycardia or cyanosis in an infant younger than 37 weeks postmenstrual age.

Apnea of infancy (AOI) generally refers to infants with a postmenstrual age of 37 weeks or more at the onset of apnea.

Periodic breathing (PB) is defined as bursts of respiratory activity of 20 seconds or less separated by central apneic pauses lasting from 3 to 10 seconds. Periodic breathing is present in almost all preterm babies and can also be seen in term babies. The cause of periodic breathing remains obscure, although the finding that it is absent until 48 hours of age suggests that inactivity of peripheral chemoreceptors at this time might play a role.[152]

Brief resolved unexplained event (BRUE) is defined as a sudden, brief, resolved episode characterized by some combination of cyanosis or pallor; absent, decreased, or irregular breathing; marked change in muscle tone (usually marked limpness); and/or an altered level of responsiveness. BRUE is a recent term intended to characterize many events previously described under the broader term **acute life-threatening event** (ALTE).[150]

Sudden Unidentified Infant Death Syndrome (SUIDS) is defined as the sudden death of an infant younger

than 1 year of age that remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history.[151]

CLASSIFICATION

Apnea traditionally is classified into three categories based on the presence or absence of upper airway obstruction:

1. Central apnea is caused by the lack of a neurologic drive to breathe, resulting in cessation of inspiratory efforts with no evidence of obstruction.
2. Obstructive apnea occurs when an infant tries to breathe against an obstructed upper airway, resulting in chest wall motion without airflow through the apneic episode.
3. Mixed apnea consists of obstructed respiratory efforts, usually after central pauses.

INCIDENCE

Apneic spells occur frequently in premature infants. The incidence of apnea increases with decreasing gestational age. More than 50% of infants weighing less than 1500 g and 90% of infants weighing less than 1000 g will have apnea. About half of moderately preterm infants, between 33 and 35 weeks gestational age, will have apnea. Even some term infants exhibit apnea, though it is rare. In these cases, other causes such as infection, seizures, intracranial hemorrhage, birth asphyxia, upper airway obstruction, or depression from medication need to be ruled out.[153] Apneic spells generally begin at 1 or 2 days after birth; if they do not occur during the first 7 days, they are unlikely to occur later. If an infant has a new onset of apneic spells after 1 week of age, other causes must be ruled out. Apneic spells persist for variable periods postnatally and usually cease by 37 weeks postmenstrual age but may persist beyond term equivalent, up to approximately 43 weeks postmenstrual age.[154]

ETIOLOGY AND PATHOPHYSIOLOGY

Developmental immaturity of the central respiratory drive is a key factor in the pathogenesis of AOP.[155] Premature infants are believed to be susceptible to apneic episodes also because of immature afferent input from chemoreceptors and lung and airway receptors, with diminished responses to both hypercapnia and hypoxia.

Sleep-related response may be a factor in apnea and periodic breathing. Nearly 80% of a preterm infant's time is spent sleeping, with approximately 90% of a sleep cycle spent in rapid eye movement (REM) sleep, and the infant often has difficulty making the transition between the sleeping and waking states. Apneic spells occur more frequently in REM states.

Weakness of both the muscles of respiration and the muscles that maintain airway patency plays an important role in contributing to airway obstruction. Nasal obstruction in premature infants who are obligate nasal breathers also may contribute to apneic spells.[156]

Although physiologic immaturity is the most common cause of apnea, secondary causes of apnea must be considered in all infants, especially those presenting with apnea after 1 week of age and increased frequency of spells, or term infants with spells. Secondary causes include the following:

1. Temperature instability: Hypothermia and hyperthermia
2. Neurologic: Birth trauma, intracranial infection, intracranial hemorrhage, perinatal asphyxia, seizures, medications including anesthetics
3. Pulmonary: RDS, pneumonia, pulmonary hemorrhage, obstructive airway lesion, pneumothorax, BPD
4. Cardiac: Congenital cyanotic heart disease, hypotension/hypertension, congestive heart failure, PDA
5. Hematologic: Anemia, polycythemia
6. Infectious: Sepsis, NEC
7. Metabolic: Hypoglycemia, hypocalcemia, hyponatremia, hypernatremia
8. Inborn errors of metabolism
9. Gastrointestinal: Gastroesophageal reflux (GER), esophagitis

Both GER and apnea are common in preterm infants, and GER is commonly cited as a cause of apnea. However, studies have not demonstrated a consistent temporal relationship between GER and apneic, bradycardic, or desaturation spells.[157] Additionally, during an apneic episode, loss of respiratory neural output may be accompanied by a decrease in lower esophageal tone, and GER may result from the apneic spell itself.

CLINICAL PRESENTATION AND DIAGNOSIS

Clinical Presentation

Apnea of prematurity typically first presents 2 to 3 days after birth. Apnea before 24 hours of life may be associated with infant or maternal pathologic conditions (e.g., neonatal sepsis, hypoglycemia, intracranial hemorrhage, maternal antepartum magnesium treatment, or maternal exposure to narcotics).

When apnea occurs in a preterm infant after the first 24 hours of life and is not associated with any other pathologic condition, it may be classified as AOP. Apnea may also occur after weaning from prolonged ventilatory support and may be associated with intermittent hypoxia secondary to hypoventilation or atelectasis. In infants with BPD, decreased pulmonary reserves may contribute to frequent occurrence of spells.

Diagnosis

Apnea is generally diagnosed with continuous cardiorespiratory monitoring. If significant apnea is detected,

an evaluation is required to make an accurate diagnosis and develop a logical treatment plan.

1. Monitoring of infants at risk: Close monitoring to evaluate possible causes of apnea should focus on respiratory rate and pattern, heart rate, circumstances preceding the apneic episode, associated bradycardia, skin color, muscle tone, and termination of the episode (whether spontaneous, with stimulation, or with resuscitation).
2. Detailed history and physical examination: After stabilization, the infant should be evaluated for a possible underlying cause. The history should be reviewed for onset of apnea and possible causes of secondary apnea, including perinatal asphyxia, maternal drugs, features of neonatal sepsis, and feeding intolerance. The infant should be examined for temperature instability, hypotension, jaundice, pallor, cardiac murmur, and poor perfusion.
3. Evaluation: The diagnostic evaluation is directed by the clinical presentation and the infant's associated findings. When there is concern for a secondary cause, the evaluation includes a sepsis screen, chest radiograph, and glucose and serum electrolyte measurements. Screening for neurologic abnormalities, such as intracranial hemorrhage, hydrocephalus, or seizures, may be warranted. An abdominal radiograph should be obtained if NEC is suspected. Other evaluation may be considered in specific cases. An echocardiogram and a cardiology consultation are necessary if the history or physical examination suggests cardiac disease. An electrocardiogram (ECG) is useful when severe unexplained tachycardia or bradycardia exists. Testing of serum ammonia levels as well as urine and serum amino acids and organic acids is indicated if a metabolic disorder is suspected. An airway evaluation for upper airway abnormalities or obstruction can be considered. In infants with persistent apnea, impedance pneumography ("pneumograms") or sleep studies can further classify apnea as obstructive, central, or mixed and can provide information about association with GER, with intraesophageal pH monitoring.

TREATMENT

General Measures

If an identifiable cause of apnea is determined, it should be treated accordingly.

- Care should be taken to avoid reflexes that may trigger apnea. Suctioning of the pharynx should be done carefully, and oral feedings should be undertaken with caution.
- Positions of extreme flexion or extension of the neck should be avoided to reduce the likelihood of airway obstruction.
- Gentle tactile stimulation is often adequate therapy for mild and intermittent episodes.
- Avoiding swings in environmental temperature may prevent apnea.[156]

Xanthine Derivatives (Caffeine and Theophylline)

Proposed mechanisms for xanthine derivatives include stimulation of skeletal and diaphragmatic muscle contraction, increase in the respiratory center's sensitivity to CO_2, and stimulation of the central respiratory drive. Caffeine appears to be a safer drug, can be given less frequently than theophylline, and is more effective in treating apnea.[158] In the Caffeine for Apnea of Prematurity (CAP) trial, early caffeine therapy in infants weighing less than 1250 g reduced the rate of bronchopulmonary dysplasia and improved neurodevelopmental outcome at 18 to 21 months of age, though the difference in neurologic outcome did not persist at 5-year follow-up.[159,160,161] Side effects include decreased initial weight gain, increased feeding intolerance, and increased heart rates. Caffeine is typically started with a loading dose of caffeine citrate 20 mg/kg, followed by maintenance doses of 5 to 10 mg/kg, though higher doses may be used. Many centers empirically begin caffeine in all infants weighing less than 1250 g shortly after birth and premature infants more than 1250 g who have symptomatic apnea. It is continued until 34 to 36 weeks postmenstrual age, though it may be required longer in extremely premature infants if spells continue beyond this age. Because caffeine has a half-life of about 3 days, its effect may continue for approximately 1 week after discontinuation.

Continuous Positive Airway Pressure and Nasal Intermittent Positive Pressure Ventilation

CPAP at moderate levels (5-7 cm H_2O) can reduce the number of mixed and obstructive apneic spells. It is especially useful in infants younger than 32 to 34 weeks gestational age and those with residual lung disease. It remains controversial whether NIPPV is a useful augmentation to CPAP to prevent spells.

Mechanical Ventilation

Some infants continue to have apneic spells despite pharmacotherapy. If the apnea is severe and is associated with hypoxia or significant bradycardia, intubation and mechanical ventilation may be indicated.

Blood Transfusions

Apneas occur with increased frequency at lower hemoglobin levels, and there seems to be a beneficial effect from blood transfusion in the setting of anemia in reducing the frequency of apneic events.[162]

Discharge Planning and Follow-up

A major issue in the management of infants with apnea is deciding when to stop administration of methylxanthines and whether the infant needs to be discharged on methylxanthines, a home monitor, or both.

The answers to these questions are still under debate. Most neonatologists allow a 5-to-7-day apnea-free

period after a subtherapeutic level of methylxanthine therapy before sending a premature infant home without a monitor.

Home monitoring is not routinely recommended for infants with a history of apnea of prematurity.[151] The theoretical purpose of home monitoring is prevention of SUIDS; however, the CHIME study, which analyzed events among a large set of healthy term infants and preterm infants discharged on home monitoring, suggested that even severe cardiorespiratory events were unlikely to be precursors to SIDS.[163] Thus home monitoring is reserved for infants on methylxanthine therapy at the time of discharge because of persistent cardiorespiratory events or infants discharged on oxygen (oximetry only). If home monitoring is arranged for persistent cardiorespiratory events, it can usually be discontinued by 44 weeks postmenstrual age. Extensive psychosocial support should be provided to parents taking home an infant with a home monitor, and parents should be skilled in the use of the monitor and cardiopulmonary resuscitation.

COMPLICATIONS AND PROGNOSIS

AOP does not alter an infant's prognosis unless it is severe, recurrent, or refractory to therapy. Although premature infants are at increased risk of SIDS, a history of apnea of prematurity does not increase this risk. Therefore all parents of premature infants should be counseled on risk-reduction strategies, including promoting a supine sleeping position on a firm surface, avoiding cosleeping, avoiding overheating, and decreasing smoking in the home.[151]

AIR LEAK SYNDROMES

DEFINITION

Air leak syndromes include pulmonary interstitial emphysema (PIE), pneumothorax, pneumomediastinum, pneumopericardium, pneumoperitoneum, subcutaneous emphysema, and **systemic air embolism**.[164]

INCIDENCE

The incidence of air leaks in newborns is inversely related to birth weight. The risk for air leaks is higher in infants with RDS, MAS, and pulmonary hypoplasia and in infants who need resuscitation at birth. PPV, CPAP, and mechanical ventilation further increase the incidence of air leaks. Surfactant and use of volume-targeted ventilation in infants who require mechanical ventilation help decrease the incidence of air leaks.

In healthy newborns, spontaneous pneumothorax occurs at a rate of about 0.07%.[164] In preterm infants, the incidence of pneumothorax decreased from 6.3% in 1999 to 4.1% in 2013, according to Vermont Oxford Network data.[165] Likewise, the incidence of PIE, pneumomediastinum, and pneumopericardium was higher in mechanically ventilated babies in the pre-surfactant era.[166]

ETIOLOGY AND PATHOPHYSIOLOGY

Macklin first described the passage of air from a ruptured alveolus in an overdistended cat lung.[167] Air moved up the vascular sheath into the mediastinum and from there into the pleural cavity.

Overdistention of terminal air spaces or airways can result from uneven alveolar ventilation, air trapping, or high alveolar distending pressure in infants on ventilatory support, particularly in noncompliant lungs. As lung volume exceeds physiologic limits, mechanical stresses occur in all planes of the alveolar or respiratory bronchial wall, with eventual tissue rupture once pressures have exceeded tensile strength of the noncartilaginous terminal airway and alveolar tissues.

Air can track through the perivascular adventitia, causing **pulmonary interstitial emphysema**, or dissect along vascular sheaths toward the hilum, causing **pneumomediastinum.** Rupture of the mediastinal pleura results in **pneumothorax. Pneumoretroperitoneum** and **pneumoperitoneum** may occur when mediastinal air tracks downward to the extraperitoneal fascial planes of the abdominal wall, mesentery, and retroperitoneum and eventually ruptures into the peritoneal cavity. Air in the mediastinum can decompress into the fascial planes of the neck and skin, causing **subcutaneous emphysema.**

CLINICAL PRESENTATION

A high index of suspicion is essential for early diagnosis and aggressive management. Extrapulmonary extravasation of air should be suspected in any infant with respiratory disease whose condition suddenly deteriorates. An increase in respiratory rate might be accompanied by grunting and increasing pallor or cyanosis.

Neonates with spontaneous pneumothorax may be asymptomatic or have mild signs of tachypnea with increased oxygen requirement. Occasionally, severe respiratory distress (grunting, nasal flaring, and intercostal retractions) may occur. In a ventilated neonate, pneumothorax may result in rapid clinical deterioration with cyanosis, hypotension, hypoxemia, hypercapnia, and respiratory acidosis. In unilateral pneumothorax, breath sounds may be decreased on the ipsilateral side, and the cardiac apex can be shifted toward the contralateral side. Some infants can develop distention of the involved hemithorax or a tensely distended abdomen from downward displacement of the diaphragm. In the event of a **tension pneumothorax**, signs of shock can occur as a result of increased intrathoracic pressure that compromises venous return and decreases cardiac output. In preterm infants with RDS, pneumothoraces may develop after surfactant administration if ventilator pressures are not concurrently reduced with rapid improvement in lung compliance.

PIE often presents with a slow, progressive deterioration of the blood gases, with the need for increasing ventilatory support. Rarely, the neonate has sudden deterioration with profound respiratory acidosis and hypoxemia. It may precede the development of a pneumothorax or occur independently. PIE has the effect of reducing lung compliance and increasing dead space, which worsens ventilation–perfusion mismatch.

Pneumomediastinum is usually asymptomatic. It may occur concurrently with pneumothorax or develop as a result of esophageal perforation. The degree of respiratory distress depends on the amount of trapped gas. If it is great, bulging of the midthoracic area is observed, the neck veins are distended, and blood pressure is low. The last two findings are a result of tamponade of the systemic and pulmonary veins. Although often asymptomatic, subcutaneous emphysema, detected by palpation of crepitus in the face, neck, or supraclavicular region, is almost pathognomonic of pneumomediastinum.

Neonatal **pneumopericardium** is almost invariably preceded by other forms of air leak. The clinical signs of pneumopericardium range from asymptomatic to the abrupt onset of cardiovascular compromise from cardiac tamponade, which is a life-threatening complication. The first sign of pneumopericardium may be a decrease in blood pressure or pulse pressure. There may also be an increase in heart rate with distant heart sounds.

Usually pneumoperitoneum resulting from extrapulmonary air is of little clinical importance, but it must be differentiated from intraperitoneal air resulting from a perforated viscus. Rarely, pneumoperitoneum can impair diaphragmatic excursion and compromise ventilation. In these cases, drainage may be necessary.

Systemic air embolism is a rare but usually fatal complication of pulmonary air leak. Air may enter the vasculature either by disruption of the pulmonary venous system or by inadvertent injection through an intravascular catheter. The presence of air bubbles in blood withdrawn from an umbilical artery catheter is diagnostic.[164]

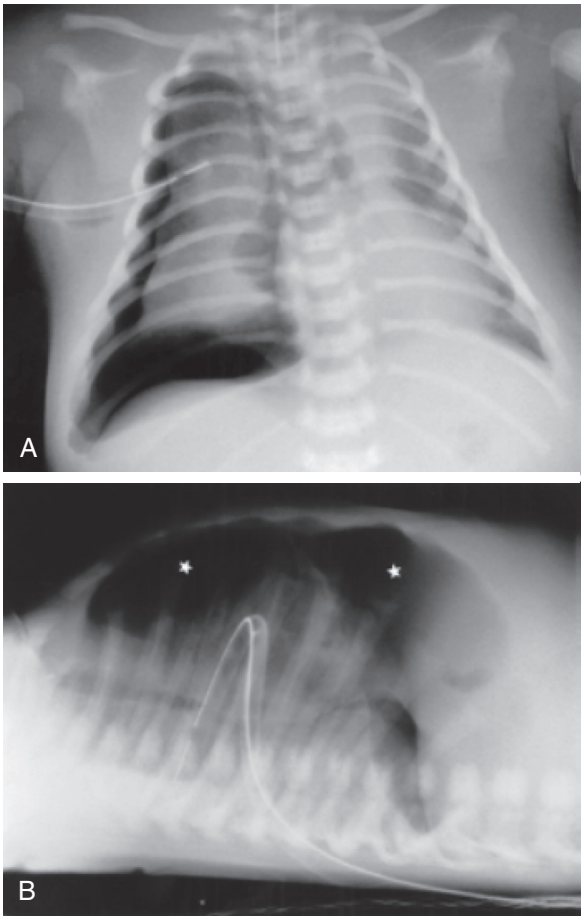


FIGURE 22-10 **(A)** Right-sided tension pneumothorax incompletely drained by the intercostal drain. There is flattening of the diaphragm and a shift of the midline with compression of the left lung. **(B)** Lateral view shows that the chest drain is angulated posteriorly and is not ideally sited to drain the anterior and subpulmonary collection of air *(asterisk)*. (From Arthur R: The neonatal chest x-ray. *Paediatr Respir Rev* 2:311, 2001.)

DIAGNOSIS

Chest Radiograph

CXR remains the gold standard for the diagnosis of air leak syndromes. Pneumothorax with anteroposterior (AP) views shows a hyperlucent hemithorax, a separation of the visceral from the parietal pleura, flattening of the diaphragm, and mediastinal shift (Figure 22-10).

Smaller collections of intrapleural air can be detected beneath the anterior chest wall by obtaining a cross-table lateral view; however, an AP view is needed to identify the affected side. The lateral decubitus view, with the side of suspected pneumothorax up, may be helpful in detecting a small pneumothorax and may help differentiate skin folds, congenital lobar emphysema, cystic adenomatoid malformations, and surface blebs that occasionally give the appearance of intrapleural air.[164]

PIE appears as linear or tiny cystic translucencies extending from the hilum to the periphery of the lungs (Figure 22-11). When more severe, the lungs become hyperexpanded and stiff, compressing the heart and mediastinal structures and reducing venous return. PIE generally affects both lungs symmetrically, but unilateral and even lobar distribution may be seen.

In pneumopericardium, AP views show air surrounding the heart; air under the inferior surface of the heart is diagnostic (Figure 22-12).

Typical radiologic signs of pneumomediastinum include the continuous diaphragm sign (interposition of air between the pericardium and the diaphragm, which becomes visible in the central mediastinal part) and linear bands of mediastinal air paralleling the left side of the heart and the descending

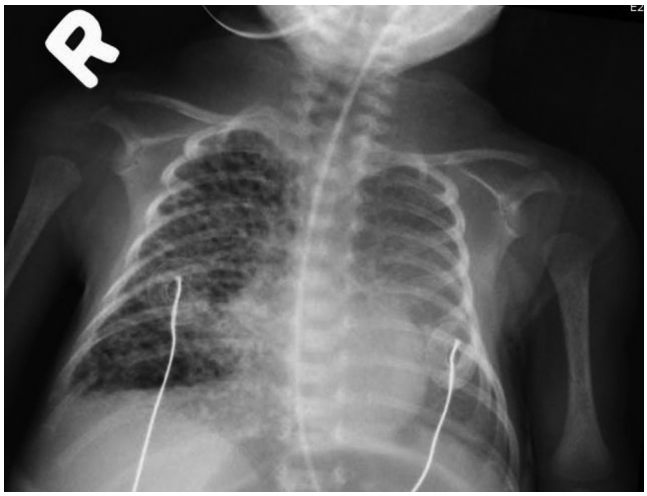


FIGURE 22-11 Severe unilateral pulmonary interstitial emphysema (PIE). This infant was born at 26 weeks' gestation, and the image was taken in the setting of a respiratory decompensation at 2 weeks of age. Note the hyperinflation of the affected lung.

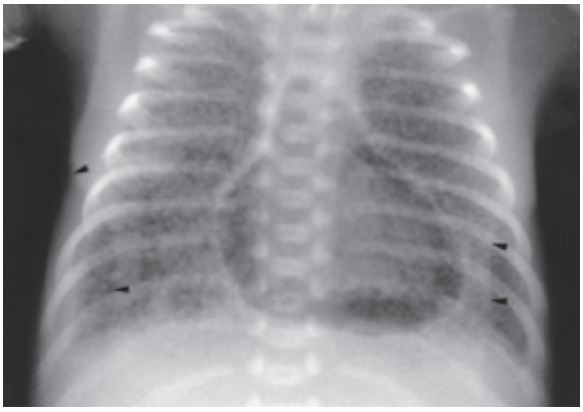


FIGURE 22-13 Neonatal pneumomediastinum. Note the thymus gland outlined by air, giving an "angel's wing" appearance *(arrow heads).* (From Arthur R: The neonatal chest x-ray. *Paediatr Respir Rev* 2:311, 2001.)

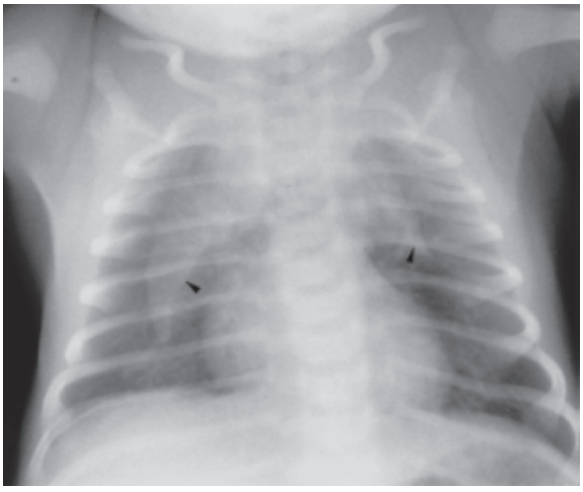


FIGURE 22-12 Pneumopericardium has developed in association with bilateral pulmonary interstitial emphysema. Note bilateral skinfolds at bases simulating a pneumothorax *(arrowheads).* (From Arthur R: The neonatal chest x-ray. *Paediatr Respir Rev* 2:311, 2001.)

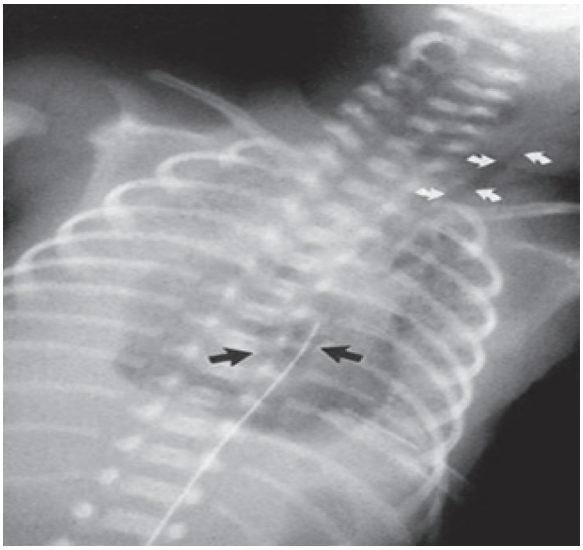


FIGURE 22-14 Postmortem x-ray of a baby who died from systemic air embolism. Gas can be seen *(black arrows)* within the heart and in the great vessels in the neck *(white arrows)*. (From Bancalari E: Bronchopulmonary dysplasia and neonatal chronic lung disease. In Fanaroff AA, Martin RJ, ed. *Neonatal-Perinatal Medicine Diseases of the Fetus and Infant,* 9th ed. St Louis: Mosby-Elsevier, 2011.)

aorta (pleura is shown as a fine opaque line) with extension superiorly along the great vessels into the neck. The sail sign or "angel's wing" appearance (an upward and outward deviation of thymic lobes) can be seen when the thymus is raised above the heart by pneumomediastinal air that elevates the thymus and separates it from the cardiac silhouette beneath (Figure 22-13).

In **systemic air embolism,** gas can be seen in the systemic and pulmonary arteries and veins (Figure 22-14).

Transillumination

A high-intensity fiberoptic light source can be used to quickly demonstrate a pneumothorax at the bedside; this is particularly useful in preterm infants with thin skin who have rapid decompensation. The affected hemithorax will light up in the presence of pneumothorax. However, transillumination of a chest with diffuse and widespread PIE will result in increased transmission of light, similar to that seen in a pneumothorax. Transillumination is also less sensitive in infants with chest-wall edema or in full-term infants with a thick chest wall or dark skin.

Needle Aspiration

In a rapidly deteriorating clinical situation, thoracentesis or pericardiocentesis may confirm the diagnosis and be therapeutic in pneumothorax or pneumopericardium, respectively. Performing needle aspiration without radiographic confirmation of air leak should be reserved for immediately life-threatening situations.

Electrocardiogram

Decreased voltages, manifested by a shrinking QRS complex, are consistent with pneumopericardium.[235]

PREVENTION

The best mode of treatment for all air leak syndromes is prevention by judicious use of ventilatory support. **Gentle ventilation** with low pressure, low V_T, low Ti, high rate, and careful use of PEEP are the keys to caring for mechanically ventilated infants at risk of air leak, such as preterm infants with RDS. The use of surfactant therapy for RDS has been shown to substantially decrease the incidence of pneumothorax and PIE, as discussed previously. In addition, the use of volume-targeted ventilatory strategies has been shown to decrease the incidence of air leak in infants with RDS.[163] Synchronized or "patient-triggered" ventilation, though in theory reducing air leak by reducing forced expiration against the ventilator's effort, has not been shown to actually reduce the incidence of air leak.[169] Nonetheless, because it improves patient comfort and decreases breath-to-breath variability, synchronized ventilation is the standard of care in neonates. Providing "routine" chemical paralysis to abolish the infant's respiratory effort does not prevent pneumothorax compared with synchronous ventilation and is not recommended.[170]

Both HFOV and HFJV can provide adequate gas exchange using extremely low V_T and supraphysiologic rates in neonates with acute pulmonary dysfunction and have the potential to reduce the risk of air leak syndromes in neonates. Although they are important components in the treatment of air leak syndromes, neither has been shown to reduce the development of air leak syndromes compared with conventional ventilation when used electively for mechanically ventilated premature infants with RDS.[171,172]

TREATMENT

Conservative Management

Without a continuing air leak, asymptomatic and mildly symptomatic small pneumothoraces require only close observation. Conservative management of a pneumothorax is effective even in selected infants requiring low amounts of ventilatory support; spontaneous resolution may occur in 24 to 48 hours.[173] Administering 100% oxygen does not improve the time to resolution, as previously proposed by the "nitrogen washout" theory. Therefore additional oxygen is provided only as needed to maintain adequate saturation.[174]

In generalized PIE, an attempt should be made to decrease ventilatory support and lessen lung trauma. Decreasing the PIP or PEEP or shortening the Ti may be required. These maneuvers will decrease ongoing injury and possibly improve PIE. During this time, some degree of hypercapnia and hypoxia may have to be accepted. In unilateral PIE, positioning the infant with the affected side down minimizes aeration of the affected lung and promotes aeration of the unaffected lung.[175] Infants who develop generalized PIE are often treated with high-frequency ventilation, as described later.

Needle Aspiration

Needle aspiration using a "butterfly" needle or an intravenous catheter with an inner needle is indicated to treat a patient with symptomatic pneumothorax. Needle aspiration may be curative in infants not receiving mechanical ventilation and is often a temporizing measure in mechanically ventilated infants. In infants with severe hemodynamic compromise, needle aspiration may be a lifesaving procedure. Typically, after raising the head of the bed 30 degrees, a 23- or 25-gauge butterfly needle is attached to a 10- or 20-mL syringe with a three-way stopcock. The needle is inserted just above the rib in the second to third intercostal space in the midclavicular line, while an assistant aspirates air using the three-way stopcock and syringe. As soon as the pleural space is entered, advancement of the needle should stop to minimize the risk of trauma to the underlying lung tissue.[164]

Needle pericardiocentesis may be a life saving procedure in the neonate with pneumopericardium and cardiac tamponade. This is performed with an intravenous catheter in the subxiphoid space, angled at 30 to 45 degrees toward the infant's left shoulder.

Chest Tube Drainage

If symptomatic pneumothorax recurs after needle aspiration, a longer-term approach to decompression is necessary. This consists of placement of a large-bore, multiple-hole chest tube into the pleural space, ideally anterior to the lung. Anterior placement in the pleural space is best achieved by insertion of the tube into the chest at or just lateral to the anterior axillary line. Typically, 8 to 12 Fr chest tubes are used in neonates, including traditional chest tubes, pigtail catheters, or safety catheters containing a ball-valve mechanism (Turkel, Covidien). The tube should then be connected to an underwater seal at a suction pressure of 10 to 20 cm H_2O. An instructional video of the procedure can be viewed in the online OpenPediatrics curriculum.[176]

Dramatic improvement in color and circulation follows relief of a tension pneumothorax, which can be confirmed by repeat transillumination and x-ray. The ease with which the lung can be reexpanded depends to a large extent on the compliance of the underlying pulmonary tissue. Expansion is particularly slow in infants with hypoplastic lungs associated with a congenital diaphragmatic hernia.

Suction should be maintained until air evacuation has ceased. At this time the tube should be placed to the water seal, and if no reaccumulation of air in the

pleural cavity occurs after 6 to 12 hours by CXR, the tube can be removed. The chest tube should be pulled out at the point in the respiratory cycle least likely to entrain room air. This is during exhalation for patients not receiving positive pressure ventilation, and during inhalation for patients receiving positive pressure ventilation. An occlusive dressing should be placed over the chest tube site to prevent reintroduction of air into the pleural space. Adequate pain control is important while a chest tube is placed, maintained, and removed.

In pneumopericardium, decompression is essential and requires repeated pericardial taps, or preferably placement of an ultrasound-guided pericardial drain inserted via the subxiphoid route.

Other Treatments

HFJV is a successful means of ventilation for infants with PIE and other types of pulmonary air leaks. This mode results in improved ventilation at lower peak and mean airway pressures with more rapid resolution of PIE.[177] Refractory cases of air leak may require placement of catheters by interventional radiology under ultrasound or fluoroscopic guidance to drain air collections inaccessible to standard techniques.

COMPLICATIONS AND PROGNOSIS

The prognosis for the infant in whom an air leak develops depends on the underlying condition. Early recognition and management are beneficial to avoid complications from hypoxemia, hypercapnia, and impaired venous return. Severe pulmonary air leak syndromes are associated with an increased risk of IVH and death.

PULMONARY HEMORRHAGE

DEFINITION

Pulmonary hemorrhage is an acute event characterized by discharge of bloody fluid from the upper respiratory tract or the ETT. It is a form of fulminant lung edema with leakage of red blood cells and capillary filtrate into the lungs.

INCIDENCE

About 1.4% of all infants admitted to the NICU have been reported to develop pulmonary hemorrhage; more than 80% have RDS. Such infants are also likely to have been treated with exogenous surfactant and were receiving mechanical ventilatory support at the time of bleeding.

The incidence is inversely proportional to gestational age, especially between 23 and 28 weeks' gestation.[178] In high-risk groups such as premature and growth-restricted infants, the incidence increases to as high as 5%. In autopsy studies, pulmonary hemorrhage of any degree is even more prevalent. Some studies report hemorrhage in up to about 70% of autopsied neonates.[179]

RISK FACTORS

Risk factors include conditions predisposing the infant to increased LV filling pressures, increased pulmonary blood volume, compromised pulmonary venous drainage, or poor cardiac contractility.

1. Prematurity, RDS, and exogenous surfactant therapy: In combination, these three are the most consistent risk factors for pulmonary hemorrhage, especially in infants younger than 28 weeks' gestation (or birth weight less than 1000 g). Exogenous surfactant therapy, particularly with synthetic surfactants, seems to increase the risk of pulmonary hemorrhage.[180] This is likely due to changes in pulmonary hemodynamics and lung compliance after surfactant therapy, particularly in the presence of a PDA. Lack of antenatal steroids also increases the risk of pulmonary hemorrhage.[181]
2. Preterm infants with echocardiographic evidence of a large left-to-right shunt across a PDA and a high pulmonary blood flow have a high incidence of pulmonary hemorrhage.[182]
3. SGA infants are more likely to suffer a pulmonary hemorrhage.
4. Lung complications: PIE and pneumothorax.
5. Infections: Overwhelming sepsis increases the risk of pulmonary hemorrhage as a result of increased pulmonary capillary permeability, possibly exacerbated by associated thrombocytopenia and coagulopathy.
6. Meconium aspiration syndrome.
7. Other risk factors include intrapartum asphyxia, metabolic acidosis, hypothermia, congenital heart disease, and coagulopathy.

Differential Diagnosis

1. Trauma: Mechanical injury to the vocal cords, trachea, or other laryngeal and oropharyngeal structures, especially from endotracheal intubation, may present with blood in the airway, similar to pulmonary hemorrhage.
2. Aspirated maternal blood (for example, from placental abruption) may present, similar to pulmonary hemorrhage.

PATHOPHYSIOLOGY

The underlying mechanisms of pulmonary hemorrhage remain uncertain. The pulmonary effluent has a very high protein content, as well as a large number of cellular elements from the blood. Thus the hemorrhage may be a consequence of increased transcapillary pore size. A series of interrelated factors may lead to an episode.

Some experts consider pulmonary hemorrhage as a manifestation of exaggerated hemorrhagic pulmonary edema brought about by an acute increase in pulmonary blood flow. The latter can occur from multiple interrelated causes, including the normal postnatal drop in pulmonary vascular resistance, rapidly

changed pulmonary compliance after surfactant therapy, left-to-right shunting through a ductus arteriosus, and acute left ventricular failure caused by hypoxia and acidosis. These changes may lead to an acute increase in pulmonary capillary pressures, injury to the capillary endothelium, and ultimately hemorrhagic pulmonary edema.[183]

CLINICAL PRESENTATION AND DIAGNOSIS

Clinical Presentation

Pulmonary hemorrhage commonly occurs between the second and fourth day of life. Clinically the onset of massive pulmonary hemorrhage is heralded by sudden deterioration of the infant with pallor, cyanosis, bradycardia, or apnea. Pink or red frothy liquid drains from the mouth or can be suctioned through an ETT. Over the next minutes to hours, the infant may require increased ventilatory and oxygen support as increasing amounts of blood are suctioned from the ETT. If severe hemorrhage occurs, the baby may become hypotensive and unresponsive.

Because the condition is commonly secondary to heart failure, the infant may have tachycardia, and the murmur of a PDA may be heard. Auscultation of the chest reveals decreased air entry. In infants who survive the acute episode, widespread pulmonary inflammation from blood in the lung tissues can lead to later complications, such as pneumonia, prolonged need for assisted ventilation, and development of BPD.

Diagnosis

CXR may be nonspecific, such as diffuse fluffy infiltrates or air bronchograms. The infant with massive pulmonary hemorrhage will have a virtual "whiteout," with just an air bronchogram visible (Figure 22-15). Rarely, a lobar pattern of consolidation is found, suggesting that the hemorrhage occurred in only part of the lung.

A CBC and coagulation studies should be obtained. Although the hematocrit of the edema fluid is usually less than 10%, considerable quantities of blood can be lost, the baby can become severely anemic, and secondary disseminated intravascular coagulation can develop.

The possibility of infection should be considered, and the infant should be screened for sepsis.

An echocardiogram is indicated to exclude hemodynamically significant PDA in infants with pulmonary hemorrhage, even in the absence of a typical "PDA murmur," a wide pulse pressure, or hyperdynamic precordium.

PREVENTION

Antenatal Corticosteroids

Enhancing lung maturity through the use of antenatal corticosteroids reduces the incidence of pulmonary hemorrhage, possibly through its indirect effect on the lungs and pulmonary vascular bed.[181]

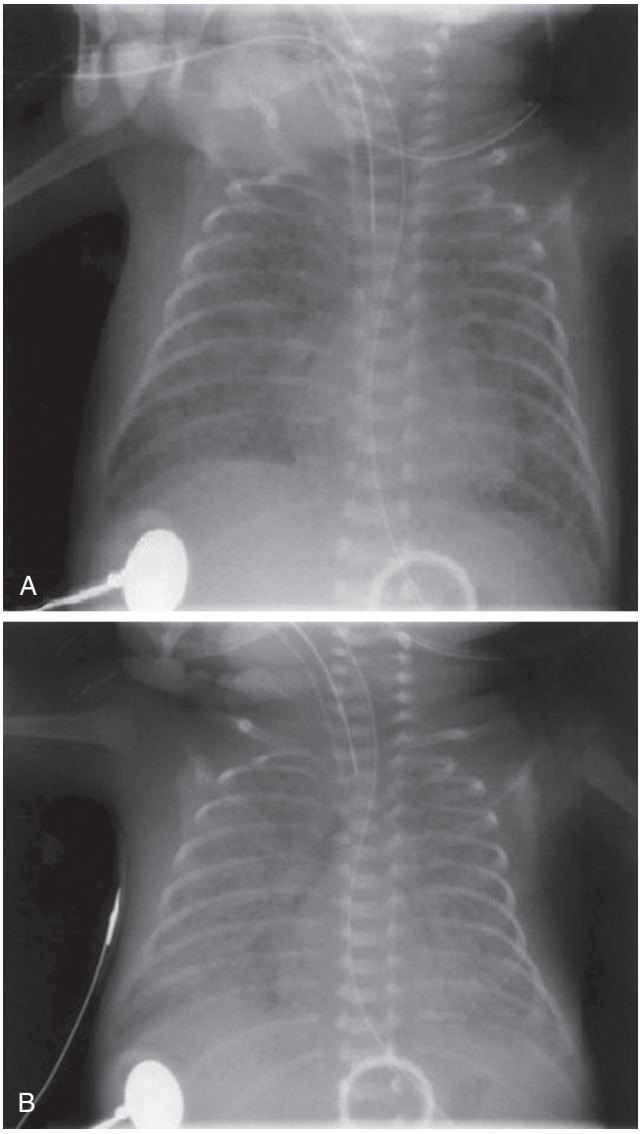


FIGURE 22-15 Chest X-ray of preterm infant (24 weeks of gestation) with severe respiratory distress syndrome **(A)** just before and **(B)** after pulmonary hemorrhage. (From Narasimhan R, Papworth S. Pulmonary hemorrhage in the neonate, *Paediatr Child Health* 2009; 19:171.)

Preventing Patent Ductus Arteriosus (PDA)

The Trial of Indomethacin Prophylaxis in Preterm Infants (TIPP) did not show a reduction in pulmonary hemorrhage overall,[184] though a post hoc analysis did find that rates of pulmonary hemorrhage were reduced in the first few days of life, likely related to PDA closure.[185] Nonetheless, prophylactic therapy to close PDA is not regularly pursued based on the results of the larger trial and the adverse effects of medical therapy.

HFOV

Data evaluating the prophylactic use of HFOV in premature infants demonstrated a decreased incidence of pulmonary hemorrhage however, the definition of pulmonary hemorrhage was not prospectively

determined, and the data should be interpreted with caution.[186]

TREATMENT

Resuscitation

Initial resuscitation is the priority. If not already receiving mechanical ventilation, the infant will likely need to be intubated to deliver adequate positive pressure ventilation and to suction the airways. The circulatory volume should be restored with boluses of saline, packed red cells, platelets, or plasma, as appropriate, based on regular reassessment. Vasoactive medications may be needed.

Ventilation

A ventilation strategy of high PEEP (up to 6 to 8 cm H_2O) is used. Although in experimental studies this did not reduce total lung water, it redistributed it back into the interstitial space, improving oxygenation and ventilation–perfusion balance.[187,188] Frequent suctioning may be required to keep the ETT clear. High-frequency ventilation may be required to provide higher mean airway pressures, which has been shown to reduce the oxygenation index in these patients.[189]

Surfactant

Paradoxically, although surfactant may precipitate pulmonary hemorrhage, after stabilizing the baby on the ventilator, a single dose of surfactant has been suggested to improve oxygenation.[190] This is because of surfactant inactivation from blood in the air spaces. However, the efficacy is not well established, and surfactant should be used on a case-by-case basis.[191]

Patent Ductus Arteriosus

An echocardiogram should be considered, and if a hemodynamically significant PDA is present, pharmacologic or surgical closure of the PDA should be considered. Mild fluid restriction may also be warranted.

Other Measures

Other measures that may be taken to stop pulmonary hemorrhage include the following:

- Endotracheal or nebulized epinephrine is often used to temporize massive bleeding, but no controlled trials have been done to demonstrate a clear benefit.
- Recombinant factor VIIa, a vitamin K–dependent glycoprotein structurally similar to the plasma-derived natural factor VII, is considered a universal hemostatic agent. This drug has also been used with success in two isolated cases of neonatal pulmonary hemorrhage at a 50 μg/kg dose, repeated every 3 hours for 2 to 3 days. More work is needed to establish the dosage and frequency of administration, as well as to assess the consistency of response in neonatal pulmonary hemorrhage.[192]
- Broad-spectrum antibiotics should be considered after taking cultures, because sepsis is a recognized cause of pulmonary hemorrhage.
- Future measures currently under investigation include hemocoagulase, a purified mixture of enzymes derived from the venom of the Brazilian snake *Bothrops atox* with thromboplastin-like effects.[193]

COMPLICATIONS AND PROGNOSIS

Mortality in the setting of acute pulmonary hemorrhage is up to 50%.[194] Babies who survive are susceptible to all the major complications of respiratory failure. High-pressure ventilation predisposes to air leaks, and BPD is a common sequela. If they suffer cardiovascular collapse, they are susceptible to neurologic damage and intraventricular hemorrhage. Although one study did not demonstrate increased rates of adverse outcomes in infants who survived pulmonary hemorrhage, post hoc analysis of data from TIPP demonstrated double the risk of death or survival with neurosensory impairment, including cognitive delay and cerebral palsy.[185]

Case Study 1

A 3.7-kg newborn female was delivered via elective cesarean section at 41 weeks of gestation. Apgar scores were 7 and 8 at 1 and 5 minutes, respectively. Maternal laboratory results were notable for negative GBS status. Rupture of membranes was at the time of delivery, and fluid was clear. The infant's temperature is 97.7° F (36.5° C), respiratory rate is 92 breaths/minute, and heart rate is 143 beats/minute. She has subcostal and intercostal retractions. The remainder of the examination is normal. The chest radiograph is shown in Figure 22-5 in the text. Over the next 6 hours she improves and no longer requires oxygen.

What is the diagnosis?

The parents are worried about her prognosis. What would you tell them?

Case Study 2

A 3.5-kg male infant is vaginally delivered with amniotic fluid stained with thick meconium. He is initially limp and without strong respiratory effort but has a heart rate greater than 100 beats/minute. He responds to appropriate resuscitation with improvement in respiratory effort, but remains cyanotic and tachypneic. Apgar scores are 4 and 6 at 1 and 5 minutes, respectively. After admission to the NICU, the infant's temperature is 98.4° F (36.9° C), heart rate is 173 beats/minute, respiratory rate is 110 breaths/minute, and mean blood pressure is 61 mm Hg. He is barrel chested and has retractions with poor to fair air entry. Coarse crepitations are audible bilaterally. The chest radiograph is shown in Figure 22-8 in the text.

What is your provisional diagnosis?

How would you resuscitate this neonate?

How would you monitor and initially manage respiratory distress in this neonate?

Key Points

- Respiratory distress is encountered often in newborns, typically caused by abnormal respiratory function during the transition from fetal to neonatal life, and represents a common indication for reevaluation of the young infant.
- Because respiratory distress in the newborn may be a potentially life-threatening condition, physicians are expected to assess and manage affected infants promptly.
- The key to successful management of the infant who has respiratory distress is the ability to obtain a complete maternal and newborn history, perform a thorough physical examination, and recognize the common respiratory disorders based on clinical presentation and radiographic evaluation.
- Therapies for neonatal respiratory diseases are in a constant state of evolution, and both new and old therapies must be continuously reevaluated.

Assessment Questions

See Evolve Resources for answers.

1. A newborn, 25-week-gestation infant appears cyanotic, and arterial blood gas (ABG) analysis indicates hypoxia and hypercapnia. The infant has severe chest wall retractions with inspiratory effort. The amniotic fluid appeared normal at birth. What is the most likely cause of respiratory distress?
   - **A.** Surfactant deficiency
   - **B.** Meconium aspiration syndrome
   - **C.** Pneumonia
   - **D.** Bronchopulmonary dysplasia
2. An infant diagnosed with RDS is receiving oxygen therapy with an Fio_2 of 0.8 and nasal CPAP set at 10 cm H_2O. The infant is experiencing progressive hypercapnia, and apneic episodes are appearing prolonged. The next logical course of action is to:
   - **A.** Increase the Fio_2 by 0.1 and look for improvements in ABG parameters.
   - **B.** Start inhaled nitrous oxide (iNO) therapy to improve the lung V/Q ratio.
   - **C.** Increase NCPAP to 12 cm H_2O and refit the nasal prongs.
   - **D.** Intubate the infant, administer surfactant, and begin mechanical ventilation.
3. A full-term infant is delivered via cesarean section and demonstrates mild symptoms of respiratory distress, including cyanosis, tachypnea, and nasal flaring. Apgar scores are 8 and 9, and the chest radiograph shows hyperexpansion and perihilar streaking. Which situation most likely fits this case?
   - **A.** This infant is in the "honeymoon" period and is expected to develop more severe RDS.
   - **B.** This infant has TTN and will likely recover completely by 72 hours.
   - **C.** This infant is in the early stages of pneumonia and should be started on broad-spectrum antibiotics.
   - **D.** This infant likely has elevated PVR, and a hyperoxia test should be performed to confirm persistent pulmonary hypertension of the newborn (PPHN).
4. A 4-day-old infant born at 27 weeks of gestation develops recurrent symptoms of respiratory distress syndrome. The infant was removed from mechanical ventilation and extubated on day 3 and was receiving NCPAP with an Fio_2 of 0.4 when lung function acutely worsened. The chest radiograph shows a widespread, diffuse granular pattern, and analysis of blood gas samples shows worsening respiratory and metabolic acidosis. Urine output has decreased. On examination, there is a widened pulse pressure, a murmur is auscultated, and palmar bounding pulses are appreciated. The most likely cause of this respiratory worsening is:
   - **A.** Progressive periods of apnea
   - **B.** Patent ductus arteriosus
   - **C.** Meconium aspiration syndrome (MAS)
   - **D.** Postnatal pneumonia
5. A newborn infant begins to develop symptoms of respiratory distress shortly after birth. The mother has a history of positive urine screen for group B *Streptococcus* carrier status in the third trimester. She received penicillin only 2 hours before delivery. She ruptured her membranes 18 hours prior at home. You are concerned for neonatal pneumonia. Adequate coverage would include:
   - **A.** Ampicillin
   - **B.** Gentamicin
   - **C.** Vancomycin
   - **D.** Acyclovir
   - **E.** A and B
   - **F.** B and C
   - **G.** A, B, and D
   - **H.** B, C, and D
6. Which intrapartum findings would lead the caregiver to anticipate MAS?
   - **A.** Fetal oligohydramnios
   - **B.** Yellowish-green stained amniotic fluid
   - **C.** Abnormal fetal heart rate tracings
   - **D.** All of the above
7. An infant is born with meconium-stained amniotic fluid. The infant is limp and without respiratory effort. Based on the updated 2015 AAP and AHA guidelines, which of the following interventions should be pursued in the delivery room?
   - **A.** All infants should be intubated for tracheal suctioning.
   - **B.** Nonvigorous infants should be intubated for tracheal suctioning.
   - **C.** The infant should be dried, suctioned, and stimulated, with further care as per routine Neonatal Resuscitation Program Guidelines.
   - **D.** The obstetrician should perform intrapartum nasopharyngeal and oropharyngeal suctioning.
8. PPHN can be associated with which underlying conditions?
   - **A.** MAS
   - **B.** Neonatal pneumonia
   - **C.** Birth asphyxia
   - **D.** All of the above

9. A full-term newborn diagnosed with PPHN is refractory to oxygen therapy and mechanical ventilation. What would be the next logical therapy to try?
   A. High-frequency ventilation
   B. Increased sedation and possible paralysis
   C. iNO therapy
   D. All would have potential benefits
10. A 3-day-old newborn of 30 weeks gestational age is experiencing brief periods of apnea, which result in bradycardia and cyanosis; most self-resolve. The infant is on continuous positive airway pressure (CPAP) at 6 Unit of measurement is missing with Fio_2 of 21% for RDS and has never been intubated. The infant is otherwise well appearing without any concerning signs of infection. Temperature is stable. Caffeine therapy is recommended. The parents are curious regarding side effects of caffeine therapy. Which of the following would you include?
   A. Tachycardia
   B. Need for frequent blood level monitoring related to toxicity
   C. Worse long-term pulmonary outcomes
   D. Worse long-term neurologic outcomes
11. A 30-weeks of gestational age newborn has been on the ventilator for 9 weeks with both $Paco_2$ values around 60 and Pao_2 values around 60, despite increased ventilator settings. Chest radiography reveals atelectasis, hyperlucencies, cystic changes, hyperinflation, and mild cardiomegaly. Bronchopulmonary dysplasia (BPD) is suspected. Which of the following strategies has been shown to decrease the incidence of BPD?
   A. Antenatal steroids
   B. Use of nasal CPAP in the delivery room and lung-protective strategies when intubation is required
   C. Early surfactant administration
   D. Fluid restriction to less than 120 mL/kg/day
   E. High-frequency ventilation
   F. All of the above
12. Among the following, the information that is most helpful in distinguishing cyanotic heart disease from pulmonary parenchymal disease in a newborn who has respiratory distress is:
   A. Hypoxia out of proportion to respiratory distress and acidosis that does not correct with administration of 100% oxygen (hyperoxia test)
   B. Equal preductal and postductal oxygen saturations
   C. Chest radiography with fluid in intralobar fissures and pulmonary vascular congestion
   D. Respiratory rate of 70 breaths per minute

REFERENCES

1. Stoll BJ, Hansen NI, Bell EF, et al. Neonatal outcomes of extremely preterm infants from the NICHD neonatal research network. *Pediatrics*. 2010;126(3):443-456.
2. Fanaroff AA, Stoll BJ, Wright LL, et al. Trends in neonatal morbidity and mortality for very low birthweight infants. *Am J Obstet Gynecol*. 2007;196(2):147.e1-8.
3. Consortium on Safe Labor, Hibbard JU, Wilkins I, et al. Respiratory morbidity in late preterm births. *JAMA*. 2010; 304(4):419-425.
4. Heron M. Deaths: leading causes for 2014. *Natl Vital Stat Rep*. 2016;65(5):1-96.
5. Avery ME, Mead J. Surface properties in relation to atelectasis and hyaline membrane disease. *AMA J Dis Child*. 1959;97(5, Part 1):517-523.
6. Wert SE, Whitsett JA, Nogee LM. Genetic disorders of surfactant dysfunction. *Pediatr Dev Pathol*. 2009;12(4):253-274.
7. Jobe AH. Glucocorticoids, inflammation and the perinatal lung. *Semin Neonatol*. 2001;6(4):331-342.
8. Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev*. 2006;(3):CD004454.
9. American College of Obstetricians and Gynecologists' Committee on Obstetric Practice; Society for Maternal–Fetal Medicine. Committee opinion no. 713: Antenatal antenatal corticosteroid therapy for fetal maturation. *Obstet Gynecol*. 2017;130:e102–109.
10. Roberts D. Antenatal corticosteroids to reduce neonatal morbidity (green-top guideline no. 7). *Royal College of Obstetricians & Gynaecoloists*. 2010.
11. Brownfoot FC, Gagliardi DI, Bain E, Middleton P, Crowther CA. Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev*. 2013;(8):CD006764. doi:10.1002/14651858.CD006764.pub3.
12. Hoekstra RE, Jackson JC, Myers TF, et al. Improved neonatal survival following multiple doses of bovine surfactant in very premature neonates at risk for respiratory distress syndrome. *Pediatrics*. 1991;88(1):10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2057245.
13. Liechty EA, Donovan E, Purohit D, et al. Reduction of neonatal mortality after multiple doses of bovine surfactant in low birth weight neonates with respiratory distress syndrome. *Pediatrics*. 1991;88(1):19. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2057268.
14. Carlo WA, Polin RACommittee on Fetus and Newborn; American Academy of Pediatrics. Respiratory support in preterm infants at birth. *Pediatrics*. 2014;133(1):171-174. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24379228. doi:10.1542/peds.2013-3442.
15. Soll RF, Blanco F. Natural surfactant extract versus synthetic surfactant for neonatal respiratory distress syndrome. *Cochrane Database Syst Rev*. 2001;(2):CD000144.
16. Singh N, Halliday HL, Stevens TP, Suresh G, Soll R, Rojas-Reyes MX. Comparison of animal-derived surfactants for the prevention and treatment of respiratory distress syndrome in preterm infants. *Cochrane Database Syst Rev*. 2015(12):CD010249. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26690260.
17. Bahadue FL, Soll R. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. *Cochrane Database Syst Rev*. 2012;11:CD001456. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23152207.
18. Rojas-Reyes MX, Morley CJ, Soll R. Prophylactic versus selective use of surfactant in preventing morbidity and mortality

in preterm infants. *Cochrane Database Syst Rev*. 2012;(3): CD000510. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22419276.
19. Dunn MS, Kaempf J, de Klerk A, et al. Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates. *Pediatrics*. 2011;128(5):e1076. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22025591. doi:10.1542/peds.2010-3848.
20. Polin RA, Carlo WA. Surfactant replacement therapy for preterm and term neonates with respiratory distress. *Pediatrics*. 2014;133(1):156-163. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24379227. doi:10.1542/peds.2013-3443.
21. Isayama T, Iwami H, McDonald S, Beyene J. Association of noninvasive ventilation strategies with mortality and bronchopulmonary dysplasia among preterm infants: a systematic review and meta-analysis. *JAMA*. 2016;316(6):611-624. Available at: http://dx.doi.org/10.1001/jama.2016.10708. doi:10.1001/jama.2016.10708.
22. The STOP-ROP Multicenter Study Group. Supplemental therapeutic oxygen for prethreshold retinopathy of prematurity (STOP-ROP), a randomized, controlled trial. I: primary outcomes. *Pediatrics*. 2000;105(2):295-310. Available at: http://pediatrics.aappublications.org/cgi/content/abstract/105/2/295. doi:10.1542/peds.105.2.295.
23. Schmidt B, Whyte RK, Asztalos EV, et al. Effects of targeting higher vs lower arterial oxygen saturations on death or disability in extremely preterm infants: A randomized clinical trial. *JAMA*. 2013;309(20):2111-2120. Available at: http://dx.doi.org/10.1001/jama.2013.5555. doi:10.1001/jama.2013.5555.
24. Carlo WA, Finer NN, Walsh MC, et al. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med*. 2010;362(21):1959-1969. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20472937. doi:10.1056/NEJMoa0911781.
25. Stenson BJ, Tarnow-Mordi WO, Darlow BA, et al. Oxygen saturation and outcomes in preterm infants. *N Engl J Med*. 2013;368(22):2094. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23642047.
26. Sahni R, Schiaratura M, Polin RA. Strategies for the prevention of continuous positive airway pressure failure. *Semin Fetal Neonatal Med*. 2016;21(3):196-203. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26936186. doi:10.1016/j.siny.2016.02.008.
27. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med*. 2010;362(21):1970-1979. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20472939. doi:10.1056/NEJMoa0911783.
28. Stevens TP, Finer NN, Carlo WA, et al. Respiratory outcomes of the surfactant positive pressure and oximetry randomized trial (SUPPORT). *J Pediatr*. 2014;165(2):249.e4. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24725582. doi:10.1016/j.jpeds.2014.02.054.
29. Vaucher YE, Peralta-Carcelen M, Finer NN, et al. Neurodevelopmental outcomes in the early CPAP and pulse oximetry trial. *N Engl J Med*. 2012;367(26):2495-2504. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23268664. doi:10.1056/NEJMoa1208506.
30. Subramaniam P, Ho JJ, Davis PG. Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants. *Cochrane Database Syst Rev*. 2016(6):CD001243. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27315509.
31. Schmölzer GM, Kumar M, Pichler G, Aziz K, O'Reilly M, Cheung PY. Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis. *BMJ*. 2013;347:f5980. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24136633.
32. Fischer HS, Bührer C. Avoiding endotracheal ventilation to prevent bronchopulmonary dysplasia: a meta-analysis. *Pediatrics*. 2013;132(5):e1351. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24144716.
33. Kirpalani H, Millar D, Lemyre B, Yoder BA, Chiu A, Roberts RS. A trial comparing noninvasive ventilation strategies in preterm infants. *N Engl J Med*. 2013;369(7):611. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23944299.
34. Salvo V, Lista G, Lupo E, et al. Noninvasive ventilation strategies for early treatment of RDS in preterm infants: an RCT. *Pediatrics*. 2015;135(3):444-451. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25667244. doi:10.1542/peds.2014-0895.
35. Stein H, Beck J, Dunn M. Non-invasive ventilation with neurally adjusted ventilatory assist in newborns. *Semin Fetal Neonatal Med*. 2016;21(3):154-61. doi:10.1016/j.siny.2016.01.006.
36. Roberts CT, Owen LS, Manley BJ, et al. Nasal high-flow therapy for primary respiratory support in preterm infants. *N Engl J Med*. 2016;375(12):1142-1151. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27653564. doi:10.1056/NEJMoa1603694.
37. Wheeler K, Klingenberg C, McCallion N, Morley CJ, Davis PG. Volume-targeted versus pressure-limited ventilation in the neonate. *Cochrane Database Syst Rev*. 2010;(11):CD003666. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21069677.
38. Cools F, Askie LM, Offringa M, et al. Elective high-frequency oscillatory versus conventional ventilation in preterm infants: a systematic review and meta-analysis of individual patients' data. *Lancet*. 2010;375(9731):2082-2091. Available at: http://www.sciencedirect.com/science/article/pii/S0140673610602784. doi:10.1016/S0140-6736(10)60278-4.
39. Levesque BM, Kalish LA, LaPierre J, Welch M, Porter V. Impact of implementing 5 potentially better respiratory practices on neonatal outcomes and costs. *Pediatrics*. 2011;128(1):e226. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21669893. doi:10.1542/peds.2010-3265.
40. Northway Jr WH, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease. *N Engl J Med*. 1967;276(7):357-368. doi:10.1056/NEJM196702162760701.
41. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med*. 2001;163(7):1723-1729.
42. Walsh MC, Wilson-Costello D, Zadell A, Newman N, Fanaroff A. Safety, reliability, and validity of a physiologic definition of bronchopulmonary dysplasia. *J Perinatol*. 2003;23(6):451-456. Available at: http://dx.doi.org/10.1038/sj.jp.7210963. doi:10.1038/sj.jp.7210963.
43. Abman SH, Collaco JM, Shepherd EG, et al. Interdisciplinary care of children with severe bronchopulmonary dysplasia. *J Pediatr*. 2017;181;12-28.e1. doi:10.1016/j.jpeds.2016.10.082.
44. Baraldi E, Filippone M. Chronic lung disease after premature birth. *N Engl J Med*. 2007;357(19):1946-1955. Available at: http://content.nejm.org/cgi/content/extract/357/19/1946. doi:10.1056/NEJMra067279.
45. Hoepker A, Seear M, Petrocheilou A, et al. Wilson–Mikity syndrome: updated diagnostic criteria based on nine cases and a review of the literature. *Pediatric Pulmonol*. 2008;43(10):1004-1012. Available at: http://onlinelibrary.wiley.com/doi/10.1002/ppul.20900/abstract. doi:10.1002/ppul.20900.
46. Horbar JD, Carpenter JH, Badger GJ, et al. Mortality and neonatal morbidity among infants 501 to 1500 grams from 2000 to 2009. *Pediatrics*. 2012;129(6):1019. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22614775.
47. Stoll BJ, Hansen NI, Bell EF, et al. Neonatal outcomes of extremely preterm infants from the NICHD neonatal research network. *Pediatrics*. 2010;126(3):443-456. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20732945. doi:10.1542/peds.2009-2959.
48. Jensen EA, Schmidt B. Epidemiology of bronchopulmonary dysplasia. *Birth Defects Res Clin Mol Teratol*. 2014;100(3):145-157. Available at: http://onlinelibrary.

wiley.com/doi/10.1002/bdra.23235/abstract. doi:10.1002/bdra.23235.
49. Jobe AJ. The new BPD: an arrest of lung development. *Pediatr Res*. 1999;46(6):641. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10590017. doi:10.1203/00006450-199912000-00001.
50. Björklund LJ, Ingimarsson J, Curstedt T, et al. Manual ventilation with a few large breaths at birth compromises the therapeutic effect of subsequent surfactant replacement in immature lambs. *Pediatr Res*. 1997;42(3):348-355. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9284276. doi:10.1203/00006450-199709000-00016.
51. Ratner V, Slinko S, Utkina-Sosunova I, Starkov A, Polin RA, Ten VS. Hypoxic stress exacerbates hyperoxia-induced lung injury in a neonatal mouse model of bronchopulmonary dysplasia. *Neonatology*. 2009;95(4):299-305. Available at: http://www.karger.com/Article/Fulltext/178798. doi:10.1159/000178798.
52. Bolivar JM, Gerhardt T, Gonzalez A, et al. Mechanisms for episodes of hypoxemia in preterm infants undergoing mechanical ventilation. *J Pediatr*. 1995;127(5):767-773. Available at: http://www.sciencedirect.com/science/article/pii/S0022347695701710. doi:10.1016/S0022-3476(95)70171-0.
53. Hartling L, Liang Y, Lacaze-Masmonteil T. Chorioamnionitis as a risk factor for bronchopulmonary dysplasia: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed*. 2012;97(1):F17. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21697236. doi:10.1136/adc.2010.210187.
54. Lahra MM, Beeby PJ, Jeffery HE. Intrauterine inflammation, neonatal sepsis, and chronic lung disease: A 13-year hospital cohort study. *Pediatrics*. 2009;123(5):1314. Available at: http://pediatrics.aappublications.org/cgi/content/abstract/123/5/1314. doi:10.1542/peds.2008-0656.
55. Ambalavanan N, Carlo WA, D'Angio CT, et al. Cytokines associated with bronchopulmonary dysplasia or death in extremely low birth weight infants. *Pediatrics*. 2009;123(4):1132-1141. Available at: http://pediatrics.aappublications.org/cgi/content/abstract/123/4/1132. doi: 10.1542/peds.2008-0526.
56. Waites KB, Katz B, Schelonka RL. Mycoplasmas and ureaplasmas as neonatal pathogens. *Clin Microbiol Rev*. 2005;18(4):757-789. Available at: http://cmr.asm.org/content/18/4/757.abstract. doi:10.1128/CMR.18.4.757-789.2005.
57. Lowe J, Watkins WJ, Edwards MO, et al. Association between pulmonary ureaplasma colonization and bronchopulmonary dysplasia in preterm infants: updated systematic review and meta-analysis. *Pediatr Infect Dis J*. 2014;33(7):697-702. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24445836. doi:10.1097/INF.0000000000000239.
58. Ballard HO, Shook LA, Bernard P, et al. Use of azithromycin for the prevention of bronchopulmonary dysplasia in preterm infants: a randomized, double-blind, placebo controlled trial. *Pediatr Pulmonol*. 2011;46(2):111-118. Available at: http://onlinelibrary.wiley.com/doi/10.1002/ppul.21352/abstract. doi:10.1002/ppul.21352.
59. Nair V, Loganathan P, Soraisham AS. Azithromycin and other macrolides for prevention of bronchopulmonary dysplasia: a systematic review and meta-analysis. *Neonatology*. 2014;106(4):337-347. Available at: http://www.karger.com/Article/Fulltext/363493. doi: 10.1159/000363493.
60. Bose C, Van Marter LJ, Laughon M, et al. Fetal growth restriction and chronic lung disease among infants born before the 28th week of gestation. *Pediatrics*. 2009;124(3):e458. Available at: http://pediatrics.aappublications.org/cgi/content/abstract/124/3/e450. doi:10.1542/peds.2008-3249.
61. Tyson JE, Wright LL, Oh W, et al. Vitamin A supplementation for extremely-low-birth-weight infants. *N Engl J Med*. 1999;340(25):1962-1968. Available at: http://content.nejm.org/cgi/content/abstract/340/25/1962. doi:10.1056/NEJM199906243402505.
62. Darlow BA, Graham PJ. Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants. *Cochrane Database Syst Rev*. 2011;(10):CD000501. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21975731.
63. Tolia VN, Murthy K, McKinley PS, Bennett MM, Clark RH. The effect of the national shortage of vitamin A on death or chronic lung disease in extremely low-birth-weight infants. *JAMA Pediatr*. 2014;168(11):1039-1044. Available at: http://dx.doi.org/10.1001/jamapediatrics.2014.1353. doi:10.1001/jamapediatrics.2014.1353.
64. Madan JC, Kendrick D, Hagadorn JI, Frantz ID, III, National Institute of Child Health and Human Development Neonatal Research Network. Patent ductus arteriosus therapy: impact on neonatal and 18-month outcome. *Pediatrics*. 2009;123(2):674-681. Available at: http://pediatrics.aappublications.org/cgi/content/abstract/123/2/674. doi:10.1542/peds.2007-2781.
65. Schmidt B, Roberts RS, Fanaroff A, et al. Indomethacin prophylaxis, patent ductus arteriosus, and the risk of bronchopulmonary dysplasia: further analyses from the trial of indomethacin prophylaxis in preterms (TIPP). *J Pediatr*. 2006;148(6):734. Available at: http://www.sciencedirect.com/science/article/pii/S0022347606000746. doi:10.1016/j.jpeds.2006.01.047.
66. Clyman R, Cassady G, Kirklin JK, Collins M, Philips JB 3rd. The role of patent ductus arteriosus ligation in bronchopulmonary dysplasia: reexamining a randomized controlled trial. *J Pediatr*. 2009;154(6):873-876. Available at: http://www.sciencedirect.com/science/article/pii/S0022347609000067. doi:10.1016/j.jpeds.2009.01.005.
67. Bhandari V, Bizzarro MJ, Shetty A, et al. Familial and genetic susceptibility to major neonatal morbidities in preterm twins. *Pediatrics*. 2006;117(6):1901-1906. Available at: http://pediatrics.aappublications.org/cgi/content/abstract/117/6/1901. doi:10.1542/peds.2005-1414.
68. Ambalavanan N, Cotten CM, Page GP, et al. Integrated genomic analyses in bronchopulmonary dysplasia. *J Pediatr*. 2015;166(3):537.e13. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25449221. doi:10.1016/j.jpeds.2014.09.052.
69. Thébaud B, Abman SH. Bronchopulmonary dysplasia: where have all the vessels gone? Roles of angiogenic growth factors in chronic lung disease. *Am J Respir Crit Care Med*. 2007;175(10):978-985. Available at: http://ajrccm.atsjournals.org/cgi/content/abstract/175/10/978. doi:10.1164/rccm.200611-1660PP.
70. Laughon MM, Langer JC, Bose CL, et al. Prediction of bronchopulmonary dysplasia by postnatal age in extremely premature infants. *Am J Respir Crit Care Med*. 2011;183(12):1715-1722. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21471086. doi:10.1164/rccm.201101-0055OC.
71. Carlo WA, Finer NN, Walsh MC, et al. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med*. 2010;362(21):1959-1969. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20472937. doi:10.1056/NEJMoa0911781.
72. Bell EF, Acarregui MJ. Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants. *Cochrane Database Syst Rev*. 2014;(12):CD000503. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25473815.
73. Doyle LW, Ehrenkranz RA, Halliday HL. Early (<8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. *Cochrane Database Syst Rev*. 2014;(5):CD001146.
74. Doyle LW, Ehrenkranz RA, Halliday HL. Late (> 7 days) postnatal corticosteroids for chronic lung disease in preterm infants. *Cochrane Database Syst Rev*. 2014;(5):CD001145.
75. Parikh NA, Lasky RE, Kennedy KA, et al. Postnatal dexamethasone therapy and cerebral tissue volumes in extremely low birth weight infants. *Pediatrics*. 2007;119(2):265-272.
76. Doyle LW, Davis PG, Morley CJ, McPhee A, Carlin JB, DART Study Investigators. Low-dose dexamethasone facilitates

extubation among chronically ventilator-dependent infants: a multicenter, international, randomized, controlled trial. *Pediatrics*. 2006;117(1):75-83.
77. Doyle LW, Davis PG, Morley CJ, McPhee A, Carlin JB, DART Study Investigators. Outcome at 2 years of age of infants from the DART study: a multicenter, international, randomized, controlled trial of low-dose dexamethasone. *Pediatrics*. 2007;119(4):716-721.
78. Rademaker KJ, Uiterwaal CS, Groenendaal F, et al. Neonatal hydrocortisone treatment: neurodevelopmental outcome and MRI at school age in preterm-born children. *J Pediatr*. 2007;150(4):351-357.
79. Watterberg KL, Shaffer ML, Mishefske MJ, et al. Growth and neurodevelopmental outcomes after early low-dose hydrocortisone treatment in extremely low birth weight infants. *Pediatrics*. 2007;120(1):40-48.
80. Patra K, Greene MM, Silvestri JM. Neurodevelopmental impact of hydrocortisone exposure in extremely low birth weight infants: outcomes at 1 and 2 years. *J Perinatol*. 2015; 35(1):77-81.
81. Watterberg KL, Gerdes JS, Cole CH, et al. Prophylaxis of early adrenal insufficiency to prevent bronchopulmonary dysplasia: a multicenter trial. *Pediatrics*. 2004;114(6): 1649-1657.
82. Baud O, Maury L, Lebail F, et al. Effect of early low-dose hydrocortisone on survival without bronchopulmonary dysplasia in extremely preterm infants (PREMILOC): a double-blind, placebo-controlled, multicentre, randomised trial. *Lancet*. 2016;387(10030):1827-1836.
83. Waber DP, Carpentieri SC, Klar N, et al. Cognitive sequelae in children treated for acute lymphoblastic leukemia with dexamethasone or prednisone. *J Pediatr Hematol Oncol*. 2000;22(3):206-213.
84. André P, Thébaud B, Odièvre MH, et al. Methylprednisolone, an alternative to dexamethasone in very premature infants at risk of chronic lung disease. *Intensive Care Med*. 2000;26(10):1496-1500.
85. Bhandari A, Schramm CM, Kimble C, Pappagallo M, Hussain N. Effect of a short course of prednisolone in infants with oxygen-dependent bronchopulmonary dysplasia. *Pediatrics*. 2008;121(2):e344-349.
86. Watterberg KL; American Academy of Pediatrics. Committee on Fetus and Newborn. Policy statement–postnatal corticosteroids to prevent or treat bronchopulmonary dysplasia. *Pediatrics*. 2010;126(4):800-808.
87. Bassler D, Plavka R, Shinwell ES, et al. Early inhaled budesonide for the prevention of bronchopulmonary dysplasia. *N Engl J Med*. 2015;373(16):1497-1506.
88. Schmidt B, Roberts RS, Davis P, et al. Caffeine therapy for apnea of prematurity. *N Engl J Med*. 2006;354(20): 2112-2121.
89. Askie LM, Ballard RA, Cutter GR, et al. Inhaled nitric oxide in preterm infants: an individual-patient data meta-analysis of randomized trials. *Pediatrics*. 2011;128(4):729-739.
90. Davis JM, Parad RB, Michele T, et al. Pulmonary outcome at 1 year corrected age in premature infants treated at birth with recombinant human CuZn superoxide dismutase. *Pediatrics*. 2003;111(3):469-476.
91. Kourembanas S. Stem cell-based therapy for newborn lung and brain injury: feasible, safe, and the next therapeutic breakthrough? *J Pediatr*. 2014;164:954–956.
92. Abman SH, Collaco JM, Shepherd EG, et al. Interdisciplinary care of children with severe bronchopulmonary dysplasia. *J Pediatr*. 2017;181:12-28.e1.
93. Lemyre B, Davis PG, De Paoli AG, Kirpalani H. Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for preterm neonates after extubation. *Cochrane Database Syst Rev*. 2017;2:CD003212.
94. Ramel SE, Gray HL, Ode KL, Younge N, Georgieff MK, Demerath EW. Body composition changes in preterm infants following hospital discharge: comparison with term infants. *J Pediatr Gastroenterol Nutr*. 2011;53(3):333-338.
95. Ho T, Dukhovny D, Zupancic JA, Goldmann DA, Horbar JD, Pursley DM. Choosing wisely in newborn medicine: five opportunities to increase value. *Pediatrics*. 2015;136(2): e482-9.
96. Stewart A, Brion LP, Ambrosio-Perez I. Diuretics acting on the distal renal tubule for preterm infants with (or developing) chronic lung disease. *Cochrane Database Syst Rev*. 2011;(9):CD001817.
97. Stewart A, Brion LP. Intravenous or enteral loop diuretics for preterm infants with (or developing) chronic lung disease. *Cochrane Database Syst Rev*. 2011;(9):CD001453.
98. Pope JC 4th, Trusler LA, Klein AM, Walsh WF, Yared A, Brock JW 3rd. The natural history of nephrocalcinosis in premature infants treated with loop diuretics. *J Urol*. 1996; 156(2 Pt 2):709-712.
99. Denjean A, Paris-Llado J, Zupan V, et al. Inhaled salbutamol and beclomethasone for preventing broncho-pulmonary dysplasia: a randomised double-blind study. *Eur J Pediatr*. 1998;157(11):926-931.
100. Ng G, da Silva O, Ohlsson A. Bronchodilators for the prevention and treatment of chronic lung disease in preterm infants. *Cochrane Database Syst Rev*. 2016;12:CD003214.
101. Bhat R, Salas AA, Foster C, Carlo WA, Ambalavanan N. Prospective analysis of pulmonary hypertension in extremely low birth weight infants. *Pediatrics*. 2012;129(3):e682-e689.
102. Ballard RA, Truog WE, Cnaan A, et al. Inhaled nitric oxide in preterm infants undergoing mechanical ventilation. *N Engl J Med*. 2006;355(4):343-353.
103. Tan K, Krishnamurthy MB, O'Heney JL, Paul E, Sehgal A. Sildenafil therapy in bronchopulmonary dysplasia-associated pulmonary hypertension: a retrospective study of efficacy and safety. *Eur J Pediatr*. 2015;174(8):1109-1115.
104. Smith VC, Zupancic JA, McCormick MC, et al. Rehospitalization in the first year of life among infants with bronchopulmonary dysplasia. *J Pediatrics*. 2004;144(6):799-803.
105. American Academy of Pediatrics Committee on Infectious Diseases; American Academy of Pediatrics Bronchiolitis Guidelines Committee. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. *Pediatrics*. 2014;134(2):e620-e638.
106. Doyle LW, Faber B, Callanan C, Freezer N, Ford GW, Davis NM. Bronchopulmonary dysplasia in very low birth weight subjects and lung function in late adolescence. *Pediatrics*. 2006;118(1):108-113.
107. Gibson AM, Reddington C, McBride L, Callanan C, Robertson C, Doyle LW. Lung function in adult survivors of very low birth weight, with and without bronchopulmonary dysplasia. *Pediatr Pulmonol*. 2015;50(10):987-994.
108. Fawke J, Lum S, Kirkby J, et al. Lung function and respiratory symptoms at 11 years in children born extremely preterm: the EPICure study. *Am J Respir Crit Care Med*. 2010;182(2):237-245.
109. Laughon M, O'Shea MT, Allred EN, et al. Chronic lung disease and developmental delay at 2 years of age in children born before 28 weeks' gestation. *Pediatrics*. 2009;124(2):637-648.
110. Ehrenkranz RA, Walsh MC, Vohr BR, et al. Validation of the National Institutes of Health Consensus Definition of Bronchopulmonary Dysplasia. *Pediatrics*. 2005;116(6):1353-1360.
111. Avery ME, Gatewood OB, Brumley G. Transient tachypnea of the newborn. Possible delayed resorption of fluid at birth. *Am J Dis Child*. 1966;111:380.
112. Stroustrup A, Trasande L, Holzman IR. Randomized controlled trial of restrictive fluid management in transient tachypnea of the newborn. *J Pediatr*. 2012;160(1):38.

113. Kassab M, Khriesat WM, Anabrees J. Diuretics for transient tachypnoea of the newborn. *Cochrane Database Syst Rev*. 2015;(11):CD003064.
114. Kao B, Stewart de Ramirez SA, Belfort MB, Hansen A. Inhaled epinephrine for the treatment of transient tachypnea of the newborn. *J Perinatol*. 2008;28(3):205-210.
115. Garenne M, Ronsmans C, Campbell H. The magnitude of mortality from acute respiratory infections in children under 5 years in developing countries. *World Health Stat Q*. 1992;45:180.
116. Stoll BJ, Hansen NI, Sánchez PJ, et al. Early onset neonatal sepsis. the burden of group B Streptococcal and E. Coli disease continues. *Pediatrics*. 2011;127(5):817–826.
117. Lowe J, Watkins WJ, Edwards MO, et al. Association between pulmonary ureaplasma colonization and bronchopulmonary dysplasia in preterm infants: updated systematic review and meta-analysis. *Pediatr Infect Dis J*. 2014; 33(7):697-702.
118. Boyer KM, Gotoff SP. Prevention of early-onset neonatal group B streptococcal disease with selective intrapartum chemoprophylaxis. *N Engl J Med*. 1986;314(26):1665.
119. Clark RH, Bloom BT, Spitzer AR, Gerstmann DR. Empiric use of ampicillin and cefotaxime, compared with ampicillin and gentamicin, for neonates at risk for sepsis is associated with an increased risk of neonatal death. *Pediatrics*. 2006;117(1):67.
120. Hocker JR, Simpson PM, Rabalais GP, Stewart DL, Cook LN. Extracorporeal membrane oxygenation and early-onset group B streptococcal sepsis. *Pediatrics*. 1992;89:1.
121. Antonowiez I, Schwachman H. Meconium in health and disease. *Adv Pediatr*. 1979;26:275.
122. Carbine DN. Meconium aspiration. *Pediatr Rev*. 2008;29:212.
123. Yoder BA, Kirsch EA, Barth WH, Gordon MC. Changing obstetric practices associated with decreasing incidence of meconium aspiration syndrome. *Obstet Gynecol*. 2002; 99(5 Pt 1):731.
124. Fraser W, Hofmeyr J, Lede R, et al. Amnioinfusion for prevention of the meconium aspiration syndrome. *N Engl J Med*. 2005;353:909.
125. Vain NE, Szyld EG, Prudent LM, Wiswell TE, Aguilar AM, Vivas NI. Oropharyngeal and nasopharyngeal suctioning of meconium-stained neonates before delivery of their shoulders: multicenter, randomized, controlled trial. *Lancet*. 2004;364:597.
126. Wiswell TE, Gannon CM, Jacob J, et al. Delivery room management of the apparently vigorous meconium-stained neonate: results of the multicenter, international collaborative trial. *Pediatrics*. 2000;105(1 Pt 1):1.
127. Narchi H, Kulaylat N. Is gastric lavage needed in neonates with meconium-stained amniotic fluid? *Eur J Pediatr*. 1999; 158:315.
128. Singh BS, Clark RH, Powers RJ, Spitzer AR. Meconium aspiration syndrome remains a significant problem in the NICU: outcomes and treatment patterns in term neonates admitted for intensive care during a ten-year period. *J Perinatol*. 2009;29(7):497.
129. Kinsella JP, Truog WE, Walsh WF, et al. Randomized, multicenter trial of inhaled nitric oxide and high-frequency oscillatory ventilation in severe, persistent pulmonary hypertension of the newborn. *J Pediatr*. 1997;131:55.
130. Findlay RD, Taeusch HW, Walther FJ. Surfactant replacement therapy for meconium aspiration syndrome. *Pediatrics*. 1996;97(1):48.
131. Wiswell TE, Knight GR, Finer NN, et al. A multicenter, randomized, controlled trial comparing Surfaxin (Lucinactant) lavage with standard care for treatment of meconium aspiration syndrome. *Pediatrics*. 2002;109:1081.
132. Hahn S, Choi HJ, Soll R, Dargaville PA. Lung lavage for meconium aspiration syndrome in newborn infants. *Cochrane Database Syst Rev*. 2013;(4):CD003486.
133. Ward M, Sinn J. Steroid therapy for meconium aspiration syndrome in newborn infants. *Cochrane Database Syst Rev*. 2003;(4):CD003485.
134. Swaminathan S, Quinn J, Stabile MW, Bader D, Platzker AC, Keens TG. Long-term pulmonary sequelae of meconium aspiration syndrome. *J Pediatr*. 1989;114(3):356.
135. Beligere N, Rao R. Neurodevelopmental outcome of infants with meconium aspiration syndrome: report of a study and literature review. *J Perinatol*. 2008;28(suppl 3):S93.
136. Van Marter LJ, McPherson CC. Persistent pulmonary hypertension of the newborn. In: Cloherty JP, Eichenwald EC, Hansen AR, Stark AR, eds. *Manual of Neonatal Care*. 8th ed. Philadelphia: Wolters Kluwer; 2017.
137. Steurer MA, Jelliffe-Pawlowski LL, Baer RJ, Partridge JC, Rogers EE, Keller RL. Persistent pulmonary hypertension of the newborn in late preterm and term infants in California. *Pediatrics*. 2017;139(1). pii: e20161165.
138. Delaney C, Cornfield DN. Risk factors for persistent pulmonary hypertension of the newborn. *Pulm Circ*. 2012;2:15.
139. Steinhorn RH, Abman SH. Persistent pulmonary hypertension. In: Gleason CA, Devaskar SU, eds. *Avery's Disease of the Newborn*. 9th ed. Philadelphia: Saunders; 2012.
140. Walsh-Sukys MC, Tyson JE, Wright LL, et al. Persistent pulmonary hypertension of the newborn in the era before nitric oxide: practice variation and outcomes. *Pediatrics*. 2000;105(1 Pt 1):14.
141. Kinsella JP, Troug WE, Walsh WF, et al. Randomized, multicenter trial of inhaled nitric oxide and high-frequency oscillatory ventilation in severe, persistent pulmonary hypertension of the newborn. *J Pediatr*. 1997;131(1 Pt 1):55.
142. Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. *N Engl J Med*. 1997;336(9):597.
143. Roberts Jr JD, Fineman JR, Morin FC 3rd, et al. Inhaled nitric oxide and persistent pulmonary hypertension of the newborn. The Inhaled Nitric Oxide Study Group. *N Engl J Med*. 1997;336(9):605.
144. Steinhorn RH, Kinsella JP, Pierce C, et al. Intravenous sildenafil in the treatment of neonates with persistent pulmonary hypertension. *J Pediatr*. 2009;155:841.
145. Lakshminrusimha S, Mathew B, Leach CL. Pharmacologic strategies in neonatal pulmonary hypertension other than nitric oxide. *Semin Perinatol*. 2016;40(3):160-173.
146. Steinhorn RH, Fineman J, Kusic-Pajic A, et al. Bosentan as adjunctive therapy for persistent pulmonary hypertension of the newborn: results of the randomized multicenter placebo-controlled exploratory trial. *J Pediatr*. 2016;177:90-96.e3.
147. Ruoss JL, McPherson C, DiNardo J. Inotrope and vasopressor support in neonates. *Neoreviews*. 2015;16(6):351-361.
148. Lazar DA, Cass DL, Olutoye OO, et al. The use of ECMO for persistent pulmonary hypertension of the newborn: a decade of experience. *J Surg Res*. 2012;177(2):263-267.
149. Kattan J, González A, Becker P, et al. Survival of newborn infants with severe respiratory failure before and after establishing an extracorporeal membrane oxygenation program. *Pediatr Crit Care Med*. 2013;14(9):876-883.
150. Tieder JS, Bonkowsky JL, Etzel RA, et al. Brief resolved unexplained events (formerly apparent life-threatening events) and evaluation of lower-risk infants: executive summary. *Pediatrics*. 2016;137(5):e20160591.
151. Task Force on Sudden Infant Death Syndrome. SIDS and other sleep-related infant deaths: updated 2016 recommendations for a safe sleeping environment. *Pediatrics*. 2016;138(5):pii e20162938.
152. Barrington KJ, Finer NN. Periodic breathing and apnea in preterm infants. *Pediatr Res*. 1990;27:118.
153. Levin JC, Jang J, Rhein LM. Apnea in the otherwise healthy, term newborn: national prevalence and utilization during the birth hospitalization. *J Pediatr*. 2017;181:67-77.

154. Rhein LM, Dobson NR, Darnall RA, et al. Effects of caffeine on intermittent hypoxia in infants born prematurely: a randomized clinical trial. *JAMA Pediatr*. 2014;168(3):250-257.
155. Darnall RA, Ariagno RL, Kinney HC. The late preterm infant and the control of breathing, sleep, and brainstem development: a review. *Clin Perinatol*. 2006;33:883.
156. Stark, AR. Apnea. In: Cloherty JP, Eichenwald EC, Hansen AR, Martin C, Stark AR, eds. *Manual of Neonatal Care.* 8th ed. Philadelphia: Wolters Kluwer; 2017.
157. Peter CS, Sprodowski N, Bohnhorst B, Silny J, Poets CF. Gastroesophageal reflux and apnea of prematurity: no temporal relationship. *Pediatrics*. 2002;109:8.
158. Henderson-Smart DJ, De Paoli AG. Methylxanthine treatment for apnoea in preterm infants. *Cochrane Database Syst Rev*. 2010;(12):CD000140.
159. Schmidt B, Roberts RS, Davis P, et al. Caffeine therapy for apnea of prematurity. *N Engl J Med*. 2006;354(20):2112.
160. Schmidt B, Roberts RS, Davis P, et al. Long-term effects of caffeine therapy for apnea of prematurity. *N Engl J Med*. 2007;357(19):1893.
161. Schmidt B, Anderson PJ, Doyle LW, et al. Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity. *JAMA*. 2012;307(3):275-282.
162. Zagol K, Lake DE, Vergales B. et al. Anemia, apnea of prematurity, and blood transfusions. *J Pediatr*. 2012;161(3):417.
163. Ramanathan R, Corwin MJ, Hunt CE, et al. Cardiorespiratory events recorded on home monitors: comparison of healthy infants with those at increased risk for SIDS. *JAMA*. 2001;285:2199.
164. Pammi M. Pulmonary air leak. In: Cloherty JP, Eichenwald EC, Hansen AR, Stark AR, eds. *Manual of Neonatal Care.* 8th ed. Philadelphia: Wolters Kluwer; 2017.
165. Vermont Oxford Network Database. Burlington, VT: Vermont Oxford Network; 2014.
166. Yu VY, Wong PY, Bajuk B, Szymonowicz W. Pulmonary air leak in extremely low birthweight infants. *Arch Dis Child*. 1986;61:239.
167. Macklin CC. Transport of air along sheaths of pulmonic blood vessels from alveoli to mediastinum. *Arch Intern Med*. 1939;64:913.
168. Wheeler K, Klingenberg C, McCallion N, Morley CJ, Davis PG. Volume-targeted versus pressure-limited ventilation in the neonate. *Cochrane Database Syst Rev*. 2010;(11):CD003666.
169. Greenough A, Rossor TE, Sundaresan A, Murthy V, Milner AD. Synchronized mechanical ventilation for respiratory support in newborn infants. *Cochrane Database Syst Rev*. 2016;9:CD000456.
170. Shaw NJ, Cooke RW, Gill AB, Shaw NJ, Saeed M. Randomised trial of routine versus selective paralysis during ventilation for neonatal respiratory distress syndrome. *Arch Dis Child*. 1993;69:479.
171. Cools F, Offringa M, Askie LM. Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants. *Cochrane Database Syst Rev*. 2015;(3):CD000104.
172. Wiswell TE, Graziani LJ, Kornhauser MS, et al. High-frequency jet ventilation in the early management of respiratory distress syndrome is associated with a greater risk for adverse outcomes. *Pediatrics*. 1996;98(6 Pt 1):1035.
173. Litmanovitz I, Carlo WA. Expectant management of pneumothorax in ventilated neonates. *Pediatrics*. 2008;122(5): e975-e979.
174. Shaireen H, Rabi Y, Metcalfe A, et al. Impact of oxygen concentration on time to resolution of spontaneous pneumothorax in term infants: a population based cohort study. *BMC Pediatr*. 2014;14:208.
175. Cohen RS, Smith DW, Stevenson DK, Moskowitz PS, Graham CB. Lateral decubitus position as therapy for persistent pulmonary interstitial emphysema in neonates: a preliminary report. *J Pediatr*. 1984;104:441.
176. Doherty E, Fleck P. Neonatal Chest Tube Placement. Video in Open Pediatrics Online Curriculum. Available at: https://www.openpediatrics.org/assets/video/neonatal-chest-tube-placement. Accessed February 16, 2017.
177. Keszler M, Donn SM, Bucciarelli RL, et al. Multicenter controlled trial comparing high frequency jet ventilation in preterm infants with pulmonary interstitial emphysema. *J Pediatr*. 1991;119:85.
178. Raju TNK. Neonatal pulmonary hemorrhage. In: Donn SM, Sinha SK, eds. *Manual of Neonatal Respiratory Care*. 3rd ed. New York: Springer; 2012.
179. Plosa EJ. Pulmonary hemorrhage. In: Cloherty JP, Eichenwald EC, Martin, C, Hansen AR, Stark AR, eds. *Manual of Neonatal Care.* 8th ed. Philadelphia: Wolter Kluwer; 2017.
180. Raju TN, Langenberg P. Pulmonary hemorrhage and exogenous surfactant therapy: a metaanalysis. *J Pediatr*. 1993; 123(4):603-610.
181. Berger TM, Allred EN, Van Marter LJ. Antecedents of clinically significant pulmonary hemorrhage among newborn infants. *J Perinatol*. 2000;20(5):295-300.
182. Kluckow M, Evans N. Ductal shunting, high pulmonary blood flow, and pulmonary hemorrhage. *J Pediatr*. 2000;137:68.
183. Narasimhan R, Papworth S. Pulmonary haemorrhage in the neonate. *Paediatr Child Health*. 2009;19(4):171.
184. Schmidt B, Davis P, Moddemann D, et al. Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. *N Engl J Med*. 2001;344(26):1966-1972.
185. Alfaleh K, Smyth JA, Roberts RS, et al. Prevention and 18-month outcomes of serious pulmonary hemorrhage in extremely low birth weight infants: results from the trial of indomethacin prophylaxis in preterms. *Pediatrics*. 2008;121(2):e233-e238.
186. Courtney SE, Durand DJ, Asselin JM, et al. High-frequency oscillatory ventilation versus conventional mechanical ventilation for very-low-birth-weight infants. *N Engl J Med*. 2002;347:643-652.
187. Malo J, Ali J, Wood LD. How does positive end-expiratory pressure reduce intrapulmonary shunt in canine pulmonary edema? *J Appl Physiol Respir Environ Exerc Physiol*. 1984;57:1002.
188. Paré PD, Warriner B, Baile EM, Hogg JC. Redistribution of pulmonary extravascular water with positive end-expiratory pressure in canine pulmonary edema. *Am Rev Respir Dis*. 1983;127:590.
189. AlKharfy TM. High-frequency ventilation in the management of very-low-birth-weight infants with pulmonary hemorrhage. *Am J Perinatol*. 2004;21(1):19-26.
190. Pandit PB, Dunn MS, Colucci EA. Surfactant therapy in neonates with respiratory deterioration due to pulmonary hemorrhage. *Pediatrics*. 1995;95:32.
191. Aziz A, Ohlsson A. Surfactant for pulmonary haemorrhage in neonates. *Cochrane Database Syst Rev*. 2012;(7):CD005254.
192. Poralla C, Hertfelder HJ, Oldenburg J, Müller A, Bartmann P, Heep A. Treatment of acute pulmonary haemorrhage in extremely preterm infants with recombinant activated factor VII. *Acta Paediatr*. 2010;99:298.
193. Lodha A, Kamaluddeen M, Akierman A, Amin H. Role of hemocoagulase in pulmonary hemorrhage in preterm infants: a systematic review. *Indian J Pediatr*. 2011;78(7):838-844.
194. Tomaszewska M, Stork E, Minich NM, Friedman H, Berlin S, Hack M. Pulmonary hemorrhage: clinical course and outcomes among very low-birth-weight infants. *Arch Pediatr Adolesc Med*. 1999;153(7):715-721.

Surgical Disorders in Childhood that Affect Respiratory Care

23

Arin L. Madenci, Samuel E. Rice-Townsend, Christopher B. Weldon

Outline

Learning Objectives

After completing this chapter the reader will be able to:

1. Discuss the anatomy and pathophysiology of the various congenital anomalies and surgical conditions in newborns and infants that affect respiratory care.
2. Recognize and manage an infant in respiratory distress resulting from choanal atresia or other upper airway anomalies.
3. Discuss the anatomy and pathophysiology of esophageal atresia with or without a tracheoesophageal fistula.
4. Recognize and manage the signs and symptoms of esophageal atresia with or without a tracheoesophageal fistula.
5. Recognize symptomatic mediastinal tumors and understand the tenets of airway management in this high-risk patient group.
6. Discuss the embryology, anatomy, and pathophysiology of congenital diaphragmatic hernia.
7. Recognize and perform the steps related to immediate management of a neonate born with congenital diaphragmatic hernia.
8. Discuss the anatomy, diagnosis, and management of an infant with congenital lung lesions, including congenital pulmonary airway malformations and sequestrations.
9. Discuss the embryology, anatomy, and management of chest wall deformities.
10. Recognize the signs and symptoms of abdominal compartment syndrome.
11. Discuss the embryology and management of abdominal wall defects (gastroschisis and omphalocele).

Key Terms

abdominal compartment syndrome
bronchogenic cyst
bronchopulmonary sequestration
CHARGE syndrome
choanal atresia
congenital diaphragmatic hernia
congenital lobar emphysema
congenital pulmonary airway malformation
esophageal atresia
extracorporeal membrane oxygenation
gastroschisis
omphalocele
pectus excavatum
tracheoesophageal fistula
tracheomalacia
VACTERL syndrome

Acronyms

ACS, abdominal compartment syndrome
ALTE, acute life-threatening event
CDH, congenital diaphragmatic hernia
CHARGE syndrome, *c*oloboma of the iris or choroid, congenital *h*eart defects, *a*tresia of the choanae, *r*etarded growth and development, *g*enitourinary anomalies, and *e*ar and hearing anomalies
CLE, congenital lobar emphysema
CPAM, congenital pulmonary airway malformation
CT, computed tomography

EA, esophageal atresia
ECMO, extracorporeal membrane oxygenation
GA, general anesthesia
GER, gastroesophageal reflux
iNO, inhaled nitric oxide
LA, local anesthesia
MR, magnetic resonance
NICU, neonatal intensive care unit
PDA, patent ductus arteriosus
RT, respiratory therapist
TEF, tracheoesophageal fistula
VACTERL syndrome, *v*ertebral defects, *a*nal atresia, *c*ardiac defects, *t*racheoesophageal fistula, *r*enal anomalies, and *l*imb abnormalities

For children who require respiratory support, optimal treatment requires an underlying knowledge and understanding of surgical conditions that affect respiration, including their operative and nonoperative management. These disorders require a multidisciplinary team, and the respiratory therapist (RT) commonly is the first caregiver to recognize that a pathologic condition requiring surgery or supportive interventions exists. Early discovery and efficient treatment can improve respiratory care and outcomes, especially in urgent situations. Additionally, many surgically treated conditions result in new or changed respiratory mechanics and physiology that may require the RT to have a well-founded understanding of the anatomy, pathophysiology, and surgical course of the disease. This chapter focuses on the following themes: (1) the anatomic and pathophysiologic characteristics of common congenital anomalies that may require surgery and (2) the respiratory problems that may arise postoperatively from a number of common surgical diseases of childhood.

NOSE AND MOUTH

CHOANAL ATRESIA

The choanae, or posterior nasal apertures, connect the nasal passage with the nasopharynx. **Choanal atresia,** defined as unilateral or bilateral obstruction of the posterior nasal apertures, occurs in approximately 1 in 700 live births.[1] A number of theories explain the occurrence of this malformation, including disordered neural crest cell migration and abnormal persistence of membranes or other structures.[2] Most cases of choanal atresia involve an obstructive bony choanal plate, whereas a minority involve a membranous obstruction.[3]

Because neonates are obligate nasal breathers, bilateral choanal atresia may result in early severe respiratory distress or feeding difficulties. During the newborn's first breaths, the tongue often becomes directly associated with the hard and soft palates, creating a vacuum. One clue to this diagnosis may be observing cyanosis that resolves with crying or with an open mouth. The suspected diagnosis can then be established with the inability to pass a catheter from the naris into the nasopharynx. Because about two-thirds of cases of choanal atresia are unilateral, not bilateral, diagnosis is more commonly suggested by subtle signs such as chronic unilateral rhinorrhea, without frank respiratory distress.[2,4]

Roughly 50% of patients with choanal atresia have associated congenital anomalies. The most common associated pattern is **CHARGE syndrome,** which includes *c*oloboma of the iris or choroid, congenital *h*eart defects, *a*tresia of the choanae, *r*etarded growth and development, *g*enitourinary anomalies, and *e*ar and hearing anomalies. Other craniofacial defects are also commonly associated with choanal atresia.

Bilateral choanal atresia in a neonate with severe respiratory distress may require emergent management. A neonate in distress will be stabilized by immediately inserting an oral airway. After completing the initial resuscitation, possible choanal atresia and associated anomalies should be investigated. Although inability to pass a catheter may suggest the diagnosis, computed tomography imaging and endoscopy delineate the choanal anomaly.

Definitive treatment involves resection of the posterior nasal septum, with or without stent placement.[5] Before surgical repair, however, optimization of respiratory care by maintaining the orotracheal airway is critical. The timing and surgical approach depend on the presence and urgency of coinciding medical problems. Once the repair is performed, a standard folded endotracheal tube is used to stent the choanae in a U configuration. A suction catheter is measured so that it passes through the end of the stent into the nasopharynx. The catheter is passed through each side of the stent to prevent obstruction.[5] Postoperatively, suction and saline are used to ensure patency in the stent. Prophylactic antibiotics and steroid drops are typically administered, and, when the infant is medically ready, the stent is removed (often with the patient under general anesthesia).

Continuing respiratory problems caused by nasal congestion may be expected for 3 to 4 weeks postoperatively. The prognosis after reconstruction is excellent and generally uncomplicated, with the most significant complication being restenosis of the choanae. In one study of 73 patients who underwent endoscopic resection, a 12% restenosis rate was reported.[2] This complication may be managed by dilations of the choanae under endoscopic visualization, repeat resection, and stenting. Rarely, tracheostomy or long-term

endotracheal intubation may be required, especially if choanal atresia is complicated by other severe craniofacial abnormalities.

MACROGLOSSIA

Macroglossia, or an enlarged tongue, may lead to respiratory distress by pharyngeal obstruction, and there are three recognized subtypes. First, generalized macroglossia is associated with other congenital disorders, such as Beckwith-Wiedemann syndrome, inborn errors of metabolism, and hypothyroidism, each of which may carry its own complicating medical issues. Second, relative macroglossia, or a comparatively large tongue relative to abnormally small craniofacial structures, may be seen with trisomy 21 and other disorders. Finally, focal macroglossia can arise from tumors of the tongue, including vascular or lymphatic malformations. Each of these types of macroglossia may present with symptoms ranging from stridor with airway obstruction to speech impairment, feeding intolerance, or drooling. Patients presenting with severe obstruction may require more urgent intervention ranging from oral airway placement to intubation. The most severe cases of macroglossia may require surgical intervention, including tongue reduction procedures or, in the most severe cases, tracheostomy.[6] Prone positioning may improve the respiratory symptoms of mild isolated macroglossia. Feeding intolerance typically resolves with upright positioning. Further evaluation can be performed with polysomnography for suspected obstructive sleep apnea.[7]

MANDIBULAR HYPOPLASIA

Mandibular hypoplasia, or micrognathia, is a craniofacial abnormality resulting in a small jaw that may lead to respiratory distress from obstruction in the neonate. This condition, by definition, leads to relative macroglossia. Micrognathia often accompanies other developmental anomalies seen in congenital syndromes such as Pierre Robin sequence and Treacher Collins syndrome. Pierre Robin is the most common of these associations and includes the constellation of micrognathia, glossoptosis (or posterior displacement of the tongue), and cleft palate. In a series of 25 full-term neonates with isolated Pierre Robin sequence, more than 95% were found to have obstructive apnea.[8] Left untreated, infants may eventually develop severe cardiopulmonary complications, such as pulmonary hypertension and cor pulmonale. Recent polysomnographic studies using oximetry have demonstrated that hypoxia and carbon dioxide retention can occur even without overt signs of airway obstruction.[9] Other complications of Pierre Robin sequence include failure to thrive, malnutrition, chronic hypoxia, and pneumonia. In an early series published in 1993 of 125 patients with Pierre Robin, 45% had normal respiration in prone position and normal feeding, 32% had normal respiration in prone position but required gavage feeds, and 23% had respiratory distress requiring intubation and required gavage feeds.[10]

Given the risk of airway obstruction, close monitoring and efficient intervention and evaluation are essential among patients with micrognathia. Patients with Treacher Collins syndrome often present a particular challenge because of the combination of micrognathia, relative macroglossia, and limited mouth opening. Such patients may be extremely difficult not only to intubate, but also to bag–valve mask ventilate, especially if there are temporomandibular joint abnormalities.[11] Initial treatments for patients with micrognathia are similar to those for macroglossia and include prone positioning and intraoral (or nasopharyngeal) airway placement. Airway securement may be optimized by using a video laryngoscope, laryngeal mask airway, or fiberoscopy.[12] In severe cases, tracheostomy may provide an appropriate long-term solution. For mild cases of micrognathia, prone positioning combined with supplemental oxygen administration and carefully supervised feedings may comprise adequate treatment. Surgical procedures designed to hold the tongue forward (tongue–lip adhesion) may improve airway patency and feeding among those patients for whom noninvasive interventions are insufficient.[13] Finally, distraction osteogenesis of the mandible is a surgical technique designed to correct micrognathia that may be used for severe symptomatic forms of the disorder. In general, treatments for micrognathia are temporizing measures that "buy time," because the consequences of this anomaly gradually improve with growth of the facial structures.

TRACHEA

EMBRYOLOGY OF THE RESPIRATORY TRACT

In early fetal development, a tube of endodermal epithelium is present along the entire longitudinal axis of the fetus. This tube, which ultimately develops into the gastrointestinal tract, is referred to as the *primitive foregut.* At approximately 3 weeks of gestation, a small groove appears in the floor of the primitive foregut, near the oral end of the fetus (Figure 23-1). The groove develops into a ridge, and the ridge branches into two blind pouches at its distal end. This ridge eventually develops into the trachea, and the thickenings are referred to as *lung buds.* The entire ridge with the lung buds will eventually migrate away from the main epithelial tube, thus separating the early pulmonary system from the esophagus. As these endodermal structures develop, their blood supply is formed from the fourth and sixth aortic arches, which are the primitive tributaries to the aorta. The lung derives its blood supply from two distinct sources: (1) the pulmonary artery (sixth arch), which brings oxygen-poor blood from systemic veins for oxygenation, and (2) the bronchial arteries (direct branches of the arch), which bring

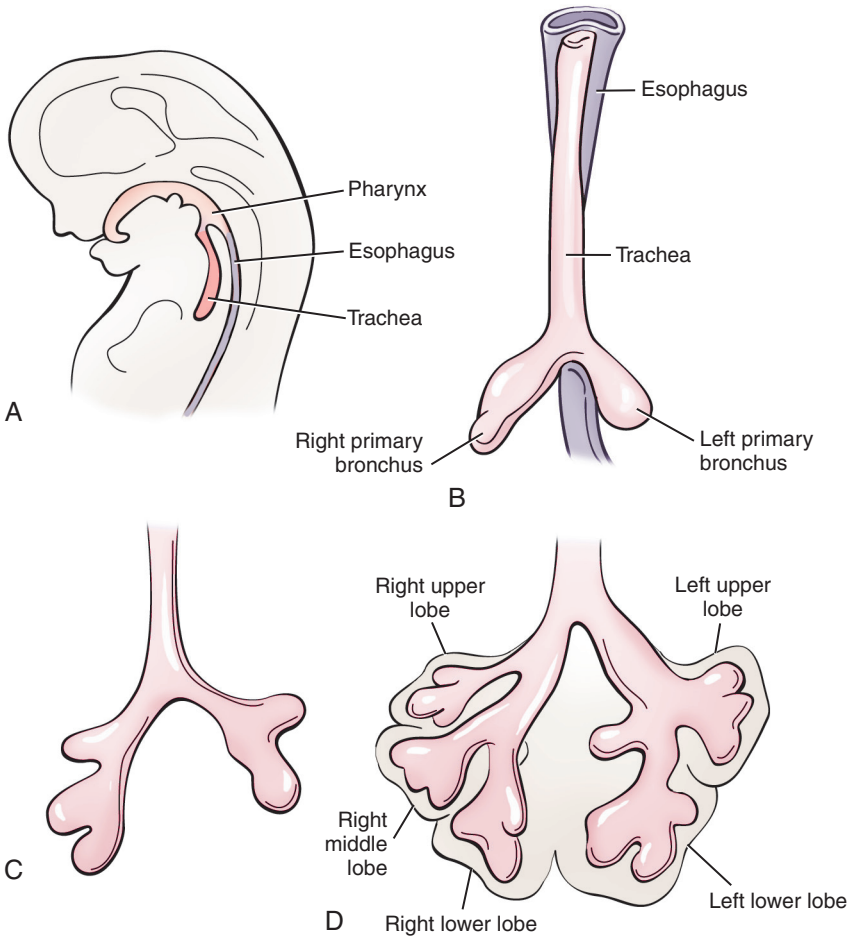


FIGURE 23-1 Developmental anatomy of the lung. **(A)** The pulmonary tree develops from a common tube with the esophagus. By 3 weeks of gestation, the trachea (anterior) is separate from the esophagus. **(B)** Two blind pouches that represent the left and right lung buds at the distal end of the primitive pulmonary system. (C and D) Further dichotomous branching of the bronchi.

oxygen-rich blood to the parenchyma of the lung for nutritive purposes. The budding part of the tube is composed of endoderm, a multipotent tissue in the embryo that forms the functional aspect of each organ (e.g., the alveoli of the lungs, the mucosa of the gastrointestinal tract, the nephron of the kidney). The lung buds grow into the mesoderm, which is also a multipotent tissue that forms the connective tissue and the supporting framework of each organ.[14]

The interaction between these tissues is important in the development of each organ. In the primitive pulmonary system, the bud-forming endoderm induces important changes in the surrounding mesoderm that lead to a cohesive functioning organ. Knowledge of these processes may help to explain how each anomaly occurs. For example, if the longitudinal groove with its attached buds fails to completely separate from the epithelial tube, a laryngoesophageal cleft or tracheoesophageal fistula may result.

LARYNGEAL CLEFT

Laryngeal cleft, or an abnormal connection between the larynx-trachea and hypopharynx-esophagus, occurs in 1 in 10,000 to 20,000 live births.[15] Most cases are sporadic; however, many laryngeal clefts occur in conjunction with syndromes such as **VACTERL syndrome** (a syndrome including *v*ertebral defects, *a*nal atresia, *c*ardiac defects, *t*racheo*e*sophageal fistula, *r*enal anomalies, and *l*imb abnormalities), Pallister-Hall, and CHARGE syndromes. The cleft length can be as short as a small defect between the arytenoid cartilages or span the length of the entire trachea. Children with minor laryngeal clefts may present with cyanosis with feeding, aspiration with recurrent pneumonia, stridor, and increased secretions.[16] In severe cases, the diagnosis must immediately be suspected when the endotracheal tube repeatedly falls into the esophagus, despite visualized placement between the cords, resulting in an inability to ventilate. **Extracorporeal membrane oxygenation** (ECMO) may be necessary in such cases. Diagnosis is confirmed on direct laryngoscopy and bronchoscopy or contrast study of the esophagus. Less severe clefts (limited to the supraglottic or intraarytenoid areas) may be either managed nonoperatively (with a focus on limiting aspiration events with thickened feeds) or repaired endoscopically. The most

severe clefts (extending to the intrathoracic esophagus) require surgical repair with cardiopulmonary bypass.

ESOPHAGEAL ATRESIA AND TRACHEOESOPHAGEAL FISTULA

Esophageal atresia (EA) results when the esophagus is not in continuity. When present, it can significantly impact neonatal respiratory function, largely because of its common association with an abnormal connection between part of the esophagus and the airway called a **tracheoesophageal fistula** (TEF). The various combinations of anomalies are best described using the anatomic findings in each case, rather than the varied classification schemes (Figure 23-2). The embryology is not fully understood, although some authors postulate that TEF results from an anomalous outgrowth of the early respiratory tract.[17] EA and TEF are commonly accompanied by additional anomalies in the distribution of VACTERL association.[18]

Esophageal atresia with tracheoesophageal fistula occurs in 2 to 3 instances per 10,000 births, with a male predisposition.[19] Because of the obstruction of amniotic fluid during fetal swallowing, esophageal atresia may initially be suspected when polyhydramnios and an abnormally small stomach are visualized on prenatal imaging studies. With or without prenatal suspicion, diagnosis is most often definitively made shortly after birth. The postnatal presentation of each type of anomaly across the spectrum of EA and TEF varies with the lesion and its respective consequences of obstruction or aspiration. An isolated tracheoesophageal fistula may present as late as early adulthood with subtle symptoms of wheezing and recurrent respiratory infections. More typically, choking, drooling, and coughing episodes will be evident shortly after birth, and inability to pass an orogastric tube into the stomach confirms the diagnosis. Patients may even present with significant abdominal distention caused by excessive air moving from the respiratory tract to the gastrointestinal tract through a fistulous connection.

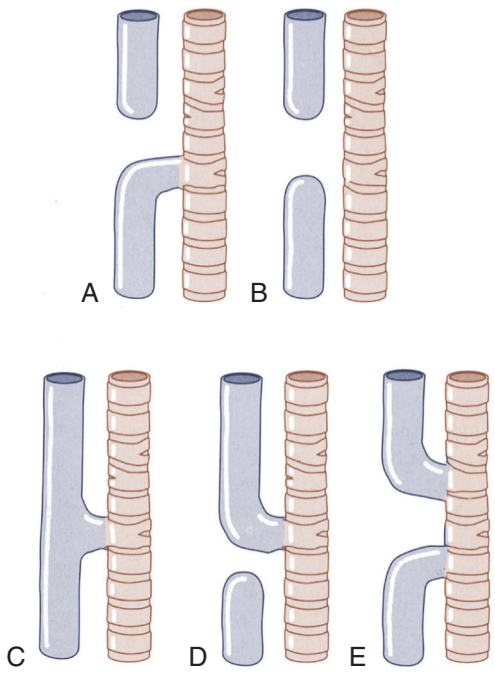


FIGURE 23-2 Five anatomic classifications describing tracheoesophageal fistula and esophageal atresia. **(A)** Esophageal atresia with distal tracheoesophageal fistula. **(B)** Isolated esophageal atresia. **(C)** Tracheoesophageal fistula without esophageal atresia ("H-type"). **(D)** Esophageal atresia with proximal fistula. **(E)** Esophageal atresia with both proximal and distal tracheoesophageal fistulae.

In cases of esophageal atresia, respiratory distress may develop from aspiration of secretions from the blind proximal pouch, aspiration of gastric contents via the fistula, or loss of ventilation through the fistula. A proximal TEF places patients at elevated risk of aspiration of oropharyngeal contents. Alternatively, a distal TEF, the most common type of fistula, may lead to aspiration of gastric contents. Even in the absence of a TEF, the accumulation of saliva or feeds in the atretic upper esophageal pouch may lead to aspiration of these contents. Similarly, drooling, along with frothing and bubbling at the nose and mouth, may be the first symptom in most newborns with esophageal atresia. The first feedings often result in aspiration with coughing and episodes of cyanosis. When esophageal atresia is suspected, a nasal or oral feeding tube or suction catheter should be gently introduced until resistance is met. In a stable infant, while awaiting definitive surgical repair, risk of complications from EA and TEF may be minimized by maintaining a patent nasoesophageal or oroesophageal sump. If possible, infants should be left to breathe spontaneously on room air.

With radiographic evaluation, a plain film will commonly demonstrate a coiled orogastric tube. Proximal atresia with air in the gastrointestinal tract indicates a distal tracheoesophageal fistula, whereas no distal air may indicate a proximal fistula or pure atresia. In cases of later diagnosis, the lung fields may show parenchymal changes resulting from recurrent aspiration. Evaluation for concomitant congenital anomalies must be undertaken, most critically with preoperative echocardiography. The laterality of the aortic arch is especially important for operative planning. Patients should also, less urgently, undergo renal ultrasound, spinal ultrasound, and spinal plain film for completion of VACTERL workup.

Once the diagnosis is made, the overall clinical condition of the infant largely dictates the timing of repair.[20] For patients who present with severe respiratory distress and low birth weight, mechanical ventilation may be required. It may be necessary to perform an urgent temporizing procedure in the setting of a distal tracheoesophageal fistula if tidal volume delivery is compromised and the patient remains in recalcitrant respiratory failure. This procedure may

involve a right thoracotomy for ligation of the fistula. Other possible temporizing interventions include balloon catheter occlusion of the fistula or stapling of the distal esophagus.[21] After stabilization, a primary anastomosis of the esophagus can be performed when the infant has grown larger, but this scenario generally requires interval placement of a gastrostomy tube for enteral feeding to allow for growth off parenteral nutrition. Patients with so-called *long gap esophageal atresia,* marked by a distance between the upper and lower esophageal pouches of greater than 2.5 cm, may require an interposition graft (jejunum, colon, and stomach have been described) or a staged procedure including interval traction growth.[22,23]

The most significant postoperative complications after primary esophageal anastomosis are anastomotic leak, esophageal stricture, and recurrent TEF formation.[24,25] These complications have important implications for postoperative respiratory care. Even infants with successful anastomoses may develop persistent respiratory problems. In a study of 31 adolescents who had previously undergone esophageal atresia repair, 41% experienced ongoing respiratory symptoms.[26] Complications range from apnea and bradycardia to aspiration, recurrent pneumonia, and even respiratory arrest.[26,27] A common cause of persistent respiratory disease after esophageal atresia repair is gastroesophageal reflux (GER), which may be especially severe because of esophageal dysmotility, the shorter length of the esophagus, and possible concomitant hiatal hernia.[28] All infants with esophageal atresia must be treated medically for GER; however, many of these infants may later require operative management with an antireflux procedure.

With precise preoperative, perioperative, and postoperative management, the survival rate for infants with esophageal atresia is greater than 95%, with mortality associated with low birth weight and cardiac comorbidities.[29] The respiratory care during each phase must be tailored with an understanding of the pathophysiology of each malformation and its related complications.

Clinical Highlight

A 36-week gestational age baby boy was born by normal spontaneous vaginal delivery. Apgar scores were noted as 1 at 1 minute, 6 at 5 minutes, and 8 at 10 minutes. The patient had continued apnea after deep suctioning and was subsequently endotracheally intubated. On examination, breath sounds revealed inspiratory stridor, a holosystolic murmur was noted on cardiac auscultation, and a nasogastric tube was unable to pass, with resistance met at 10 cm. The infant was also seen to have low-set, simple hypoplastic cupped ears. Echocardiogram revealed patent ductus arteriosus (PDA) with intact ventricular septum and hypoplastic right ventricle. The patient was diagnosed with CHARGE (*c*oloboma, *h*eart defects, *a*tresia choanae, growth *r*etardation, *g*enital abnormalities, and *e*ar abnormalities) syndrome.

TRACHEOMALACIA

Tracheomalacia is defined by excessive tracheal collapse from anterior cartilaginous abnormalities, posterior coaptation, or extrinsic compression from aberrant vasculature (Figure 23-3). It is commonly associated with esophageal atresia. In its mild form, the disorder may present with chronic cough (often described as "barking") and recurrent infection in the setting of poor clearance of secretions. In its more severe form, patients may present with stridor, respiratory distress, or acute life-threatening events (ALTEs).[30] Diagnosis is made by bronchoscopy while spontaneously breathing. A collapse of greater than 50% during expiration is diagnostic. Tracheomalacia can be treated by suspending the aorta (and thus the attached anterior wall of the trachea) by aortopexy and more recently by posterior tracheopexy, with promising early results.[31]

MEDIASTINAL TUMORS

Mediastinal tumors can be an important threat to the airway in the pediatric population. If they are compressing the airway and are unrecognized, even light sedation can result in obstruction and an airway emergency.

Mediastinal tumors are typically classified by the anatomic compartment from which they arise: anterior, middle, or posterior. The anterior compartment lies behind the sternum, medial to the pleura and anterior to the pericardium, great vessels, and trachea. This area of the mediastinum notably houses the thymus, as well as lymph nodes, fatty tissue, and sometimes thyroid tissue. Approximately half of mediastinal tumors arise in the anterior compartment, and they are often found to be lymphomas (B-cell, T-cell, Hodgkin), germ cell tumors, tumors or cysts of the thymus, or thyroid goiters. The middle mediastinum lies beneath the anterior compartment and anterior to the anterior border of the spine. The heart and great

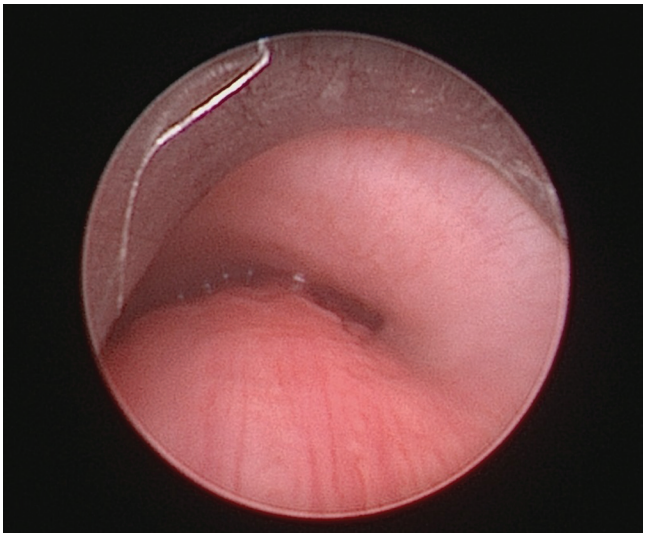


FIGURE 23-3 Bronchoscopic view of tracheomalacia demonstrating collapse of the airway.

Table 23-1 Shamberger Risk Assessment Box for Anterior Mediastinal Masses

RISK CLASS	PEAK EXPIRATORY FLOW RATE (% PREDICTED)	TRACHEAL CROSS-SECTIONAL AREA (% PREDICTED)	ANESTHETIC TECHNIQUE
(A) Moderate	>50%	<50%	LA or GA with spontaneous respiration (avoid muscle relaxation)
(B) Low	>50%	>50%	GA
(C) High	<50%	<50%	LA only
(D) Moderate	<50%	>50%	LA or GA with spontaneous respiration (avoid muscle relaxation)

GA, General anesthesia; *LA*, local anesthesia.

vessels are contained here as well as the trachea, major bronchi, and hilar lymph nodes. Masses found in this compartment are commonly lymphomas (Hodgkin and non-Hodgkin), **bronchogenic cysts,** pericardial cysts, germ cell tumors, or vascular anomalies. The posterior compartment contains the esophagus, aorta, sympathetic chain, and lymphatics. This is a common location in which to find neuroblastoma, ganglioneuroma, and foregut cysts.

Anterior tumors may present with respiratory complaints or compromise, at times acutely. Mass effect on the airway can result in dyspnea, stridor, and wheezing. Ominous findings include a patient who refuses to leave a seated position because of difficulty breathing. A chest radiograph for nonspecific respiratory symptoms often picks up the underlying problem. The RT may be asked to assist with respiratory support during a follow-up computed tomography (CT) scan. These patients must be approached with significant caution, because even light sedation or supine positioning can result in severe compression of the airway and inability to intubate using standard techniques. Emergent intubation by rigid bronchoscopy or even ECMO may be needed in such situations. Similarly, planning for a biopsy must be approached with extreme care. The Shamberger Risk Assessment Box (Table 23-1) is used to estimate the patient's risk for loss of the airway with general anesthesia based on measured peak expiratory flow rate and tracheal compression seen on imaging.[32] High-risk patients often require awake biopsy under local anesthesia, sitting upright.

LUNG

CONGENITAL DIAPHRAGMATIC HERNIA AND EVENTRATION

Congenital Diaphragmatic Hernia

The diaphragm forms when the pleura and peritoneum fuse between the fourth and tenth weeks of embryonic life. A **congenital diaphragmatic hernia** (CDH) occurs with failure of fusion of these layers. The location of the diaphragmatic hernia is typically posterolateral (Bochdalek hernia) and most commonly identified on the left but may also be right-sided, retrosternal or peristernal (Morgagni), or central. The overall incidence of CDH is about 1 per 2500 live births. The defect ranges in size from 2 to 3 mm to complete absence of the diaphragm. The herniated contents cause compression of the ipsilateral lung bud during branching of the vasculature and bronchi, which is a critical phase of lung development. The timing and development of the defect may underlie subsequent issues with pulmonary hypoplasia and pulmonary hypertension, although unifying underlying genetic mutations may also explain the interplay between the diaphragmatic hernia, pulmonary hypertension, and pulmonary hypoplasia. The contralateral lung may be compressed as well from shifting of the mediastinum (Figure 23-4). For patients with CDH, all lung tissue is hypoplastic, including the pulmonary vasculature, even on the contralateral "good" side. Histologic studies demonstrate increased musculature in the media of the arterioles. After birth, hypoxia, hypercapnia, and acidosis develop, causing constriction of the arterioles, which exacerbates pulmonary hypertension and persistent fetal circulation.

The diagnosis of CDH may be established with prenatal ultrasound. Estimates of lung volume directly or

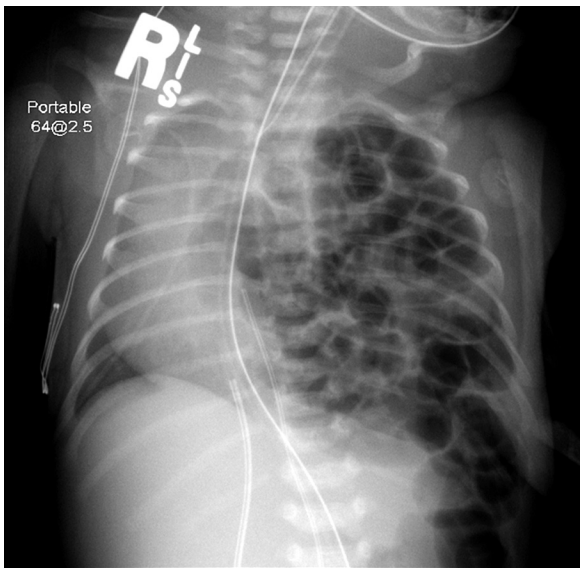


FIGURE 23-4 Radiograph of a left-sided congenital diaphragmatic hernia. Note the shift of the mediastinum to the right.

by comparison to other anatomic structures (lung-to-head ratio) may prognosticate outcome, but there is no agreed-upon precise method. Further detail may be obtained with fetal magnetic resonance imaging, with which a percentage of predicted lung volume may be calculated.[33]

Clinically, infants with CDH develop respiratory distress shortly after birth from pulmonary hypoplasia and associated pulmonary hypertension. The diagnosis of CDH is confirmed by chest radiography showing bowel in the chest and often the tip of a nasogastric tube superior to the diaphragm, but it is suggested in a tachypneic newborn with a scaphoid abdomen. Breath sounds are diminished on the side of the lesion, and heart sounds may be shifted contralaterally.

After diagnosis, resuscitation must begin immediately in the delivery room. The aim is to prevent hypoxia or significant hypercapnia and acidosis. A large orogastric tube is placed to decompress the stomach and gastrointestinal tract. Bag–valve mask ventilation is avoided when possible, to prevent the intrathoracic stomach and intestine from becoming distended and causing tension physiology and to avoid barotrauma. An endotracheal tube (ideally cuffed, if feasible) is inserted without delay, and the infant is placed on mechanical ventilation, while avoiding high-peak inspiratory pressures that may, again, cause barotrauma to the hypoplastic lungs. Close attention must be paid to acid-base balance and $Paco_2$. A "permissive hypercapnia" strategy is typically adopted, exchanging mildly increased $Paco_2$ and decreased pH for gentler ventilation and decreased potential for barotrauma.[34,35] Conventional and alternative ventilation strategies are discussed later. Lines are placed for central venous access and arterial blood pressure monitoring. A mean arterial blood pressure goal greater than 50 mm Hg may be needed to assist the right heart in overcoming potential pulmonary vascular resistance. In cases of cardiopulmonary collapse, ECMO is used as rescue therapy.

Operative repair of the hernia reverses neither pulmonary hypertension nor hypoplasia. The timing of operative repair is controversial but does not appear to affect outcome. Repair is generally delayed until the infant becomes clinically stable.[36] If small, the defect is repaired with permanent sutures alone. Larger defects may require a prosthetic patch. After surgical repair, air and then fluid may remain in the ipsilateral pleural space, because the hypoplastic lung parenchyma does not completely fill its hemithorax. A chest tube is often left in place for 1 to 2 days postoperatively on waterseal; however, this practice varies. When present, negative-pressure drainage should be used with caution, because rapid ipsilateral shifting of the mediastinal structures and contralateral lung may cause tissue damage or obstruction of central vascular structures.

After repair, most infants remain intubated for days to weeks. Low-volume strategies are continued to avoid barotrauma. During this time, patients remain at risk of persistent pulmonary hypertension. This elevation in pulmonary vascular resistance will increase right-to-left shunting via a patent ductus arteriosus or patent foramen ovale, therefore worsening hypoxia and acidosis. Both preoperatively and postoperatively, multiple modalities are used to decrease the amount of pulmonary artery vasoconstriction and support the right heart, including inotropes, lusitropes, and pulmonary vasodilators. Epinephrine, dopamine, dobutamine, and milrinone may be used to augment right heart contractility and overcome pulmonary hypertension. The side-effect profile of each medication is important to consider. Epinephrine and dopamine also cause vasoconstriction and elevate systemic vascular resistance, which may reverse right-to-left shunting at the cost of requiring increased work from the right heart. Dobutamine increases contractility, with mild vasodilatory effects. Milrinone increases contractility and diastolic relaxation but can cause significant vasodilation. Sildenafil, a phosphodiesterase inhibitor, is a pulmonary vasodilator. To limit right heart strain, prostaglandins are often administered to preserve the patency of the ductus arteriosus and permit ongoing right-to-left shunting. Bosentan, an endothelin inhibitor, may decrease pulmonary vasoconstriction. Additionally, inhaled nitric oxide (iNO) is a potent pulmonary vasodilator, and its use in pulmonary hypertension has been established; however, survival benefit is unclear.[36,37] A randomized double-masked controlled multicenter trial indicated that using iNO for infants with CDH did not reduce mortality or the need for ECMO.[38] ECMO is used to stabilize patients with pulmonary hypertension refractory to all other measures. There is substantial variability among centers regarding the use of conventional ventilation, nonconventional ventilation (high-frequency oscillatory ventilation and high-frequency jet ventilation), and ECMO.[36]

Diaphragmatic Eventration

Eventration of the diaphragm is an abnormal intrusion of the diaphragm into the thoracic space on one or both sides. It can be congenital or acquired. In congenital cases, there is no true defect (unlike CDH), but normal musculature is either thinned or completely absent, resulting in doming of the diaphragm. Acquired eventration is usually the result of a phrenic nerve injury during cardiothoracic surgery or birth trauma.

Respiratory impairment as a result of eventration is variable. Neonates may have severe respiratory distress resulting in the need for mechanical ventilation. On the other hand, eventration in older children is not uncommonly an incidental finding in a previously asymptomatic child. The diagnosis typically can be confirmed with ultrasound or fluoroscopy demonstrating paradoxical movement of the affected side. Surgical treatment involves diaphragm plication or

resection, and repair is often recommended in symptomatic congenital cases. In acquired cases, however, nerve function may return over 6 months to a year; thus initial care is often supportive. However, surgical repair may be performed if function does not return and the patient remains symptomatic.

CONGENITAL PULMONARY AIRWAY MALFORMATION

Congenital lung lesions include a range of developmental anomalies of the lung and tracheobronchial tree, including **congenital pulmonary airway malformations, bronchopulmonary sequestration, congenital lobar emphysema,** and bronchogenic cyst. It is not uncommon to find congenital lung lesions that simultaneously demonstrate features of more than one type at a time, suggesting a common underlying etiology.

Congenital pulmonary airway malformation (CPAM) is an anomaly of the lower respiratory tract that results in a cystic mass of abnormal lung tissue (Figure 23-5). Histologically, there is an overabundance of terminal respiratory bronchioles, resulting in abnormal alveoli. CPAM lesions are often characterized by the Stoker classification system; however, it is more useful clinically to group them into microcystic or macrocystic subtypes.[39] In both subtypes, the lesions found are not true cysts, and they do in fact communicate with the airways. Macrocystic lesions tend to affect one lobe with a dominant cyst and smaller daughter cysts. Microcystic lesions are more uniform in appearance and confer a worse overall prognosis, in part because of their association with other developmental anomalies. Lesions are often discovered prenatally and can be asymptomatic at birth.[40] Symptoms can result, however, from air trapping and compression of normal surrounding lung. Larger lesions may even require intervention *in utero,* because compression caused by the expanding lesion can be associated with hydrops fetalis and myocardiopathy, both of which are associated with a poor prognosis.[41] In such cases, prenatal interventions ranging from thoracoamniotic shunt to fetal thoracotomy have been used.[42]

Although CPAMs are benign lesions, they can result in recurrent infections. In addition, these lesions can harbor or in fact represent undiagnosed malignancy, especially pleuropulmonary blastoma. Hence lesions that are both solid and cystic or those that grow disproportionately to the size of the child are of concern for being malignant tumors that require aggressive investigation and treatment. Resection of the lesion with a lobectomy is recommended, in part because preoperative imaging has poor sensitivity for detecting secondary lesions distant from the primary lesion.[43] Depending on the size of the lesion, the resection can often be performed using minimally invasive techniques (i.e., thoracoscopically).

BRONCHOPULMONARY SEQUESTRATION

Bronchopulmonary sequestration describes a focus of nonfunctioning lung tissue that lacks a bronchial connection to the normal tracheobronchial tree. Typically sequestrations appear as solid lesions; however, they may in some cases be aerated through collateral channels (i.e., pores of Kohn). There are two types of bronchopulmonary sequestrations, based on whether the lesion is contained within investing pleura of the lung: intralobar and extralobar. Both types typically have a systemic arterial blood supply (Figure 23-6). In intralobar sequestrations, the venous drainage is usually into the pulmonary veins. In contradistinction, in extralobar sequestrations, the drainage is into systemic veins (azygos or hemiazygos vein, inferior vena cava, or right atrium). However, vascular inflow and outflow patterns are widely variable. The extralobar subtype has a separate visceral pleural envelope and may even lie within the abdomen. The defect in development

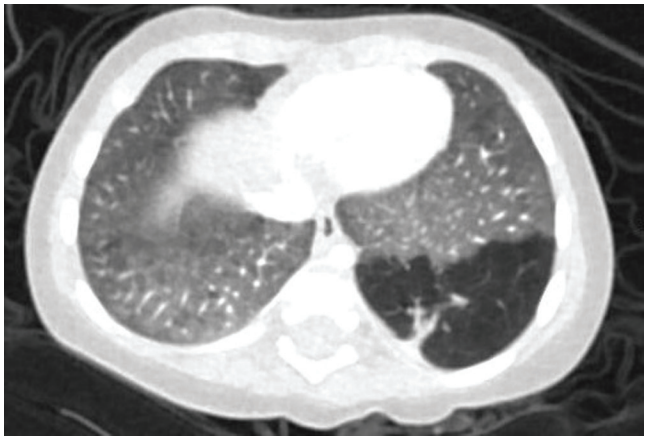


FIGURE 23-5 Computed tomographic appearance of left lower lobe congenital pulmonary airway malformation.

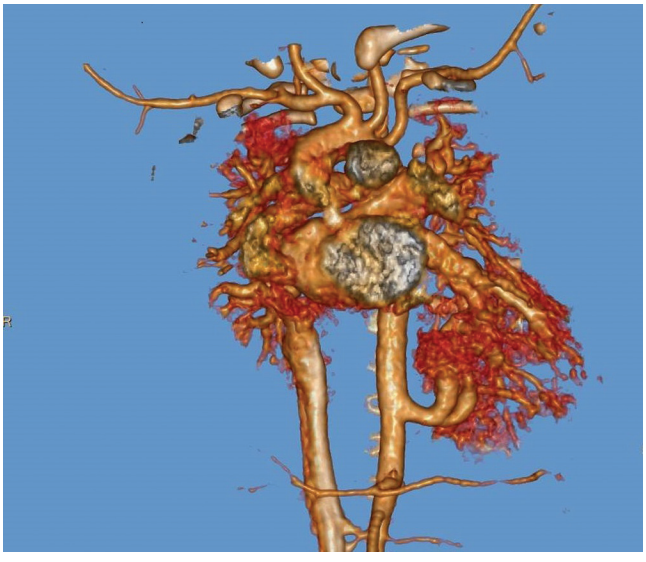


FIGURE 23-6 Bronchopulmonary sequestration with direct arterial supply from the descending aorta.

may be caused by migration of an accessory lung bud before separation of the systemic and pulmonary circulations.[44] Sequestrations are most commonly located in the posterior basal segment of the left lower lobe.

Delayed diagnosis of sequestration is common. For intralobar lesions, presentation typically occurs later in life with recurrent infection of an occult lesion. Extralobar lesions are often associated with other congenital anomalies, including cardiac disease, congenital diaphragmatic hernia, and vertebral deformities. Early symptoms may be related to a vascular shunt through the sequestration, which can lead to heart failure if severe. A homogeneous dense lesion may be seen on a chest radiograph.[45] If sequestration is suspected, CT angiogram may be diagnostic and also help define the vascular anatomy for operative planning. The systemic arterial supply may arise directly from the aorta, including potentially from the intraabdominal aorta with branches traversing the diaphragm.

Curative resection is performed early in the course for patients with symptomatic lesions as well as patients with large lesions. Elective resection is typically performed for asymptomatic sequestrations, largely because of infectious risk. Thoracoscopic resection is often possible.

CONGENITAL LOBAR EMPHYSEMA

Congenital lobar emphysema (CLE) is defined by overdistention of one or more lobes of the lung, most frequently the left upper lobe.[46] Air enters but cannot escape because of obstruction of a segmental or lobar bronchus. This often occurs due to a weakness in the bronchial cartilage (a variant of bronchomalacia), leading to air trapping. An aberrant artery or vascular ring may alternatively compress the bronchus during expiration. Progressive lobar distension leads to emphysematous changes of the parenchyma. In severe cases, massive overdistention can prevent normal gas exchange in the surrounding lung and even cause cardiovascular collapse by obstructing systemic venous return to the right atrium.[47]

CLE may be confused on radiography with pneumothorax, pneumonia, and other conditions. If pneumothorax is suspected, a chest tube may be inadvertently inserted into the emphysematous lobe. Normal lung in proximity to the diseased lung tissue may be collapsed and appear atelectatic or consolidated (Figure 23-7). Thus a child with respiratory distress and such a radiograph may be erroneously thought to have pneumonia. The true diagnosis is critical to recognize early in the symptomatic course, especially given the general tendency to hyperventilate a child in respiratory distress. In the case of lobar emphysema, hyperventilation can hasten circulatory collapse by rapidly overdistending the affected lobe.

Treatment of symptomatic lesions involves early resection. In severe cases, emergent thoracotomy in the newborn period may be needed to release compression of surrounding structures by a quickly expanding lesion. Alternatively, for asymptomatic patients with congenital lobar emphysema, nonoperative management is feasible, given the low long-term risk of complications, but serial surveillance studies and attentive examinations would be required.

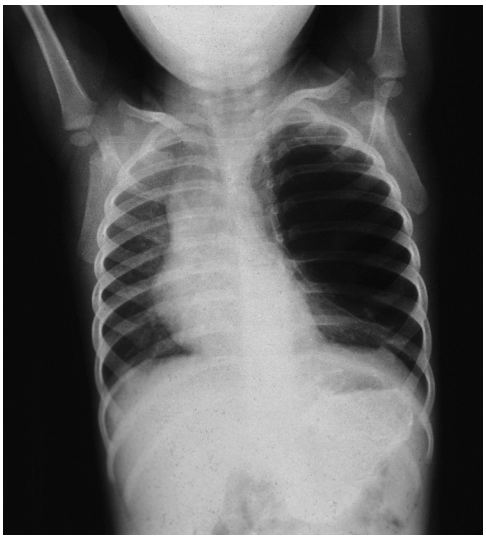


FIGURE 23-7 Radiograph of a newborn child with left-sided congenital lobar emphysema.

FOREGUT DUPLICATION CYST

Bronchogenic cyst is the most common foregut duplication cyst and can occur throughout the trachea and bronchi. They are embryologically related to other types of foregut cysts such as esophageal duplication cysts, gastric and duodenal duplication cysts, and neurenteric cysts and thus may have mixed characteristics shared with these lesions. Most commonly, bronchogenic cysts are lined by respiratory epithelium. However, the lumen is not connected to the bronchial tree, and the lesions are nonfunctional. They can be located within or outside the thoracic cavity. When intrathoracic, the cyst may be located in the bronchial wall, the pleura, the mediastinum, or the lung parenchyma.[48]

Presenting symptoms and timing of diagnosis are often dictated by the anatomic level of the lesion. Most bronchogenic cysts are discovered within the first few years of life. The diagnosis may be apparent radiologically in a newborn with respiratory distress or an older child with recurrent pulmonary infection. Symptoms are often related to airway compression and include dyspnea, wheezing, and recurrent pneumonias. Plain film radiographs may reveal a circular or ovoid mass with smooth edges. CT imaging will confirm the suspected diagnosis and should include the abdomen for the possibility of a concurrent abdominal duplication cyst.

Resection is recommended and can often be accomplished thoracoscopically. The extent of resection will

depend on the location of the cyst and any associated inflammatory conditions. If vertebral anomalies are also seen, magnetic resonance (MR) imaging should be performed to rule out a neurenteric cyst (i.e., foregut cyst with extension into the spinal canal), which would require a multidisciplinary team, including neurosurgery, for adequate treatment. Cysts that cannot be safely resected from the airway may be partially resected (i.e., subtotal resection) with mucosal stripping performed on the retained segment. Controversy persists regarding the need for resection of asymptomatic lesions. However, resection is generally recommended because of the potential for bleeding, rupture, infection, and malignant transformation.[49]

POSTOPERATIVE MANAGEMENT AFTER THORACIC SURGERY

Postoperatively after thoracic surgery, the patient may have a chest tube depending on the risk of air leak from the lung parenchyma or fluid accumulation. This is often removed within days of the operation, provided there is not excessive drainage or persistent pneumothorax. Adequate pain control is crucial, enabling the patient to breathe deeply and avoid ventilation–perfusion mismatch from atelectasis. For children too young to understand the use of incentive spirometry, instructing them to blow soap bubbles or spin a windmill will achieve the same effect. Patient-controlled analgesia (for an older child), epidural analgesia, paravertebral and intercostal nerve blocks, and intravenous narcotics are all important postoperative pain control strategies. Adequate analgesia also permits chest physiotherapy, which is crucial in the recovery process.[50]

THORAX

PECTUS EXCAVATUM

Chest wall and thoracic malformations can have significant effects on a child's self-esteem, respiratory performance, and overall quality of life. They can range from mild deformities that have primarily cosmetic implications, with the attendant impact on self-esteem, to severe deformities with nontrivial morbidity.

The most common congenital disorder of the chest wall is **pectus excavatum,** comprising almost 90% of chest wall deformities.[51] The defect can range from small to large and shallow to deep. There is no consensus as to the etiology of pectus excavatum. Familial cases have been reported; however, most occurrences of pectus excavatum are sporadic. A male-to-female ratio of 4:1 is reported in the literature.[52] Connective tissue disorders, such as Marfan syndrome, Ehlers-Danlos, and osteogenesis imperfecta, are also associated with pectus excavatum.[53] For clarification, neonates may present with chest wall retraction during respiration as a result of the pliability of the chest wall. This has been termed *pseudopectus excavatum* and often disappears by 6 months of age.

Chest wall defects progress with the child's growth. During infancy the defect may be asymptomatic, but as the chest wall becomes more rigid and activity is increased, symptoms subsequently may develop. With a decreased anteroposterior diameter of the chest, the lungs may not fully expand. The pectus defect may reduce ventricular filling and stroke volume, further decreasing exercise tolerance.[54] Arrhythmias are another potential sequela of the altered chest wall diameter. Significant psychosocial effects are seen in these patients. Embarrassment in front of peers when they take off their shirt may decrease self-esteem. Surgical repair has been shown to alleviate these effects.[55]

Pectus excavatum repairs are believed to be optimally performed after 13 to 14 years of age, although a consensus has not been reached. Repairing the defect at too young an age may predispose to recurrence during the pubertal growth spurt.[52,56] As children progress through puberty, cartilage ossifies. The ossification of chest wall cartilage will make more extensive procedures necessary in the future. Secondary scoliosis may also develop if the defect is not repaired.

Choice of operative approach is currently dictated by surgeon preference. The standard open approach for repair of pectus excavatum was first described in 1912 and modified by Ravitch in 1949. This repair involves a transverse incision along the inframammary crease with exposure and resection of the involved cartilage. The sternum is then elevated and a strut is left in place. Within the last 15 years, a minimally invasive approach pioneered by Nuss has gained traction.[57] Bilateral incisions are made on the lateral chest, and a retrosternal bar is passed between the sternum and the heart. The bar is then rotated 180 degrees, forcing the sternum anteriorly. The bar is left in place, with annual follow-up appointments documenting growth and activity level. Although most bars are left in place at least 2 years, some authors recommend delaying bar removal at least 4 years and until the patient is older than 18 years.[58]

Postoperative pain is significant after either repair and should be aggressively controlled to allow deep breaths. Practices vary; however, regional blocks and epidurals can be highly successful and avoid the constipation issues seen commonly with narcotic-based regimens.

ASPHYXIATING THORACIC DYSTROPHY (JEUNE SYNDROME)

Jeune syndrome, or asphyxiating thoracic dystrophy, is a rare osteochondrodystrophy with an autosomal recessive inheritance pattern. Development of the cartilage and bones is affected, impacting the rib cage, pelvis, and extremities. Symptoms can range from mild to severe. It is a type of thoracic insufficiency syndrome, because the chest cavity is decreased in both the anteroposterior and superoinferior orientations.

This leads to pulmonary hypoplasia as a result of the decreased cavity size, and after birth the lungs are not able to fully expand. Multiple associated defects, including polydactyly, hypoplastic iliac wings, and fixed clavicles, may be seen. Heart, renal, and airway abnormalities (subglottic stenosis) may also be present. Surgical efforts typically focus on augmenting the volume of the thoracic cavity to allow for greater lung expansion. Recent surgical advances with expansion thoracoplasty have been successful.[59] The technique involves anterior and posterior rib osteotomies. This creates a mobilized segment that is then attached to the titanium prosthesis, which is anchored to the superior and inferior ribs. This procedure expands the chest cavity and allows the lungs to expand and grow. Respiratory failure requiring chronic ventilation and tracheostomy can result.

SCOLIOSIS AND KYPHOSCOLIOSIS

Scoliosis is curvature of the spine in a side-to-side direction, whereas kyphosis describes anteroposterior curvature. The resulting chest wall deformity seen with these malformations, especially early in life, may decrease lung capacity and lead to restrictive pulmonary function. In the most severe form, kyphoscoliosis may lead to secondary chest wall deformities. Severe cases may be treated with bracing or surgery.[60]

ABDOMEN

GASTROESOPHAGEAL REFLUX

GER is defined as the passage of gastric contents into the esophagus. GER is common even among healthy neonates and may cause only mild symptoms involving feeding intolerance and feeding irritability. More severe cases, however, may contribute to respiratory events. Reflux leading to aspiration can result in recurrent pneumonias and chronic lung disease. During RT evaluation of a child requiring respiratory support, any child with a history of reflux seen in the hospital should be considered for aspiration precautions with elevation of the head of the bed, right lateral decubitus positioning, acid blockade, and/or decompression of the stomach to avoid aspiration. In addition, there may be an association between GER and ALTEs, which sometimes improve with acid blockade. Other respiratory symptoms exacerbated by GER include reactive airway disease and chronic cough, although other underlying causes should be carefully evaluated.

ABDOMINAL COMPARTMENT SYNDROME

After intraperitoneal fluid shifts related to prior surgery or intraabdominal pathology (e.g., pancreatitis), intraabdominal hypertension may develop and lead to **abdominal compartment syndrome** (ACS).[61] ACS is defined as an intraabdominal pressure of more than 20 mm Hg with associated organ dysfunction. Symptoms of ACS include acute kidney injury related to proinflammatory cytokines, venous compression, and local renal compression, as well as competition with diaphragmatic excursion. Abdominal pressures can be measured via the bladder using a Foley catheter transducer. Treatment involves relieving intraabdominal hypertension by positioning (flat and supine), gastric and rectal tube placement, neuromuscular blockade, peritoneal drainage catheter placement, or decompressive laparotomy.[62] Patients with a tense abdomen and increasing peak inspiratory pressures on the ventilator should be promptly evaluated for this diagnosis.

ABDOMINAL WALL DEFECTS (OMPHALOCELE AND GASTROSCHISIS)

Congenital abdominal wall defects such as **omphalocele** and **gastroschisis** have important implications for respiratory performance in a newborn infant. The abdominal wall is formed from four embryonic folds—one cephalic, one caudal, and two lateral—composed of splanchnic and somatic tissue. If these folds that contribute to the body wall fail to develop normally, an abdominal wall defect may occur.[63]

Omphalocele

The defect in an omphalocele always occurs at the umbilicus, and the eviscerated abdominal contents are covered by a peritoneal sac (although rupture may occur) (Figure 23-8). Omphalocele is differentiated from gastroschisis by its sac, its location through the umbilicus, and common association with other defects. An omphalocele occurs early during fetal development, at the time of organogenesis, and other defects are common. Concomitant anomalies may include cardiac, sternal, hindgut, and bladder defects. Associated cardiac defects are the most common, and thus an echocardiogram is required in all infants with omphalocele. Many patients have aneuploidy. Diagnosis is often made during prenatal visits with ultrasonography. Elevated levels of alpha fetoprotein in the maternal serum and amniotic fluid are often present.[64] After

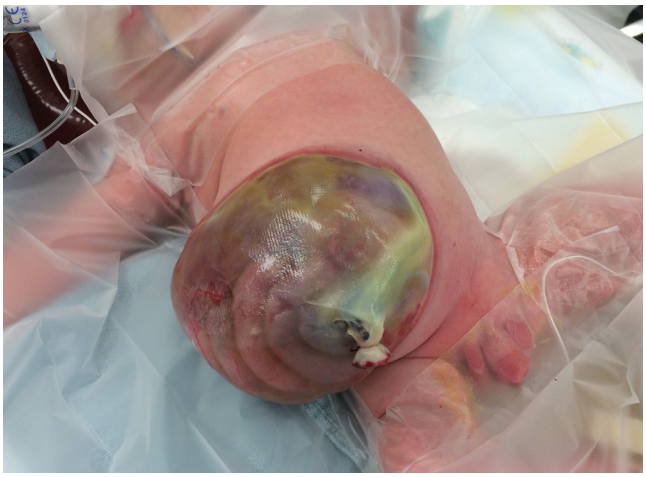


FIGURE 23-8 Omphalocele.

delivery, the gastrointestinal tract should be decompressed with nasogastric suction. Timing and type of repair are determined by the size of the defect and associated anomalies. If the defect is small and no congenital heart disease exists, early primary repair is often performed. Even in the case of relatively small omphalocele repair, there may be significant abdominal competition after the operation, affecting respiratory care. At the time of closure in the operating room, gastric pressures and respiratory mechanics can be assessed. For larger omphaloceles or those associated with heart disease, a delayed repair or "paint and wait" approach is commonly adopted. The sac is treated with silver sulfadiazine cream to allow it to thicken, and repair is performed months to years later, when it is safer and the necessary abdominal domain has been gained. In large omphaloceles, the defect may include the liver, which should be handled with care to prevent liver laceration or hepatic vein injury. Postoperative complications after repair of giant omphalocele include prolonged mechanical ventilation and other sequelae of increased abdominal competition.[65]

Gastroschisis

Gastroschisis is another disorder of abdominal wall formation. In this defect, the herniation occurs to the right of the umbilicus, rather than through it. This anomaly develops later in gestation than does omphalocele; associated defects are not usually seen, with the exception of intestinal atresias, which occur in 15% of patients.[66] The herniated viscera are not covered by peritoneum. After delivery, the gastrointestinal tract should be decompressed via a nasogastric tube, as in the case of omphalocele. Because the viscera are exposed, the infant should be placed in a sterile bowel bag to prevent evaporative fluid loss and protect the bowel. Operative repair is aimed at reducing the viscera and closing the defect. Often this may be done primarily and soon after birth. In other cases, the abdominal contents may be too distended or matted to achieve primary closure. In these instances a spring-loaded silo is placed over the intestines (Figure 23-9). The spring-loaded portion is placed in the abdominal cavity. Sequential tightening of the sac reduces the viscera until they are contained within the abdominal cavity, which then allows definitive closure. Similar to omphalocele, reduction of the herniated intestines can result in abdominal competition, affecting a neonate's respiratory performance.

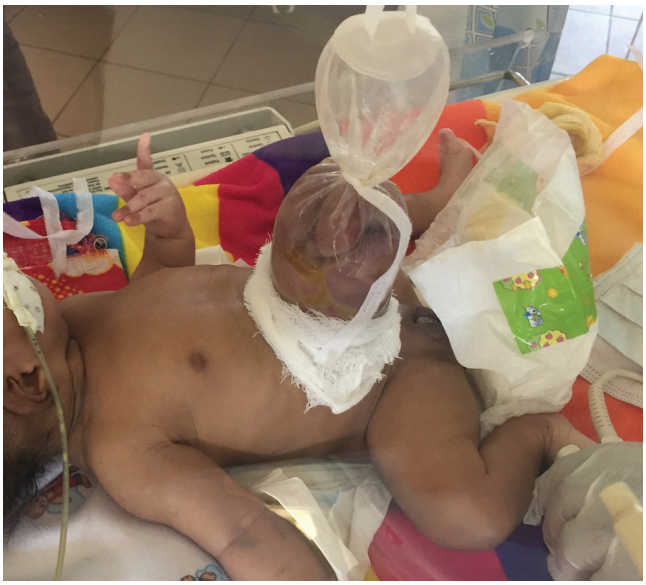


FIGURE 23-9 Gastroschisis in silo.

Reports in the literature have described different methods for closure of the abdominal wall defect. Bianchi and colleagues developed a method of reducing the abdominal contents without anesthesia in the neonatal intensive care unit. This technique avoids the complications of endotracheal intubation and mechanical ventilation. The extent and rate of reduction are monitored using the awake infant's reactions.[67] A sutureless closure has been reported by Sandler et al.[68,69] In this technique, the eviscerated contents are reduced until they can be contained within the abdominal cavity, and the defect is closed with the umbilical cord used as a biologic patch. An adhesive dressing is then applied. There may be improved cosmetic outcome with the umbilicus in the natural position. The technique's simplicity may comprise another advantage, given that it can be performed at the bedside.

Key Points

- Infants diagnosed with bilateral choanal atresia may develop immediate respiratory distress. An oral airway should be inserted and maintained until the infant is taken to the operating room for definitive care.
- Treatment for macroglossia is dependent on the severity of respiratory obstruction and may require treatments ranging from simple prone positioning to surgical reduction of the tongue.
- Esophageal atresia and tracheoesophageal fistula most commonly present with a blind-ending upper esophageal pouch with an associated fistula from the lower trachea that leads to the distal esophagus.
- Symptoms associated with esophageal atresia with tracheoesophageal fistula include drooling, choking, and cyanosis with feeding and inability to pass a nasogastric tube. Continuous suction of the nasogastric tube with frequent saline irrigations should be initiated to prevent aspiration and respiratory complications.

- The *in utero* formation of the diaphragm occurs between the fourth and tenth weeks of gestation. Failure of closure is most commonly posteriorly on the left side, called a *Bochdalek congenital diaphragmatic hernia.* This allows herniation of abdominal contents, subsequent compression of the contralateral thoracic structures, mediastinal shift, and pulmonary hypoplasia.
- Infants with congenital diaphragmatic hernia present in respiratory distress. Important practices include immediate gastric decompression with an orogastric tube, endotracheal tube intubation (with avoidance of excessive bag–mask ventilation and high airway pressures), and permissive hypercapnia.
- Bronchogenic cysts and congenital pulmonary airway malformations may present in a newborn with respiratory distress or in an older child with recurrent pneumonia. Pulmonary sequestrations present with a potentially large shunt, heart murmur, obstructive respiratory symptoms, and possibly recurrent infection. Congenital lobar emphysema may present with airway obstruction at the main bronchus or trachea, requiring emergent surgical intervention.
- Pectus excavatum occurs as a result of deformity of the cartilaginous ends of the ribs, causing inward curvature of the sternum. Surgical correction includes passing a retrosternal bar between the sternum and heart to apply anterior pressure on the sternum.
- Patients with anterior mediastinal tumors must be approached with caution, given that light sedation or supine positioning can result in airway compression, respiratory distress, and difficult intubation.

Assessment Questions

1. An infant brought to the neonatal intensive care unit (NICU) presents with cyanosis and upper airway obstruction relieved by crying, with improvement in color. Suspecting choanal atresia, the best action is to:
   - **A.** Insert a no. 8 Fr suction catheter to verify the diagnosis.
   - **B.** Insert an oral airway.
   - **C.** Start nasal continuous positive airway pressure.
   - **D.** Provide heated humidity.
   - **E.** Stimulate the infant to induce crying.
2. Complications related to chronic upper airway obstruction from anatomic malformations result in which of the following?
   - **I.** Chronic hypoxia and carbon dioxide retention
   - **II.** Pulmonary hypertension and cor pulmonale
   - **III.** Hyperventilation and acidosis
   - **IV.** Failure to thrive
   - **V.** Congestive heart failure
   - **A.** I, III
   - **B.** I, II, IV
   - **C.** I, II, III, V
   - **D.** II, III, IV
   - **E.** II, IV, V
3. The most common tracheoesophageal fistula and esophageal atresia lesion is classified as which type?
   - **A.** Esophageal atresia with a long gap
   - **B.** Esophageal atresia with distal tracheoesophageal fistula
   - **C.** H-type tracheoesophageal fistula
   - **D.** Esophageal atresia with proximal fistula
   - **E.** Esophageal atresia with proximal and distal tracheoesophageal fistulae
4. A drooling newborn infant with polyhydramnios *in utero* and suspected kidney and cardiac anomalies is admitted to the NICU and presents with coughing, respiratory distress, and cyanosis during feedings. The most likely diagnosis is:
   - **A.** Gastroschisis
   - **B.** Tetralogy of Fallot
   - **C.** Pulmonary sequestration
   - **D.** Esophageal atresia with tracheoesophageal fistula
   - **E.** Choanal atresia
5. Which of the following statements are true concerning congenital diaphragmatic hernia (CDH)?
   - **I.** Pulmonary hypoplasia is present in both lungs.
   - **II.** Persistent pulmonary hypertension is the main complication.
   - **III.** Surgical correction results in complete reversal of the respiratory distress.
   - **IV.** CDH formation is a defect that occurs very early in gestational age.
   - **V.** The right lung (contralateral side) is not usually affected.
   - **A.** I, II, IV
   - **B.** I, III, IV, V
   - **C.** I, IV, V
   - **D.** II, III, IV, V
   - **E.** II, III, V
6. A 3200-g term infant male is born to a healthy mother. Apgar scores are 7 and 5, with the infant gasping and heart rate decreasing to 90. Physical examination reveals cyanosis, a scaphoid abdomen, and visible tracheal deviation to the right. Considering this information, the only appropriate action would be to:
   - **A.** Get a blood gas.
   - **B.** Bag–mask ventilate.
   - **C.** Suction and stimulate vigorously.
   - **D.** Insert an oral suction catheter to vent the stomach.
   - **E.** Vigorously stimulate and give 100% blow-by oxygen.
7. Considering a likely diagnosis of congenital diaphragmatic hernia, which of the following would be appropriate concerning ventilator strategy?
   - **A.** Hypoxic gases
   - **B.** Rapid rate and low pressures
   - **C.** High pressure and long inflation times
   - **D.** Slow rate and short inflation times
   - **E.** Low pressure with high positive end-expiratory pressure

8. A female infant was born with a large gastroschisis. The reduction surgery will most likely affect the respiratory system by causing:
   - **A.** An increase in airway resistance
   - **B.** A decrease in pulmonary compliance
   - **C.** A decrease in transpulmonary pressure
   - **D.** An increase in the respiratory time constant
   - **E.** B and D
9. When comparing gastroschisis and omphalocele, which of the following is true?
   - **A.** They are both full-thickness defects of the abdominal wall.
   - **B.** They are both commonly associated with other anomalies.
   - **C.** Omphalocele is a midline defect, whereas gastroschisis is a lateral wall defect.
   - **D.** An omphalocele is covered by epidermal tissue.
   - **E.** Gastroschisis requires surgical reductions that often must be performed in several stages, whereas omphalocele is completed in a single surgery.
10. Pectus excavatum may be associated with which of the following?
    - **A.** Secondary scoliosis
    - **B.** Decreased exercise capacity
    - **C.** Ehlers-Danlos syndrome
    - **D.** Decreased self-esteem
    - **E.** All of the above

REFERENCES

1. Myer CM, Cotton RT. Nasal obstruction in the pediatric patient. *Pediatrics*. 1983;72:766-777.
2. Hengerer AS, Brickman TM, Jeyakumar A. Choanal atresia: embryologic analysis and evolution of treatment, a 30-year experience. *Laryngoscope*. 2008;118:862-866.
3. Stankiewicz JA. The endoscopic repair of choanal atresia. *Otolaryngol Head Neck Surg*. 1990;103:931-937.
4. Elden LM, Wetmore RF, Potsic WP. *Otolaryngologic Disorders* in Pediatric Surgery. 7th ed. Elsevier; 2012:707-728.
5. Szeremeta W, Parikh TD, Widelitz JS. Congenital nasal malformations. *Otolaryngol Clin North Am*. 2007;40:97-112; vi–vii.
6. Mueller DT, Callanan VP. Congenital malformations of the oral cavity. *Otolaryngol Clin North Am*. 2007;40:141-160; vii.
7. Follmar A, Dentino K, Abramowicz S, Padwa BL. Prevalence of sleep-disordered breathing in patients with Beckwith-Wiedemann syndrome. *J Craniofac Surg*. 2014;25:1814-1817.
8. Renault F, Flores-Guevara R, Soupre V, Vazquez MP, Baudon JJ. Neurophysiological brainstem investigations in isolated Pierre Robin sequence. *Early Hum Dev*. 2000;58:141-152.
9. Freed G, Pearlman MA, Brown AS, Barot LR. Polysomnographic indications for surgical intervention in Pierre Robin sequence: acute airway management and follow-up studies after repair and take-down of tongue-lip adhesion. *Cleft Palate J*. 1988;25:151-155.
10. Caouette-Laberge L, Bayet B, Larocque Y. The Pierre Robin sequence: review of 125 cases and evolution of treatment modalities. *Plast Reconstr Surg*. 1994;93:934-942.
11. Nargozian C. The airway in patients with craniofacial abnormalities. *Paediatr Anaesth*. 2004;14:53-59.
12. Sethi D. Airway management in a child with Treacher Collins syndrome using C-MAC videolaryngoscope. *Anaesth Crit Care Pain Med*. 2016;35:67-68.
13. Bijnen CL, Don Griot PJW, Mulder WJ, Haumann TJ, Van Hagen AJ. Tongue-lip adhesion in the treatment of Pierre Robin sequence. *J Craniofac Surg*. 2009;20:315-320.
14. MacKenzie TC, Guttenberg ME, Nisenbaum HL, Johnson MP, Adzick NS. A fetal lung lesion consisting of bronchogenic cyst, bronchopulmonary sequestration, and congenital cystic adenomatoid malformation: the missing link? *Fetal Diagn Ther*. 2001;16:193-195.
15. Ferrari LR, Zurakowski D, Solari J, Rahbar R. Laryngeal cleft repair: the anesthetic perspective. *Paediatr Anaesth*. 2013;23:334-341.
16. Rahbar R, Rouillon I, Roger G, et al. The presentation and management of laryngeal cleft: a 10-year experience. *Arch Otolaryngol Head Neck Surg*. 2006;132:1335-1341.
17. Crisera CA, Grau JB, Maldonado TS, Kadison AS, Longaker MT, Gittes GK. Defective epithelial-mesenchymal interactions dictate the organogenesis of tracheoesophageal fistula. *Pediatr Surg Int*. 2000;16:256-261.
18. Solomon BD, Bear KA, Kimonis V, et al. Clinical geneticists' views of VACTERL/VATER association. *Am J Med Genet A*. 2012;158A:3087-3100.
19. Cassina M, Ruol M, Pertile R, et al. Prevalence, characteristics, and survival of children with esophageal atresia: a 32-year population-based study including 1,417,724 consecutive newborns. *Birth Defects Res A Clin Mol Teratol*. 2016;106:542-548.
20. Foker JE, Kendall TC, Catton K, Khan KM. A flexible approach to achieve a true primary repair for all infants with esophageal atresia. *Semin Pediatr Surg*. 2005;14:8-15.
21. Chang JW, Choo OS, Shin YS, Hong J, Kim CH. Temporary closure of congenital tracheoesophageal fistula with Fogarty catheter. *Laryngoscope*. 2013;123:3219-3222.
22. Foker JE, Kendall Krosch TC, Catton K, Munro F, Khan KM. Long-gap esophageal atresia treated by growth induction: the biological potential and early follow-up results. *Semin Pediatr Surg*. 2009;18:23-29.
23. Gallo G, Zwaveling S, Groen H, Van der Zee D, Hulscher J. Long-gap esophageal atresia: a meta-analysis of jejunal interposition, colon interposition, and gastric pull-up. *Eur J Pediatr Surg*. 2012;22:420-425.
24. Liszewski MC, Bairdain S, Buonomo C, Jennings RW, Taylor GA. Imaging of long gap esophageal atresia and the Foker process: expected findings and complications. *Pediatr Radiol*. 2014;44:467-475.
25. Smithers CJ, Hamilton TE, Manfredi MA, et al. Categorization and repair of recurrent and acquired tracheoesophageal

fistulae occurring after esophageal atresia repair. *J Pediatr Surg*. 2017;52(3):424-430.
26. Malmström K, Lohi J, Lindahl H, et al. Longitudinal follow-up of bronchial inflammation, respiratory symptoms, and pulmonary function in adolescents after repair of esophageal atresia with tracheoesophageal fistula. *J Pediatr*. 2008;153:396-401.
27. Delius RE, Wheatley MJ, Coran AG. Etiology and management of respiratory complications after repair of esophageal atresia with tracheoesophageal fistula. *Surgery*. 1992;112:527-532.
28. Tong S, Mallitt KA, Krishnan U. Evaluation of gastroesophageal reflux by combined multichannel intraluminal impedance and pH monitoring and esophageal motility patterns in children with esophageal atresia. *Eur J Pediatr Surg*. 2016;26:322-331.
29. Malakounides G, Lyon P, Cross K, et al. Esophageal atresia: improved outcome in high-risk groups revisited. *Eur J Pediatr Surg*. 2016;26:227-231.
30. Fraga JC, Jennings RW, Kim PCW. Pediatric tracheomalacia. *Semin Pediatr Surg*. 2016;25:156-164.
31. Bairdain S, Smithers CJ, Hamilton TE, et al. Direct tracheobronchopexy to correct airway collapse due to severe tracheobronchomalacia: short-term outcomes in a series of 20 patients. *J Pediatr Surg*. 2015;50:972-977.
32. Shamberger RC. Preanesthetic evaluation of children with anterior mediastinal masses. *Semin Pediatr Surg*. 1999;8:61-68.
33. Madenci AL, Sjogren AR, Treadwell MC, et al. Another dimension to survival: predicting outcomes with fetal MRI versus prenatal ultrasound in patients with congenital diaphragmatic hernia. *J Pediatr Surg*. 2013;48:1190-1197.
34. Boloker J, Bateman DA, Wung JT, Stolar CJ. Congenital diaphragmatic hernia in 120 infants treated consecutively with permissive hypercapnea/spontaneous respiration/elective repair. *J Pediatr Surg*. 2002;37:357-366.
35. Wilson JM, Lund DP, Lillehei CW, Vacanti JP. Congenital diaphragmatic hernia–a tale of two cities: the Boston experience. *J Pediatr Surg*. 1997;32:401-405.
36. Puligandla PS, Grabowski J, Austin M, et al. Management of congenital diaphragmatic hernia: a systematic review from the APSA outcomes and evidence based practice committee. *J Pediatr Surg*. 2015;50:1958-1970.
37. Putnam LR, Tsao K, Morini F, et al. Evaluation of variability in inhaled nitric oxide use and pulmonary hypertension in patients with congenital diaphragmatic hernia. *JAMA Pediatr*. 2016;170:1188-1194.
38. The Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide and hypoxic respiratory failure in infants with congenital diaphragmatic hernia. *Pediatrics*. 1997;99:838-845.
39. David M, Lamas-Pinheiro R, Henriques-Coelho T. Prenatal and postnatal management of congenital pulmonary airway malformation. *Neonatology*. 2016;110:101-115.
40. Parikh DH, Rasiah SV. Congenital lung lesions: postnatal management and outcome. *Semin Pediatr Surg*. 2015;24:160-167.
41. Baird R, Puligandla PS, Laberge JM. Congenital lung malformations: informing best practice. *Semin Pediatr Surg*. 2014;23:270-277.
42. Wilson RD, Hedrick HL, Liechty KW, et al. Cystic adenomatoid malformation of the lung: review of genetics, prenatal diagnosis, and in utero treatment. *Am J Med Genet A*. 2006;140:151-155.
43. Muller CO, Berrebi D, Kheniche A, Bonnard A. Is radical lobectomy required in congenital cystic adenomatoid malformation? *J Pediatr Surg*. 2012;47:642-645.
44. Correia-Pinto J, Gonzaga S, Huang Y, Rottier R. Congenital lung lesions–underlying molecular mechanisms. *Semin Pediatr Surg*. 2010;19:171-179.
45. John PR, Beasley SW, Mayne V. Pulmonary sequestration and related congenital disorders. A clinico-radiological review of 41 cases. *Pediatr Radiol*. 1989;20:4-9.
46. Shanti CM, Klein MD. Cystic lung disease. *Semin Pediatr Surg*. 2008;17:2-8.
47. Riedlinger WFJ, Vargas SO, Jennings RW, et al. Bronchial atresia is common to extralobar sequestration, intralobar sequestration, congenital cystic adenomatoid malformation, and lobar emphysema. *Pediatr Dev Pathol*. 2006;9:361-373.
48. Sarper A, Ayten A, Golbasi I, Demircan A, Isin E. Bronchogenic cyst. *Tex Heart Inst J*. 2003;30:105-108.
49. Jiang JH, Yen SL, Lee SY, Chuang JH. Differences in the distribution and presentation of bronchogenic cysts between adults and children. *J Pediatr Surg*. 2015;50:399-401.
50. Mcllvaine WB, Chang JH, Jones M. The effective use of intrapleural bupivacaine for analgesia after thoracic and subcostal incisions in children. *J Pediatr Surg*. 1988;23:1184-1187.
51. Fokin AA, Steuerwald NM, Ahrens WA, Allen KE. Anatomical, histologic, and genetic characteristics of congenital chest wall deformities. *Semin Thorac Cardiovasc Surg*. 2009;21:44-57.
52. Kelly RE, Shamberger RC. *Congenital Chest Wall Deformities* in Pediatric Surgery. 7th ed. Elsevier; 2012.
53. Williams AM, Crabbe DCG. Pectus deformities of the anterior chest wall. *Paediatr Respir Rev*. 2003;4:237-242.
54. Tardy MM, Filaire M, Patoir A, et al. Exercise cardiac output limitation in pectus excavatum. *J Am Coll Cardiol*. 2015;66:976-977.
55. Lawson ML, Cash TF, Akers R, et al. A pilot study of the impact of surgical repair on disease-specific quality of life among patients with pectus excavatum. *J Pediatr Surg*. 2003;38:916-918.
56. Ishimaru T, Kitano Y, Uchida H, et al. Growth spurt-related recurrence after Nuss procedure. *J Pediatr Surg*. 2009;44:E13-E16.
57. Nuss D, Obermeyer RJ, Kelly RE. Nuss bar procedure: past, present and future. *Ann Cardiothorac Surg*. 2016;5:422-433.
58. Gibreel W, Zendejas B, Joyce D, Moir CR, Zarroug AE. Minimally invasive repairs of pectus excavatum: surgical outcomes, quality of life, and predictors of reoperation. *J Am Coll Surg*. 2016;222:245-252.
59. Davis JT, Long FR, Adler BH, Castile RG, Weinstein S. Lateral thoracic expansion for Jeune syndrome: evidence of rib healing and new bone formation. *Ann Thorac Surg*. 2004;77:445-448.
60. Reamy BV, Slakey JB. Adolescent idiopathic scoliosis: review and current concepts. *Am Fam Physician*. 2001;64:111-116.
61. Kirkpatrick AW, Roberts DJ, De Waele J, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. *Intensive Care Med*. 2013;39:1190-1206.
62. Madenci AL, Stoffan AP, Rajagopal SK, et al. Factors associated with survival in patients who undergo peritoneal dialysis catheter placement following cardiac surgery. *J Pediatr Surg*. 2013;48:1269-1276.
63. Ledbetter DJ. Congenital abdominal wall defects and reconstruction in pediatric surgery: gastroschisis and omphalocele. *Surg Clin North Am*. 2012;92:713-727, x.
64. Morrow RJ, Whittle MJ, McNay MB, Raine PA, Gibson AA, Crossley J. Prenatal diagnosis and management of anterior abdominal wall defects in the west of Scotland. *Prenat Diagn*. 1993;13:111-115.
65. Biard JM, Wilson RD, Johnson MP, et al. Prenatally diagnosed giant omphaloceles: short- and long-term outcomes. *Prenat Diagn*. 2004;24:434-439.
66. Snyder CL, Miller KA, Sharp RJ, et al. Management of intestinal atresia in patients with gastroschisis. *J Pediatr Surg*. 2001;36:1542-1545.
67. Bianchi A, Dickson AP, Alizai NK. Elective delayed midgut reduction-No anesthesia for gastroschisis: selection and conversion criteria. *J Pediatr Surg*. 2002;37:1334-1336.
68. Orion KC, Krein M, Liao J, Shaaban AF, Pitcher GJ, Shilyansky J. Outcomes of plastic closure in gastroschisis. *Surgery*. 2011;150:177-185.
69. Sandler A, Lawrence J, Meehan J, Phearman L, Soper R. A "plastic" sutureless abdominal wall closure in gastroschisis. *J Pediatr Surg*. 2004;39:738-741.

Congenital Cardiac Defects

24

Asha Nair, John Kheir

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. Describe normal cardiac anatomy and blood flow in newborns.
2. Describe the normal transition from intrauterine to extrauterine blood flow.
3. Define *shunt* and understand the different types of shunts seen with congenital heart disease.
4. Understand the basic classifications of congenital cardiac defects.
5. Explain the most common congenital cardiac defects.
6. Recognize the various factors affecting pulmonary vascular resistance.
7. Describe the importance of balancing pulmonary and systemic blood flow (Q_P/Q_S) associated with various defects.
8. Recommend ventilator strategies commonly used with various congenital cardiac defects.
9. Recommend and understand the limitations of various types of physiologic monitoring necessary for the care of patients with congenital cardiac defects.

Key Terms

atrioventricular septal defect
coarctation of the aorta
Fontan procedure
Glenn procedure
hypoplastic left heart syndrome
left-to-right shunt
Norwood procedure
patent ductus arteriosus
right-to-left shunt
tetralogy of Fallot
transposition of the great arteries
truncus arteriosus

More than 40,000 children with congenital heart disease are born each year, making it the most common birth defect in the United States.[1] Major developments in the identification of children with congenital heart disease (CHD) along with new surgical techniques and improved postoperative care all resulted in significant improvements in mortality over the last 3 decades. Mortality has continued to decrease over the last decade, such that many children with congenital heart disease are surviving well into adulthood.[2,3] With CHD prevalence increasing more than 50% since 2000, adults account for nearly two-thirds of patients with CHD in the general population.[3,4] The care of patients with congenital heart disease typically occurs in specialized centers and requires a multidisciplinary team. Respiratory therapists play a key role in the perioperative care of these patients.

CARDIAC ANATOMY AND PHYSIOLOGY

ANATOMY AND BLOOD FLOW OF THE NORMAL HEART

The normal human heart has four chambers: two atria and two ventricles (Figure 24-1). Each "upper chamber," or atrium, is connected to a corresponding "lower chamber," or ventricle, by way of an atrioventricular

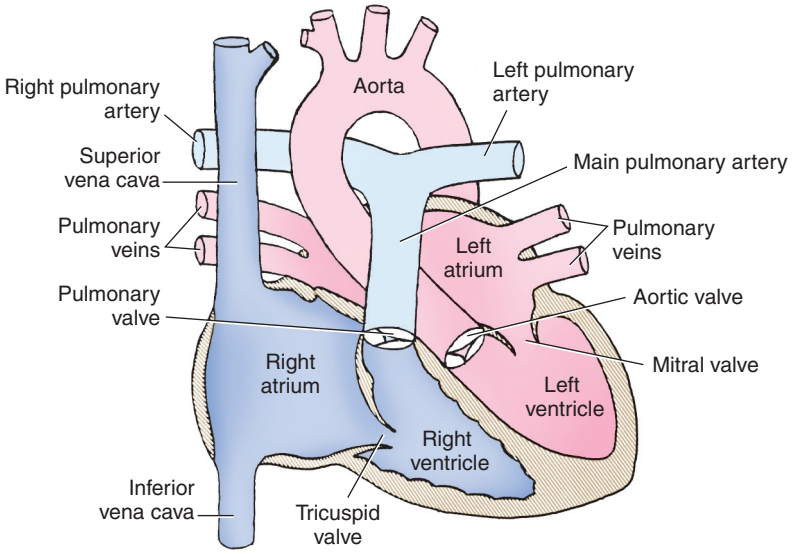


FIGURE 24-1 Anatomy of the normal heart and great vessels. (From Mullin CE, Mayer DC: *Congenital heart disease: a diagrammatic atlas,* New York, 1988, John Wiley & Sons. This material used by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

(AV) valve. The outflow from each ventricle also contains a valve, known as a *semilunar valve,* which allows blood to flow in only one direction. To understand the normal anatomy of the heart, one can trace the path of blood as it travels through the heart. This begins with deoxygenated venous blood that enters the right atrium (RA) from one of three sources. Venous blood from organs superior to the heart drains to the RA by way of the superior vena cava (SVC). Venous blood from organs below the heart enters the RA via the inferior vena cava (IVC). The coronary sinus drains venous blood supplying the heart muscle itself.

During ventricular diastole, blood is pumped from the RA into the right ventricle (RV) via the tricuspid valve (TV). During ventricular systole, blood is ejected from the RV into the pulmonary arteries through the pulmonary valve. In the lungs, oxygen diffuses from inspired air into the plasma and red blood cells, and carbon dioxide diffuses from plasma into the alveolus. Oxygenated blood returns to the heart via four pulmonary veins that are confluent with the left atrium (LA). During ventricular diastole, blood passes through the mitral valve and into the left ventricle (LV). Finally, the blood is pumped out of the LV, through the left semilunar valve, or aortic valve, and into the aorta, the main vessel supplying systemic blood flow to the entire body.

The structure of each cardiac chamber is tailored to its function. The walls of the atria are thin and compliant, allowing them the ability to expand in the setting of variable systemic and pulmonary venous return. In health, the RV is thin-walled and operates under low pressure; it is therefore typically unable to tolerate acute increases in afterload. The LV is typically thicker-walled, is concentric, and operates at systemic pressure.

TRANSITION OF FETAL TO EXTRAUTERINE LIFE

During fetal development, gas exchange takes place through the placenta. *In utero*, the lungs are fluid-filled and therefore have high resistance. In contrast, the systemic circulation includes the placenta, which has low resistance. The **patent ductus arteriosus** (PDA) typically connects the pulmonary with the systemic circulation, and most blood passing into the PA *in utero* shunts from the pulmonary artery and into the descending aorta.

Shortly after delivery, a number of anatomic and physiologic changes occur in the neonate to transition to extrauterine life. The most dramatic change occurs during the first breath, in which most air spaces fill with air, which diminishes the native pulmonary vascular resistance (PVR) dramatically. This process continues over the first several days of life. Increases in dissolved oxygen tension (PaO_2) lead to further decreases in PVR and closure of the PDA. Together, these lead to reduced right ventricular pressure and increased pulmonary blood flow. In term infants, the ductus arteriosus usually closes within 24 to 48 hours after birth.[5] Several factors may lead to delayed closure of the PDA, including prematurity, congenital heart disease, and persistent pulmonary hypertension.

CLASSIFICATION OF CARDIAC ANOMALIES

There are a number of ways to classify congenital heart anomalies, each of which represents a spectrum of disease. This chapter categorizes heart diseases functionally: those that cause a decrease in systemic oxygenation (i.e., cyanotic) and those that do not (i.e., acyanotic). It should be appreciated that cyanotic lesions, by definition, contain a right-to-left shunt. That is to say, deoxygenated blood from the systemic veins (i.e., the "right"

side of the circulation) must pass into the aorta (i.e., the "left" side of the circulation). This may happen at either the atrial or ventricular level, or both. Of course, right-to-left shunting may also take place in the lungs, as in patients with acute respiratory distress syndrome. As with every classification scheme, this schema falls short in many circumstances; for example, many patients with **tetralogy of Fallot** (TOF) are not cyanotic, because their right ventricular outflow tract obstruction is mild. Each section describes the anatomy and physiology, presurgical and postsurgical management, and surgical care of each lesion.

ACYANOTIC LESIONS

Most patients with congenital heart disease and without cyanosis exhibit a shunt that typically flows left to right. A shunt refers to blood flow that deviates from the normal flow pattern. Early in life, a left-to-right shunt may cause excessive pulmonary blood flow, high pulmonary artery pressure, or diminished systemic blood flow. Because the heart works to provide sufficient oxygen to the body, the response to a decrease in systemic blood flow is an increase in total cardiac output, a certain proportion of which may be shunted to the lungs. In extreme forms, this may result in heart failure, a clinical syndrome in which systemic blood flow is insufficient to meet demand, commonly combined with excessive pulmonary blood flow and increased work of breathing. In the absence of heart failure, left-to-right shunting may cause muscularization of the pulmonary arteries, leading to increased PVR.

PATENT DUCTUS ARTERIOSUS

During fetal life the ductus arteriosus functions to shunt blood from the pulmonary artery to the aorta, thus bypassing the lungs. Within the first 48 hours after birth, the decrease in prostaglandin E_2 (PGE2) secreted by the placenta along with an increase in Pao_2 lead to constriction of the ductus arteriosus. A number of conditions predispose infants to having a PDA, including prematurity, persistent pulmonary hypertension, and respiratory distress syndrome. In these infants, as PVR decreases, aortic pressures exceed pulmonary artery pressures, resulting in a **left-to-right shunt** through the PDA and increasing pulmonary blood flow (Figure 24-2). Of the conditions predisposing infants to PDA, prematurity is the most common, making PDA one of the most commonly seen cardiac defects in neonatal intensive care units. Delayed closure of the ductus arteriosus is inversely related to gestational age, varying from 20% in infants older than 32 weeks of gestation to 60% in infants younger than 28 weeks of gestation.[6]

In some patients with congenital heart disease, the PDA serves as a lifeline for the provision of pulmonary or systemic blood flow, so called *ductal-dependent lesions.* In patients who have obstruction of systemic blood flow, such as critical **coarctation of the aorta** or **hypoplastic left heart syndrome,** maintenance of the PDA using an infusion of prostaglandin E_1 (PGE1) provides systemic blood flow via the shunting of blood from the pulmonary artery to the aorta. In patients with obstructed pulmonary blood flow, such as pulmonary stenosis, maintenance of the PDA to provide pulmonary blood flow via a left-to-right shunt from the aorta to the pulmonary artery; these lesions have ductal-dependent pulmonary blood flow. Infants with undiagnosed ductal-dependent lesions often present with symptoms in the first days to weeks of life when the ductus arteriosus closes.

Clinical signs of PDA include tachypnea, tachycardia, and a continuous murmur. Patients with pulmonary

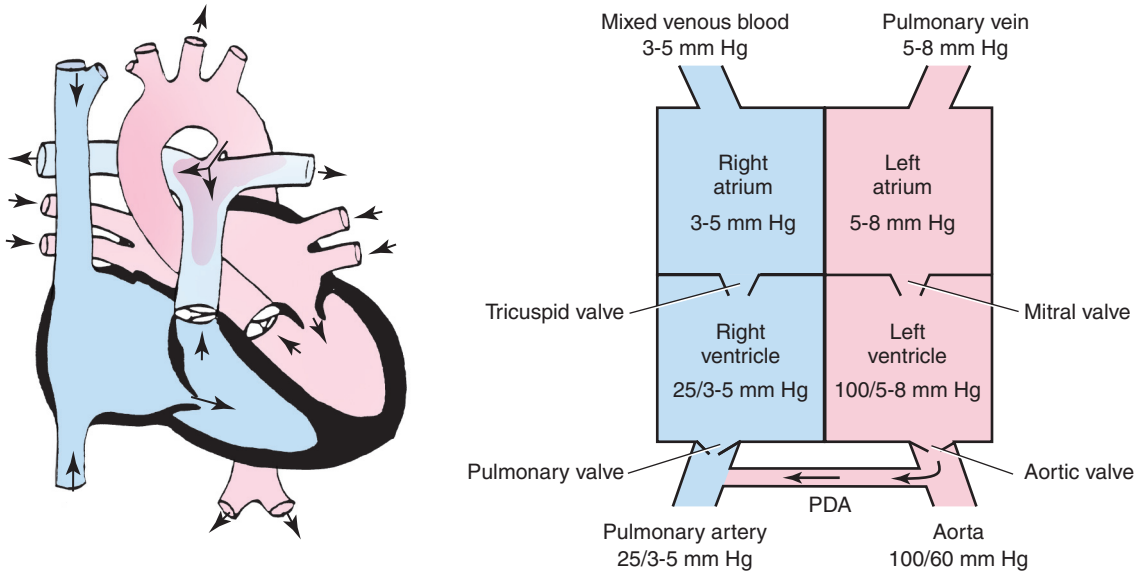


FIGURE 24-2 Patent ductus arteriosus. Communication between the pulmonary artery and the aorta. (From *Congenital heart abnormalities.* Clinical Education Aid No. 7. Columbus, OH, 1970, Ross Products Division, Abbott Laboratories.)

overcirculation may manifest cardiomegaly and pulmonary congestion, as well as failure to thrive. Blood flow through the PDA is primarily determined by the relative resistance of the systemic and pulmonary circulations. In the early postpartum period, PVR may remain at or near systemic levels, such that PDA flow may be right to left (i.e., from the pulmonary artery to the aorta). In this case, the deoxygenated blood from the PA will be detected in the lower extremities (and sometimes left arm) as postductal desaturation; a pulse oximeter placed on the left arm or a foot may show deoxygenation, with saturations in the lower 90% range or lower, whereas blood in the right arm is fed via blood coming from the left ventricle, which in normal circumstances should be fully oxygenated. It should be noted that there are many cases in which a PDA exists, even some in which flow is right to left, in which there is an abnormal preductal or postductal saturation, such that this tool should be considered a screening tool and little else.[7] Postductal desaturation should be confirmed by arterial blood gas sampling from the relevant artery to be considered accurate. If PVR has decreased to near or below systemic level, flow at the PDA may be left to right or bidirectional, in which case there will be no evidence for postductal desaturation. Definitive diagnosis is made by echocardiography.

Over time, the increase in pulmonary blood flow caused by the left-to-right shunting through a PDA can lead to left ventricular volume overload, which may result in congestive heart failure. Untreated PDA may also lead to pulmonary vascular changes and pulmonary hypertension. Increased pulmonary blood flow may delay the ability to wean infants from respiratory support as a result of pulmonary edema and poor lung mechanics. PDA may spontaneously close at any time, though this is unlikely to occur after 1 year of life.

There are both medical and surgical options for the management of PDA. Nonsteroidal antiinflammatory agents such as indomethacin and ibuprofen are often used in the medical treatment of PDA. Indomethacin may be used both prophylactically and therapeutically to enhance closure of the PDA. Adverse effects include bleeding events (including cerebral and pulmonary hemorrhage), necrotizing enterocolitis, renal insufficiency, and oliguria. Ibuprofen or acetaminophen may also be used, though a recent metaanalysis found that the use of ibuprofen was associated with increased incidence of chronic lung disease compared with indomethacin.[8,9]

Surgical closure involves dissection, identification, ligation, and division of the PDA via lateral thoracotomy. This is typically performed in the operating room. Complications after surgery are rare but can be significant, including life-threatening bleeding, occlusion of a major vessel, or injury to the recurrent laryngeal nerve, which may result in vocal cord paresis.

ATRIAL SEPTAL DEFECT

An atrial septal defect (ASD) is a communication between the right and left atria (Figure 24-3). There are several morphologies of ASD, each defined by the location of the defect along the atrial septum and other associated defects. The pathophysiology of an ASD is left-to-right shunting atrial flow. Blood flow at the atrial level is primarily determined by the relative compliance of the two receiving ventricles; because the LV is thicker-walled and has a higher systolic pressure, its compliance during ventricular diastole is slightly lower than that of the RV. For this reason, the LA pressure is usually 2 to 3 mm Hg higher than the RA pressure. In the presence of an ASD, RA and LA pressure are typically equal (because there is a hole connecting

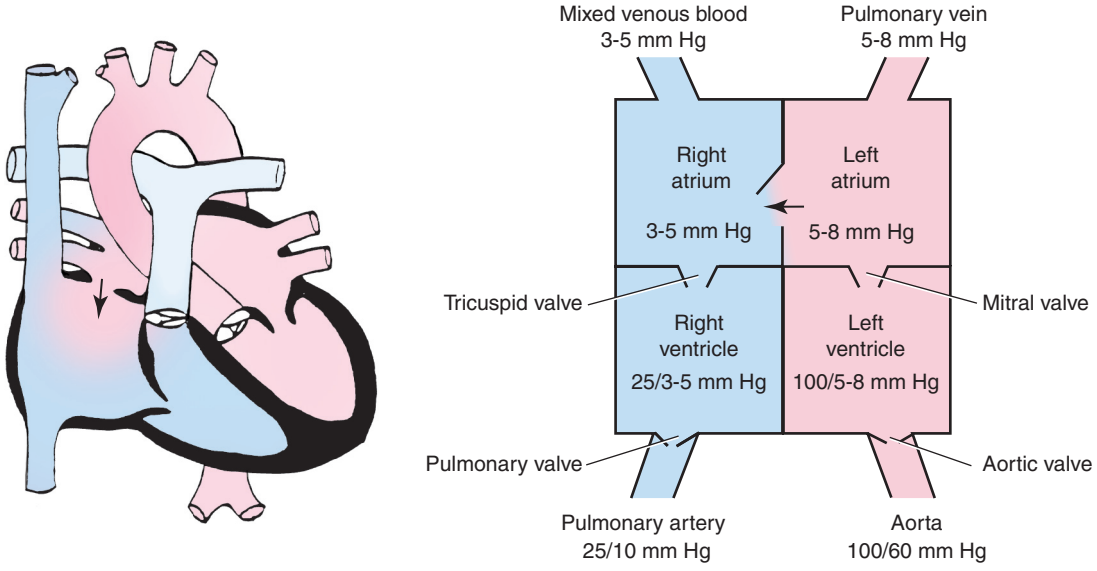


FIGURE 24-3 Atrial septal defect. Communication between the right and left atria through the septum. (From Mullin CE, Mayer DC: *Congenital heart disease: a diagrammatic atlas*, New York, 1988, John Wiley & Sons. This material used by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

the two chambers) and blood flows left to right. When it does so, it creates right ventricular volume overload, a term that implies that the RV must pump more volume than normal to provide a single "cardiac output" worth of blood to the body. In the case of an ASD, the RV must pump all of the blood that fills the LV for each heartbeat, in addition to all of the blood that shunts back from the LA to the RA at the atrial level. Over time, this results in right ventricular hypertrophy and pulmonary vascular disease. Infants with ASDs rarely are symptomatic (although premature infants with ASDs may be), and children may remain asymptomatic into adulthood. Less than 10% of children with ASDs develop symptoms before 2 years of age.[10] However, ASDs are commonly identified by flow-related murmur or RV heave present on physical examination and confirmed by echocardiography. Chest radiographs are typically normal unless the child has congestive heart failure, which may result in cardiomegaly and prominent pulmonary vascular markings.

Spontaneous closure of small ASDs may occur within the first year of life; thus repair is typically delayed until the child is 3 to 5 years of age.[10-12] Some ASDs may be closed via a catheter-based approach, with excellent long-term outcomes.[13,14] In other cases, surgical repair of an ASD takes place via a median sternotomy and cardiopulmonary bypass, with closure of the defect by suture or patch. After surgery, early extubation is common. In the absence of intrapulmonary shunts, patients should have normal blood gases and oxygen saturations. Long-term outcomes after ASD closure is excellent.

VENTRICULAR SEPTAL DEFECTS

Ventricular septal defect (VSD) is one of the most common congenital heart defects and involves a communication between the right and left ventricles (Figure 24-4). Like ASDs, VSDs can be described in terms of their location along the ventricular septum: perimembranous (along the membranous septum), subpulmonary (just below the pulmonary valve), muscular (in the middle of the muscular portion), or inlet (just below the tricuspid valve, typically associated with a complete AV canal defect). VSDs may be singular or multiple, and may be pinhole or large and unrestrictive. The pathophysiology the VSD depends upon its size. Small VSDs, particularly those within the muscular septum, may close spontaneously and remain asymptomatic. Large and unrestrictive VSDs (i.e., there is no pressure difference between the right and left ventricle) create a large left-to-right shunt and pulmonary arterial hypertension. Unlike ASDs, because the pulmonary artery pressure in the presence of an unrestrictive VSD is equal to that in the aorta, patients with unrestrictive VSDs may develop signs of pulmonary overcirculation and pulmonary edema more quickly than patients with ASDs, even when the shunt fraction is the same. Over time, patients with unrestrictive and unrepaired VSDs may develop muscularization of the pulmonary arteries, which may lead to pulmonary hypertension. If PVR is close to systemic vascular resistance, the left-to-right shunt may reverse to a **right-to-left shunt,** a condition known as *Eisenmenger syndrome.*

Some types of VSDs, including perimembranous and muscular, commonly close spontaneously in the first 2 years of life. In infants with unrestrictive VSDs and symptoms of heart failure, definitive therapy is surgical closure. In settings in which cardiopulmonary bypass is excessively high risk (or not available), a restrictive band may be placed on the pulmonary artery to decrease distal pulmonary artery pressure and

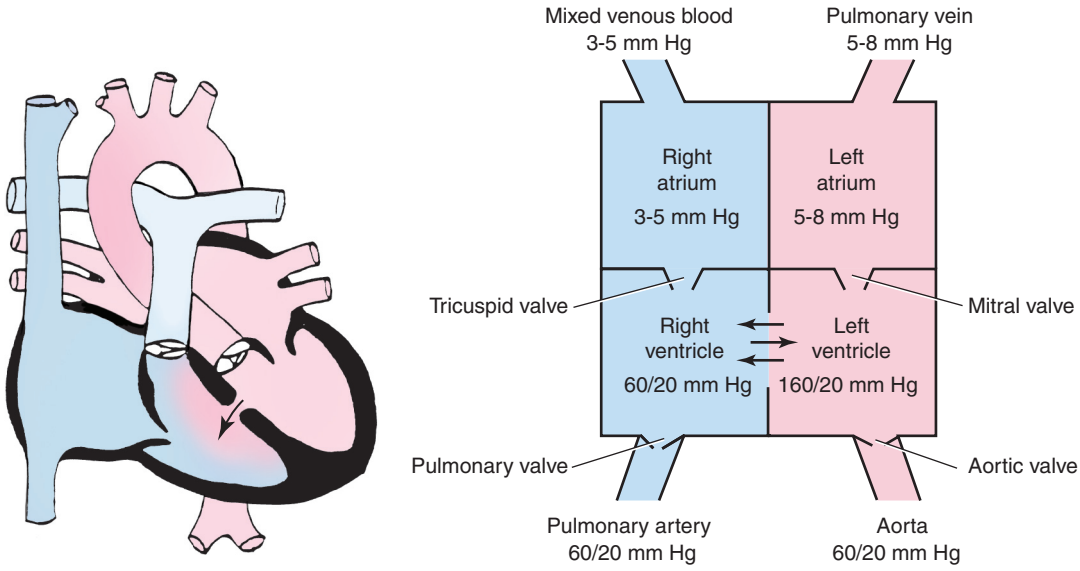


FIGURE 24-4 Ventricular septal defect. Communication between the right and left ventricles through the septum. (From *Congenital heart abnormalities.* Clinical Education Aid No. 7. Columbus, OH, 1970, Ross Products Division, Abbott Laboratories.)

pulmonary blood flow. Mild symptoms may be treated with diuretics and digoxin.[15] Recently, percutaneous transcatheter closure of some VSDs has been performed in the cardiac catheterization laboratory, though this is typically reserved for older children with muscular VSDs.[16] Early extubation should be expected in patients after surgical repair of an isolated VSD, particularly if there was no significant heart failure before the repair. Infants or those with heart failure may require a few days of mechanical ventilation and diuresis before extubation. After repair, these patients should have normal arterial blood gases and oxygen saturations. However, it should be noted that VSDs are common in many other types of congenital heart disease, in which case the postoperative course is primarily determined by the details of the other anatomy and physiology and the surgery.

COMPLETE ATRIOVENTRICULAR CANAL

A complete atrioventricular canal (CAVC) defect, also known as **atrioventricular septal defect** (AVSD), is a malformation of the crux of the heart normally formed by the endocardial cushion. The defect always involves a common (singular) AV valve and often involves abnormalities of the lower portion of the atrial septum (septum primum) and the inlet portion of the ventricular septum. Partial AVSDs are characterized by a primum ASD and common AV valve, but there is no defect in the ventricular septum. Complete AVSDs are characterized by absence of a portion of the atrial septum and the ventricular septum and the presence of a single common AV valve (Figure 24-5). AVSDs occur in approximately 5% of patients with congenital heart disease, but they are the most common congenital heart lesions in infants with trisomy 21.[17] The pathophysiology of this defect involves left-to-right shunting at both the atrial and ventricular level, and at times AVV regurgitation, in which case blood returns to the atrium during ventricular systole, another form of ventricular volume load. If left untreated, this leads to congestive heart failure, increased pulmonary blood flow, and irreversible pulmonary hypertension.[18]

Children with partial AVSDs may not have obvious clinical manifestations initially. Those with complete AVSDs usually develop signs of heart failure in early life, including respiratory distress, pulmonary edema, and growth failure. Chest radiography usually reveals cardiomegaly and increased pulmonary vascular markings. Infants without severe heart failure may be managed as outpatients for a time with diuretics and digoxin. Oxygen saturations in these children may be low (75-90%) as a result of venous admixing but are tolerated well by most patients. Supplemental oxygen may be given judiciously, given the potential for oxygen to induce pulmonary vascular dilation and increased pulmonary blood flow. Surgical repair of a complete CAVC defect is usually performed before 6 to 12 months of age, depending on the degree of shunting and symptomatology. Surgical repair of CAVC includes septation (i.e., separation) of the common AVV into a right and left side, closure of extra commissures (called *clefts*) in the AVV, and closure of any atrial or ventricular level defects. Like patients with isolated VSDs, children with comorbid conditions who are poor candidates for early repair may be managed with banding of the pulmonary artery for stabilization or to allow more growth until definitive repair can be performed.[19,20]

After repair, patients should have normal arterial saturations and arterial blood gases. Arrhythmias or conduction abnormalities (e.g., heart block) may take place in the postoperative period, requiring patients to

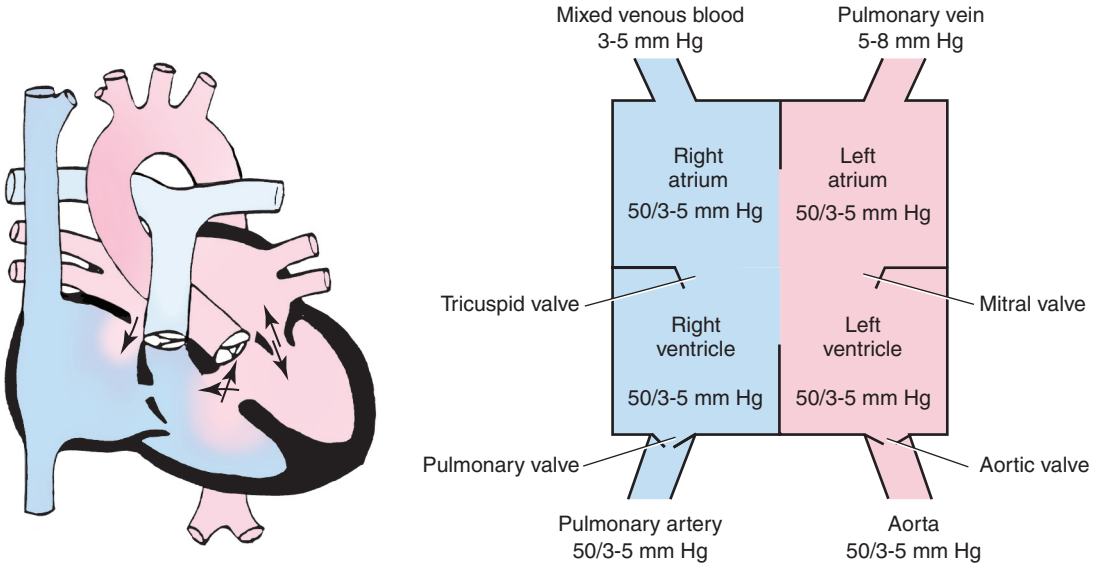


FIGURE 24-5 Atrioventricular canal defect. Incomplete development of the atrial and ventricular septa, which allows complete cardiac mixing of blood. (From Mullin CE, Mayer DC: *Congenital heart disease: a diagrammatic atlas,* New York, 1988, John Wiley & Sons. This material used by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

undergo temporary pacing. Patients without significant heart failure preoperatively may be extubated early after surgery, though this may vary based on preoperative condition, the presence of an abnormal heart rhythm (including junctional tachycardia, which may require active cooling of the patient), and operative complications. Recall that patients with trisomy 21, common in this heart disease, may exhibit anatomically smaller airways for their age, as well as macroglossia, which may complicate spontaneous breathing postoperatively.[21]

LEFT-SIDED OBSTRUCTIVE LESIONS

Left ventricular outflow tract (LVOT) obstructions exist along a spectrum that likely results from impaired flow through the left side of the heart *in utero.* Defects may include an abnormal mitral valve, an abnormal left ventricle (e.g., subnormal cavity volume), obstruction of the LVOT, aortic valve stenosis, or narrowed aorta (including coarctation). The presence of a VSD with left heart obstruction compounds this problem, because blood flow from the left ventricle passes through the VSD and may exacerbate LVOT obstruction or aortic arch hypoplasia.[22] In its extreme form, left heart lesions may result in hypoplastic left heart syndrome, a disorder in which the left heart structures are too small to sustain normal circulation.

AORTIC STENOSIS

Aortic stenosis (AS) as strictly defined is a narrowing of the aortic valve orifice itself. The narrowing may alternatively be below the valve annulus (i.e., subvalvular) or above the valve in the sinuses of Valsalva (i.e., supravalvular; Figure 24-6).

The clinical presentation and natural history of aortic stenosis are determined primarily by the degree of stenosis. If not diagnosed prenatally, neonates with critical (i.e., dependent on PDA flow for survival) aortic stenosis may present in cardiogenic shock with hypotension, poor perfusion, and metabolic acidosis. The chest radiograph may include pulmonary edema from left atrial hypertension. These infants must be rescued by immediately opening the PDA to provide systemic blood flow, mechanical ventilation to minimize oxygen demands, and aortic balloon valvotomy.[23,24] Infants and older children may present with lesser degrees of aortic stenosis, often associated with left ventricular hypertrophy and outflow tract obstruction, as well as a risk for bacterial endocarditis. Surgical interventions for AS may include aortic valvuloplasty, artificial aortic valve replacement, or replacement with a pulmonary valve autograft (Ross procedure). At times an atrial fenestration may be left to decompress the LA into the RA, though given the left-to-right flow in such patients, normal arterial blood gases and pulse oximetry should be expected. Hypertension should be aggressively controlled in these patients to avoid undue stress on the repair site.

COARCTATION OF THE AORTA

Coarctation of the aorta is a severe narrowing of the thoracic aorta at the insertion site of the ductus arteriosus, known as the aortic isthmus. The obstruction, which may occur proximal to, at, or distal to the ductus (i.e., preductal, juxtaductal, or postductal), may present in the neonatal period or later in infancy or childhood (Figure 24-7). The pathophysiology includes diminished systemic perfusion and increased LV afterload, which may lead to increased wall stress, myocardial

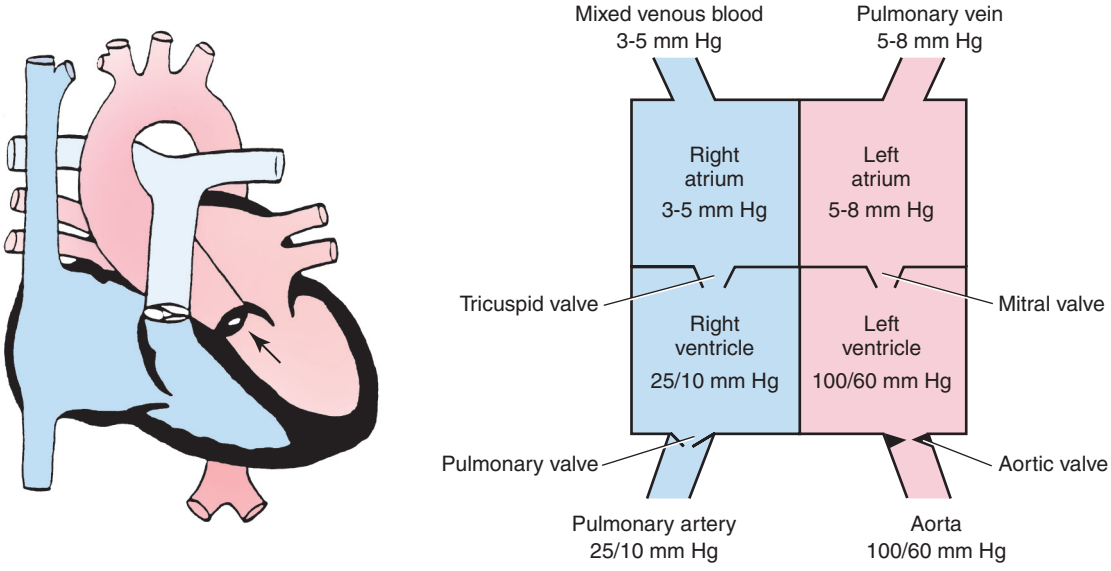


FIGURE 24-6 Aortic stenosis. Outflow obstruction of the aorta, impeding blood flow from the left ventricle. (From *Congenital heart abnormalities.* Clinical Education Aid No. 7. Columbus, OH, 1970, Ross Products Division, Abbott Laboratories.)

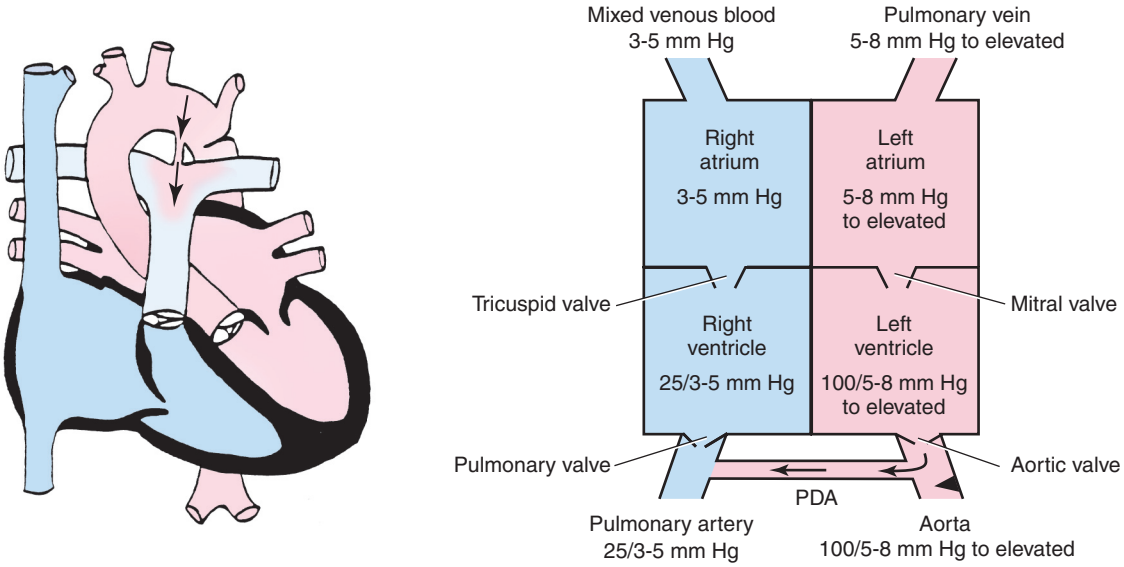


FIGURE 24-7 Coarctation of the aorta. Severe narrowing of the aortic lumen, which decreases blood flow through the aorta. A patent ductus arteriosus is often present to allow pulmonary blood flow when the coarctation is severe. *PDA*, Patent ductus arteriosus. (Modified from Mullin CE, Mayer DC: *Congenital heart disease: a diagrammatic atlas*, New York, 1988, John Wiley & Sons. This material used by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

work, and in some cases progressive ventricular dysfunction. Neonates with critical coarctation may present *in extremis* as previously described for critical AS (and sometimes they occur in association), a situation that must be rescued with emergent opening of the PDA using PGE1 infusion, mechanical ventilation, and diuresis of the pulmonary edema that results from left atrial hypertension. Older children with less severe coarctation may be asymptomatic, presenting with upper extremity hypertension as the only sign of the underlying lesion. Left unrepaired, the increased work of the LV will lead to left ventricular hypertrophy and arterial collateralization around the site of the aortic narrowing.

The chest radiograph of an infant with severe coarctation may demonstrate cardiomegaly and pulmonary congestion. Older children with coarctation have classic findings of cardiomegaly and rib notching, which results from collateral vessels dilating over time to bypass the site of obstruction. Surgery for severe coarctation in neonates is usually not delayed, but for less severe coarctation in older infants and children may be performed electively.

A number of different surgical techniques are used in the repair of aortic coarctation. The most common approaches are (1) resection of the stenotic segment with end-to-end anastomosis of the transected ends; (2) patch aortoplasty, which includes using a synthetic patch to enlarge the area of narrowing; (3) subclavian patch aortoplasty, which uses a flap from the subclavian artery to enlarge the site; and (4) extended resection with primary anastomosis. The most commonly used procedure in neonates is resection with end-to-end anastomosis, which can typically be performed via a left thoracotomy. If the neonate has significant arch hypoplasia, an extended end-to-end procedure may be performed, which involves an end-to-side connection of the descending aorta to an incision on the underside of the aortic arch proximal to the narrow portion.[25,26]

Postoperatively, normal blood gas and pulse oximetry values should be expected. A residual coarctation may be present postoperatively. Systolic pressure gradients less than 20 mm Hg in the setting of adequate lower body perfusion (including renal perfusion) is generally considered acceptable. After surgery, older children are commonly extubated in the operating room or within the first few hours after surgery. Infants and younger children may require 12 to 24 hours of mechanical ventilation postoperatively. On extubation, patients should be evaluated for stridor, which may result from intraoperative injury to the recurrent laryngeal nerve, leading to vocal cord paralysis. Hemidiaphragmatic paralysis from an intraoperative phrenic nerve injury is another potential complication and is diagnosed by an elevated hemidiaphragm on chest radiograph. Finally, injury to the thoracic duct intraoperatively may lead to a chylothorax, which may affect the duration of mechanical ventilation in these patients.

HYPOPLASTIC LEFT HEART SYNDROME

Hypoplastic left heart syndrome (HLHS) describes the most extreme end of the spectrum of left heart obstructive lesions. Patients with HLHS typically exhibit underdevelopment of most or all of the left heart structures, including the mitral valve, LV, aortic valve, and aortic arch (Figure 24-8). Because the left side of the heart is sufficiently underdeveloped

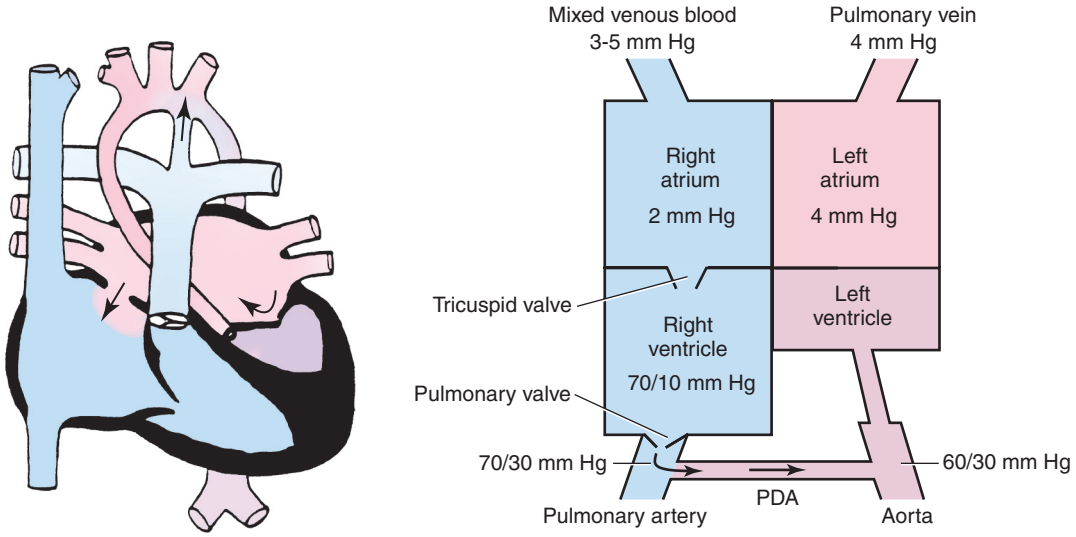


FIGURE 24-8 Hypoplastic left ventricle. Underdeveloped left ventricle and severe narrowing of the ascending aorta. It may include mitral atresia (pictured here), lack of the mitral valve, aortic atresia, lack of the aorta, or a combination. A patent ductus arteriosus is necessary for systemic blood flow. *PDA,* Patent ductus arteriosus. (From Mullin CE, Mayer DC: *Congenital heart disease: a diagrammatic atlas,* New York, 1988, John Wiley & Sons. This material used by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

(i.e., hypoplastic), blood flow to the body must be supplemented or completely provided by the RV. To accomplish this (before operative intervention), all of the pulmonary venous return must either pass through the small LV (which is impossible in the setting of aortic or mitral atresia) or through the foramen ovale to the RA. This oxygenated blood mixes with deoxygenated blood on the right side of the heart before being pumped to the pulmonary artery. A portion of this cardiac output travels to the lungs, and the remainder travels through the ductus arteriosus and into the aorta. In the setting of aortic atresia, blood travels completely retrograde in the transverse aortic arch to supply the head and neck vessels as well as the coronary arteries. The crux of this so-called *single ventricle physiology* is that blood flows to the body and to the lungs in parallel rather than in series. Because the two circulations are anatomically connected by an unrestrictive shunt (i.e., there normally is no pressure gradient across the PDA), the ratio of blood flow to circulation is exclusively determined by the ratio of systemic vasculature resistance to PVR. As PVR decreases over the first days of life, patients become at risk for excessive pulmonary blood flow (and pulmonary edema), as well as inadequate systemic perfusion. Preoperatively, most neonates exhibit an abundance of cardiac output and are able to maintain adequate systemic perfusion even in the presence of abundant pulmonary blood flow. Because of this, saturations in the mid to high 90s are common. Nonetheless, maneuvers that further diminish PVR, such as supplemental oxygen, are counterproductive and should be avoided in most cases.

HLHS is often diagnosed prenatally or shortly after birth, though infants with PDA and unrestrictive foramen ovale may present beyond the neonatal period. As in all patients with left heart obstructive lesions, premature closure of the PDA causes immediate hypoperfusion, metabolic acidosis, and circulatory collapse and death.

The preoperative management of infants with HLHS is targeted at ensuring adequate intracardiac mixing, right-to-left flow at the PDA, and balance between the pulmonary and systemic circulations. If blood flow across the atrial septum is restrictive (present in approximately 10% of patients with HLHS), neonates can be born *in extremis,* with profound cyanosis, acidosis, and severe lung disease. In these cases, emergent balloon atrial septostomy is required to allow for left atrial decompression and adequate pulmonary blood flow (otherwise, the pulmonary circulation may terminate in a dead-end LA). In these cases, patients often require high-frequency oscillatory ventilation or extracorporeal membrane oxygenation (ECMO) for stabilization. However, the clinical examination of most infants with HLHS after birth approaches normal. PGE1 should be started immediately when the diagnosis of HLHS is confirmed to ensure patency of the ductus arteriosus. In the vast majority of patients, the pulmonary and systemic circulations balance naturally after birth. The use of diuretics is common to diminish pulmonary edema, particularly in the presence of a restrictive atrial septum *in utero.* Subambient oxygen and hypercarbia are no longer used at most institutions.[27] Patients with pulmonary edema and increased work of breathing may be supported using noninvasive ventilation and fraction of inspired oxygen (Fio_2) of 21%. It should be noted that intubation and mechanical ventilation in these patients may

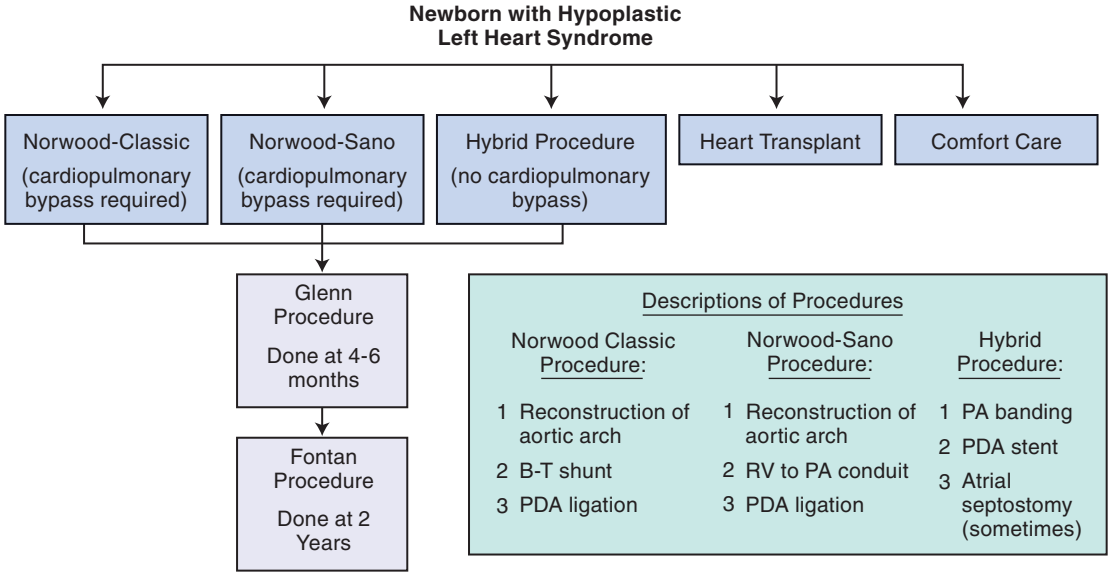


FIGURE 24-9 Sequence of procedures for the treatment of hypoplastic left heart syndrome. *B-T, PA,* pulmonary artery; *PDA,* patent ductus arteriosus; *RV,* right ventricle.

recruit atelectatic alveoli and cause a decrease in PVR, resulting in abrupt hypotension or hypoperfusion. In these cases, pulmonary artery banding may be required for stabilization, as is common after induction of anesthesia for these patients.

Outcomes for infants with HLHS have improved dramatically since the introduction of stage 1 palliation (S1P) at Boston Children's Hospital in the 1980s.[28,29] As with most procedures, S1P begins with an incision in the front of the chest and exposure of the heart, lungs, and great vessels (pulmonary artery and aorta). After cannulation for cardiopulmonary bypass, the aorta, which had previously only received blood from the ductus arteriosus and any small amount of blood coming through the aortic valve, is reconstructed to receive blood from both the aortic valve and the pulmonary artery (now called the *neoaorta*). The remainder of the hypoplastic aorta is augmented using a homograft, providing a widely patent aortic arch. An atrial septectomy permits free left-to-right flow of pulmonary venous return. Pulmonary blood flow is provided through either a modified Blalock-Taussig shunt (BTS) (Figure 24-10), which connects the subclavian artery to the pulmonary artery with a synthetic shunt, or the right ventricle–pulmonary artery (RV–PA) shunt or conduit, known as the Sano modification (Figure 24-11). The purpose of either of these shunts is to provide a fixed resistor to pulmonary blood flow (Q_P), serving as the primary limiter of Q_P in these patients. In patients who are deemed to be at high risk for the **Norwood procedure,** such as extremely low-birth-weight or preterm infants, S1P may be delayed

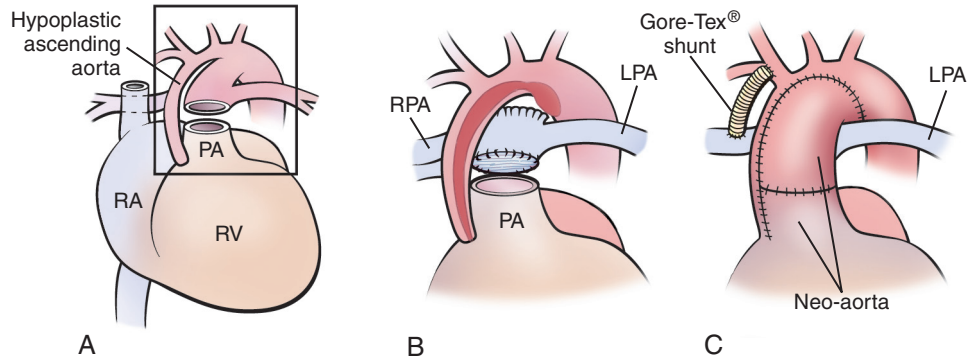


FIGURE 24-10 The Norwood procedure. **(A)** A heart with aortic atresia and a hypoplastic ascending aorta and aortic arch is shown. The main pulmonary artery *(PA)* is transected. **(B)** The distal PA is closed with a patch. An incision that extends around the aortic arch to the level of the ductus is made in the ascending aorta. The ductus is ligated. **(C)** A modified right Blalock-Taussig shunt is created between the right subclavian artery and the right PA *(RPA)* as the sole source of pulmonary blood flow. By the use of an aorta or PA allograft *(shaded area),* the main PA is anastomosed to the aorta and the aortic arch to create a large arterial trunk. The procedure to widen the atrial communication is not shown. *LPA,* Left pulmonary artery; *RA,* right atrium; *RV,* right ventricle. (From: Park MK, Troxler RG: *Pediatric cardiology for practitioners,* St. Louis, 2002, Mosby.)

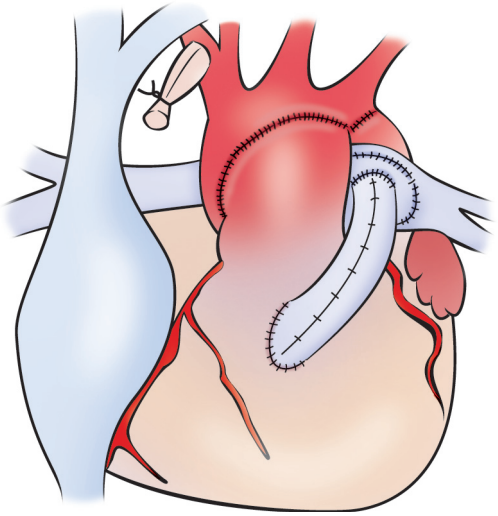


FIGURE 24-11 The Sano shunt. (Redrawn from Sano S, Ishino K, Kawada M, et al.: Right ventricle-pulmonary artery shunt in first-stage palliation of hypoplastic left heart syndrome. *J Thorac Cardiovasc Surg* 126(2):504-509, 2003.)

and the pulmonary arteries may be banded and ductal patency maintained by using PGE1 or placing a stent.[30-32]

Infants undergoing S1P are at extremely high risk for complications, and their care must be meticulous. First, arterial oxyhemoglobin saturation (Sao_2) and pulse oximetry (Spo_2) should be interpreted appropriately. As discussed below, Spo_2 is largely a trend monitor and is generally inaccurate in the cyanotic range. Regardless, interpretation of SaO_2 or SpO_2 should be as follows. In patients with aortic atresia, Sao_2 is determined by three factors: systemic venous saturation, pulmonary venous saturation, and the ratio of pulmonary (Qp) to systemic (Qs) blood flow. Systemic venous saturation can be measured by sampling from the SVC. A low Svo_2 is indicative of low systemic oxygen delivery, often from low Sao_2 or low systemic blood flow. The pulmonary venous saturation is rarely measured directly, but is often assumed (at times erroneously) to be in the mid-90s. Several factors may compromise this assumption. First is the position of the tracheal tube, which may be easily displaced in a small infant. This should be evaluated using a chest radiograph, auscultation, and assessment of capnometry. Second is the presence of secretions in the airways. However, a skilled respiratory therapist understands the dramatic effects of suctioning on patients after S1P. Suctioning is a potent derecruitment maneuver, one that may acutely increase PVR and diminish pulmonary blood flow. More importantly, in inadequately sedated patients or those not on neuromuscular blocking agents (which should be routine in the early postoperative period), suctioning may provoke a potent catecholamine response and acutely raise systemic vascular resistance. In these cases, patients may suffer coronary insufficiency and cardiac arrest. Thus suctioning in these patients should be considered a high-risk event and should be performed after premedication, with extreme care, as few times as possible, and with a care team present. Third is the presence of lung disease related to preoperative pulmonary edema, or related to *in utero* restriction of the atrial septum. Such patients will be especially prone to intrapulmonary shunting and pulmonary venous desaturation, leading to arterial hypoxemia. In these cases (i.e., once mechanical causes of desaturation are excluded), it may be appropriate to use higher Fio_2 (often in the 0.25 to 0.4 range) to overcome an alveolar–arterial oxygen diffusion gradient.[33] As stated previously, the primary resistor in the pulmonary circulation is the Sano conduit or the BTS, such that minor increases in Fio_2 are unlikely to significantly alter total pulmonary resistance. However, the routine use of significant hyperoxia (e.g., more than 0.4) is not recommended, and any hyperoxic ventilation should be performed only after discussion with the medical team. After S1P most patients have Sao_2 (and Spo_2) in the 70% to 80% range, and Sao_2 below 70% should prompt an evaluation of the causes discussed previously, as well as of the Qp/Qs ratio. If persistent and refractory to standard maneuvers, this degree of cyanosis may prompt an evaluation for anatomic obstruction of pulmonary blood flow within the shunt or pulmonary artery, often using cardiac catheterization. Finally, after S1P, acute desaturation episodes should prompt an immediate bedside evaluation for the following differential diagnoses: tracheal tube malposition, secretion-related airway obstruction, or shunt thrombosis, the last of which can result in a complete obstruction of pulmonary blood flow. The respiratory therapist should immediately evaluate end-tidal carbon dioxide ($ETCO_2$), lung sounds, and tube position. At times, hand ventilation with a hyperoxic gas mixture can be life-saving. An $ETCO_2$ of less than 10% should raise suspicion for tube displacement (which must be addressed immediately) or shunt occlusion, which often results in the need for immediate surgical intervention or ECMO support.

After S1P, the heart has to perform extra work to provide 100% of both Qp and Qs in each stroke. To mitigate this problem, most infants with HLHS undergo a superior cavopulmonary anastomosis, also known as a bidirectional **Glenn** (BDG) **procedure** (Figure 24-12), at 4 to 6 months of age. This procedure includes a takedown of the systemic-to-pulmonary shunt, which is replaced with a direct connection of the SVC with the pulmonary artery. This reduces the amount of volume work performed by the heart by approximately 50%, making the circulation substantially more efficient. However, it raises important considerations for the respiratory therapist to consider in the postoperative period. Qp in this setting passes through two resistors in series: the cerebral circulation, which is believed to be the primary resistor (i.e., it has

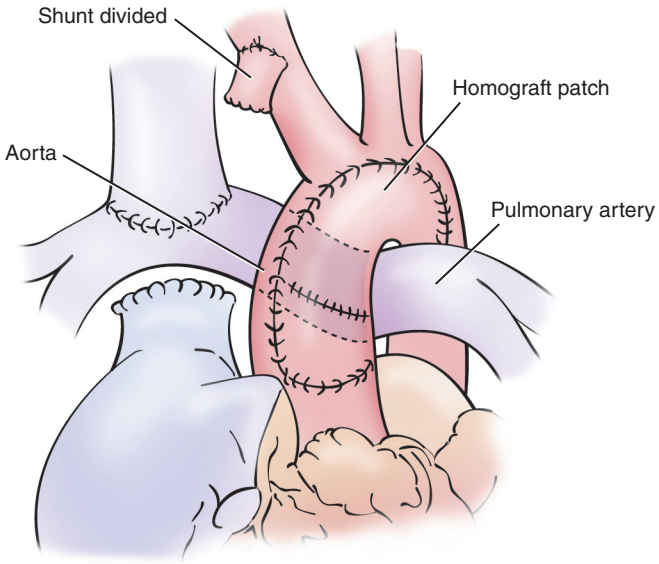


FIGURE 24-12 Bidirectional Glenn shunt. The divided right superior vena cava has been anastomosed at the previous site of the distal anastomosis of the modified right Blalock-Taussig shunt. (Redrawn from Castaneda AR, Jonas RA, Mayer JE, Hanley FL: *Cardiac Surgery of the Neonate and Infant.* New York, 1994, WB Saunders.)

a higher resistance), and PVR. It should be remembered that cerebral vascular resistance is highly responsive to Pco_2. Recall that hyperventilation, which decreases Pco_2, is a potent cerebral vasoconstrictor, as is used in the acute treatment of increased intracranial pressure. Conversely, in the case of BDG, slight respiratory acidosis may permit cerebral vasodilation and improvement in Qp. However, this point is academic in most cases. More important is the prevention of iatrogenic increases in PVR from errors in mechanical ventilation, particularly from pulmonary overdistention or (equally harmful) atelectasis. This is particularly important in the early postoperative setting where bleeding, operative compression, the presence of thoracic drainage tubes, or secretions may lead to significant atelectasis. If present, the reversal of atelectasis using large tidal volumes (approximately 8-10 mL/kg to enable tidal recruitment) and sufficient positive end-expiratory pressure (PEEP) to maintain lung recruitment may be helpful. The adequacy of Qp may be assessed using several parameters at the bedside. Pulmonary dead space, calculated as ($Paco_2$ – mixed expired CO_2)/$Paco_2$, is elevated in patients with insufficient pulmonary blood flow after BDG. Normally less than 0.1, a dead space fraction in excess of 0.2 should raise concern for elevated PVR. Second, Glenn pressure (i.e., the pressure in the SVC) in excess of 20 mm Hg or a transpulmonary gradient (difference between Glenn pressure and common atrial pressure) in excess of 10 to 12 mm Hg should raise concern for elevated PVR. Finally, Sao_2 below 75%, particularly in combination with either of the prior two signs, should raise concern for elevated PVR. These patients should be especially well evaluated for the iatrogenic causes

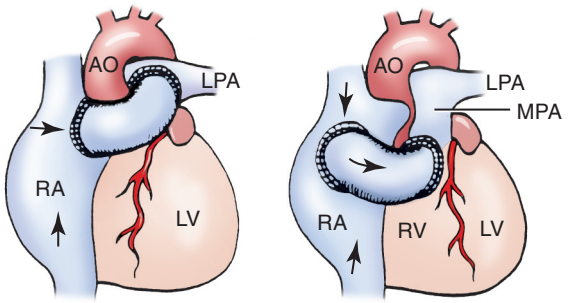


FIGURE 24-13 Fontan procedure. Blood from the right atrium is routed to the left or main pulmonary artery using a baffle, which may contain a fenestration or pop-off valve to allow blood flow to enter the ventricle in the presence of high pulmonary artery pressures. *AO,* Aorta; *LPA,* left pulmonary artery; *LV,* left ventricle; *MPA,* main pulmonary artery; *RA,* right atrium; *RV,* right ventricle.

of elevations in PVR mentioned, as well as for preoperative risk factors, including an elevated PVR (above 4 Wood units WU) on cardiac catheterization before a BDG procedure, hypoplastic pulmonary arteries, or the presence of aortopulmonary collaterals. In a minority of cases, the use of pharmacologic paralysis and/or inhalational nitric oxide may be necessary to sustain sufficient oxygenation and cardiac output. Recall that cardiac preload after BDG is nearly 50% dependent on pulmonary venous return, such that elevated PVR causes not only decreased PBF and cyanosis but also preload deficiency. Whenever possible, spontaneous ventilation and extubation should be performed early, because negative intrathoracic pressure is often effective in improving PBF and cardiac preload.

The third and final routine operation for patients with univentricular anatomy is the **Fontan procedure,** which removes the final volume load from a single-ventricle heart (Figure 24-13). In this procedure, blood flow from the inferior half of the body (i.e., IVC) is directed to the pulmonary artery through a baffle within or just outside the heart. Some centers leave a hole (i.e., fenestration) between this baffle and the atrium to permit right-to-left flow in the setting of elevated PVR. In these cases, patients may exhibit Sao_2 in the 80 or lower range in the early postoperative period, though this typically improves to the low or mid-90s after extubation and recovery. The acute postoperative considerations for Fontan patients are identical to those mentioned previously for BDG.

OTHER CYANOTIC CONGENITAL HEART LESIONS

TOTAL ANOMALOUS PULMONARY VENOUS RETURN

Total anomalous pulmonary venous return (TAPVR) refers to a spectrum of abnormalities in which the pulmonary veins drain to the systemic venous circulation rather than the LA (Figure 24-14). The site of drainage is mostly academic and includes supracardiac

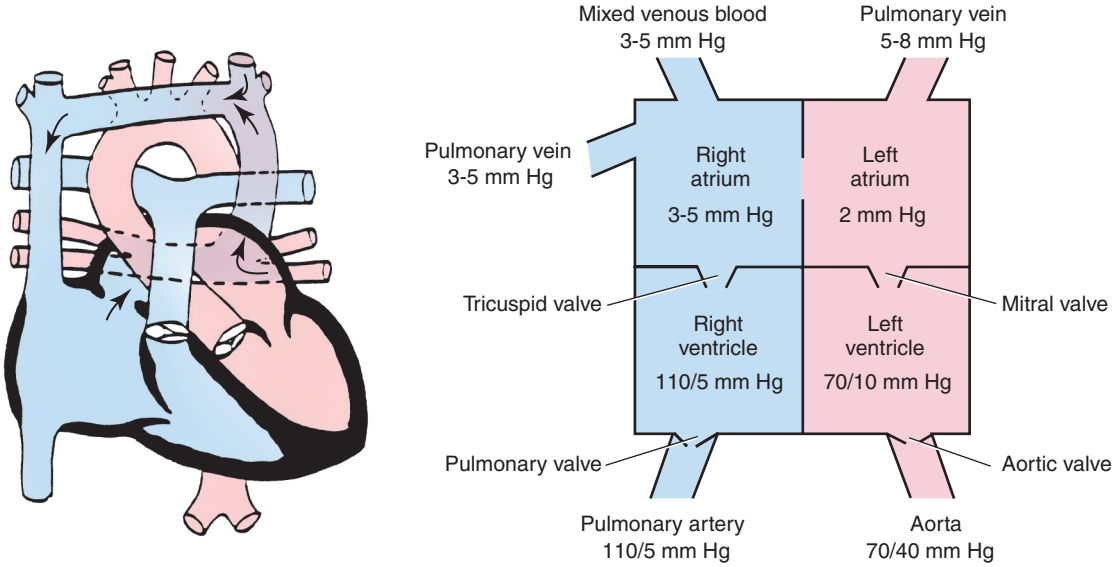


FIGURE 24-14 Total anomalous pulmonary venous return. Pulmonary venous return is routed to the right atrium instead of the left atrium. Pulmonary drainage can be routed (1) above the heart (supracardiac), as pictured here; (2) through the heart (cardiac); (3) through the portal vein, ductus venosus, hepatic vein, or inferior vena cava (infracardiac); or (4) through the diaphragm or esophageal hiatus (subdiaphragmatic). (From Mullin CE, Mayer DC: *Congenital heart disease: a diagrammatic atlas,* New York, 1988, John Wiley & Sons. This material used by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

(in which veins drain to the SVC via a vertical vein, the most common situation), cardiac (in which the veins drain to the RA via the coronary sinus), or infracardiac (in which the veins drain below the diaphragm). Infracardiac veins may drain either to the hepatic veins, to the IVC directly, or to the portal vein. In the latter case, blood must pass through hepatic sinusoids to return to the atrium. In such cases, and in some other cases of TAPVR, pulmonary venous drainage experiences high resistance and pressure (i.e., obstructed). In severe cases, this causes the same clinical presentation found in patients with HLHS and intact atrial septum discussed previously—patients may be born *in extremis* with profound cyanosis and acidosis. Resuscitation in these cases may require HFOV or ECMO support and urgent surgical repair to relieve pulmonary vein obstruction. However, such patients are the minority. More commonly, TAPVC is diagnosed postnatally (it is difficult to identify on prenatal screening except in combination with other heart defects) and is often only mildly symptomatic. Chest radiograph usually reveals a normal heart size and lungs with a modest burden of pulmonary edema.[34]

The preoperative management of infants is often routine and symptom-based. Those with mildly obstructed veins (e.g., those with supracardiac TAPVC with later presentation) may exhibit pulmonary edema and may benefit from mechanical ventilation and positive pressure ventilation.

Surgical correction for TAPVR involves redirecting pulmonary venous blood to the LA. Postoperative mechanical ventilation strategies should use applied PEEP to diminish postoperative pulmonary edema and early spontaneous breathing when possible. Patients with significantly obstructed veins preoperatively should be expected to have diminished lung compliance and may require prolonged ventilation. In such cases, the high tidal volumes often used in the acute postoperative period for tidal recruitment should be reconsidered in favor of lower tidal volumes to minimize the risk of volutrauma during prolonged ventilation. Such patients may also exhibit significant pulmonary vascular reactivity and pulmonary hypertension, such that suctioning should take place with precautions as described previously. At times, the use of inhalational nitric oxide may be helpful.

TETRALOGY OF FALLOT

TOF is the most common cyanotic congenital heart abnormality.[35] Classically, TOF includes four components: (1) pulmonary artery stenosis, (2) ventricular septal defect, (3) overriding aorta to the right, and (4) right ventricular hypertrophy (Figure 24-15). The degree of pulmonary artery stenosis can range from mild stenosis to complete pulmonary atresia. The degree of cyanosis, and the early postnatal course of each patient, depends almost exclusively on the degree of obstruction to pulmonary blood flow. Patients with atresia of the pulmonary valve or severe pulmonary stenosis are dependent on ductal flow or on flow through collaterals that look like a ductus (i.e., ductlike collateral). In most cases, these patients require an operation in the newborn period, whether for a BTS or complete repair. In the setting of less severe obstruction, patients may exhibit mild or no cyanosis at baseline and be repaired electively at several months of age.

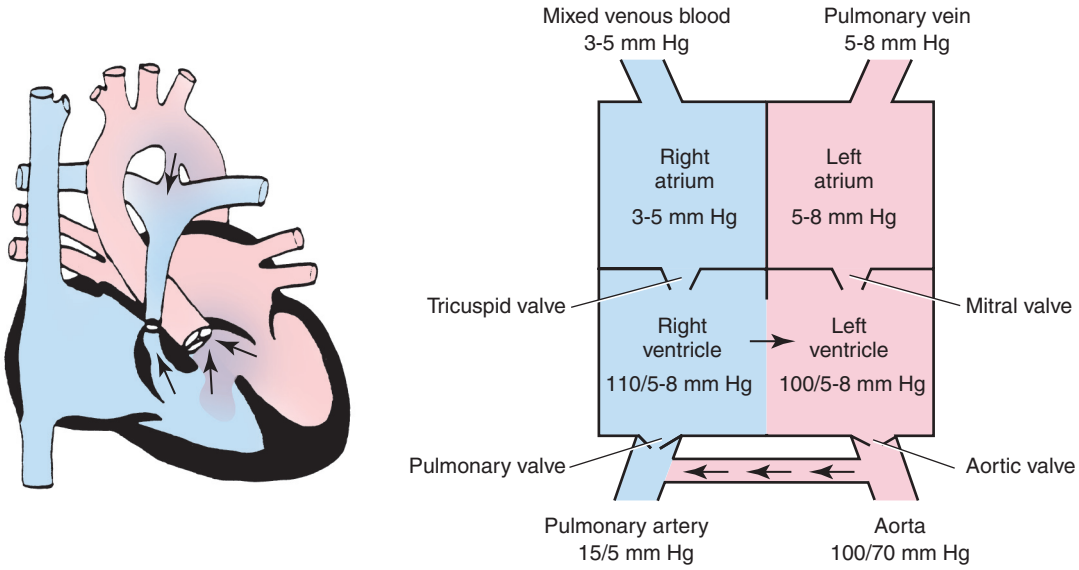


FIGURE 24-15 Tetralogy of Fallot. Overriding aorta, pulmonary artery stenosis, right atrial hypertrophy, and ventricular septal defect. A patent ductus arteriosus is often present to allow pulmonary blood flow if pulmonary stenosis is severe. *PDA,* Patent ductus arteriosus. (From Mullin CE, Mayer DC: *Congenital heart disease: a diagrammatic atlas,* New York, 1988, John Wiley & Sons. This material used by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

Infants with unrepaired TOF may exhibit hypercyanotic episodes in which pulmonary blood flow decreases and Spo_2 decreases. Of course, hypercyanosis implies a change in the color of mucous membranes to a blueish hue, which is also common. A "spell" is further defined as hyperpnea (related to diminished blood flow and dead space ventilation, presumably), irritability, and loss of consciousness (from cyanosis, presumably). Such episodes are acutely life-threatening and must be treated with hyperoxia, opiates, knee–chest position, and, if necessary, pharmacologic agents that acutely increase systemic vascular resistance (SVR) (raising ventricular pressure and favoring pulmonary blood flow through a stenotic right ventricular outflow tract [RVOT]). Rarely, sedation and mechanical ventilation are necessary (Box 24-1); this should be an indication for urgent operative intervention, which in most centers would be a complete repair.

Box 24-1 Treatment of "Tet" Spells

- Knee–chest position: Increases systemic vascular resistance (SVR) and promotes blood flow from the right ventricle to the pulmonary artery rather than the aorta.
- Morphine sulfate: Decreases irritability and may lead to pulmonary artery dilation, which will increase pulmonary blood flow.
- Oxygen: Improves oxygenation and decreases pulmonary vascular resistance (PVR).
- Beta blockers (e.g., propranolol): May relax right outflow tract muscle.
- Systemic vasoconstrictors (e.g., phenylephrine): Increase SVR to promote pulmonary blood flow.
- Sodium bicarbonate: Administered to treat acidosis; decreases PVR.

Box 24-2 Interventions That Affect Pulmonary Vascular Resistance

INCREASE
- ↓ pH
  - ↓ Minute ventilation to ↑ $Paco_2$ ≥45 mm Hg
  - ↑ Inhaled CO_2 to ↓ pH
- ↓ Fio_2
- ↑ Mean airway pressure
  - ↑ PIP, ↑ PEEP, ↑ respiratory rate, ↑ I/E ratio

DECREASE
- ↑ pH
  - ↑ Minute ventilation to ↓ $Paco_2$ to <45 mm Hg
- ↑ Fio_2
  - ↓ Mean airway pressure

PHARMACOLOGY
- PGE1
- iNO
- Prostacyclin

I/E, Inspiratory to expiratory; *iNO,* inhaled nitric oxide; *PEEP,* positive end-expiratory pressure; *PGE1,* prostaglandin E1; *PIP,* peak inspiratory pressure.

Surgical repair of TOF requires relief of RVOT obstruction and VSD closure. Opening the RVOT may require a patch across the pulmonary valve (i.e., transannular patch) or a patch above and below the valve with plasty of the pulmonary valve (i.e., valve-sparing repair).[37-39] The primary consideration after TOF repair is restrictive right ventricular physiology, which results from closure of the VSD and frequently a still hypertrophied and stiff RV. This requires that the ventricle have sufficient preload for filling. The primary benefit of mechanical ventilation in these patients is that it diminishes metabolic demand as the heart

recovers, though early extubation in these patients is possible in the majority. Sao_2 and Spo_2 may be diminished by right-to-left flow at the atrial level. At times, postoperative arrhythmia may require more prolonged ventilation for 2 to 3 days.

TOF with absent pulmonary valve is a disorder in which severe pulmonary regurgitation causes massive enlargement of the PAs and malacia of the proximal and distal airways, which may affect respiration in the newborn period. Repair of TOF/APV may involve repeated interventions to diminish PA size and palliate airway compression. Patients with severe airway disease may require prolonged ventilation, noninvasive ventilation, or tracheostomy.

TRUNCUS ARTERIOSUS

Truncus arteriosus is a rare defect in which a single great artery arises from the ventricles of the heart, supplying both systemic and pulmonary circulations (Figure 24-16). In most patients, the pulmonary arteries will be of sufficient size and minimally restrictive, raising the possibility of pulmonary overcirculation as the native PVR decreases in the first few days of life, as discussed in patients with HLHS. Infants may develop early respiratory distress, congestive heart failure, or shock. Similar to patients with HLHS, oxygen should be avoided in almost all circumstances in the preoperative setting, because there is (in most cases) no anatomic resistor to PBF.

In most cases, patients undergo complete biventricular repair in the newborn period.[40,41] Surgical correction involves VSD closure with incorporation of the truncal valve to the left ventricular outflow tract and connection of the branch pulmonary arteries to an RV-PA conduit (Figure 24-16). The postoperative course of these patients is largely determined by the function of the truncal valve, the degree of preoperative heart failure, and the technical success of the operation. As with all critically ill neonates, care should be taken when suctioning and meticulous attention should be paid to tracheal tube positioning.

TRANSPOSITION OF THE GREAT ARTERIES

Transposition of the great arteries (TGA) is a lesion in which the normal relationship between the ventricles and great arteries is inverted; the aorta arises from the RV and the pulmonary artery arises from the LV (Figure 24-17). The physiologic result of this is that the two circulations are parallel to rather than in series with each other. Deoxygenated systemic venous blood passes through the right side of the heart and to the body without flowing through the lungs. Oxygenated pulmonary venous blood passes through the left side of the heart and back to the lungs without flowing to the body. Survival depends on adequate mixing between the two circulations, most commonly occurring at the atrial level.

After birth, patients with TGA without VSD may be profoundly cyanotic. Most commonly, however, the PDA is large, which permits a significant amount of left (aorta) to right (pulmonary) flow at the PDA, which increases left atrial return relative to right atrial return, forcing blood left to right at the (stretched) PFO, which oxygenates systemic arterial blood. This dynamic is critical to mixing, even in some patients, after creation of a larger ASD using a balloon atrial septostomy. Infants may be extubated.

Surgical repair of TGA takes place via an arterial switch operation (ASO, Figure 24-18) performed in the newborn period.[42-45] On bypass, the aorta and pulmonary artery are transected and moved to their proper root location. The coronary arteries are transferred to

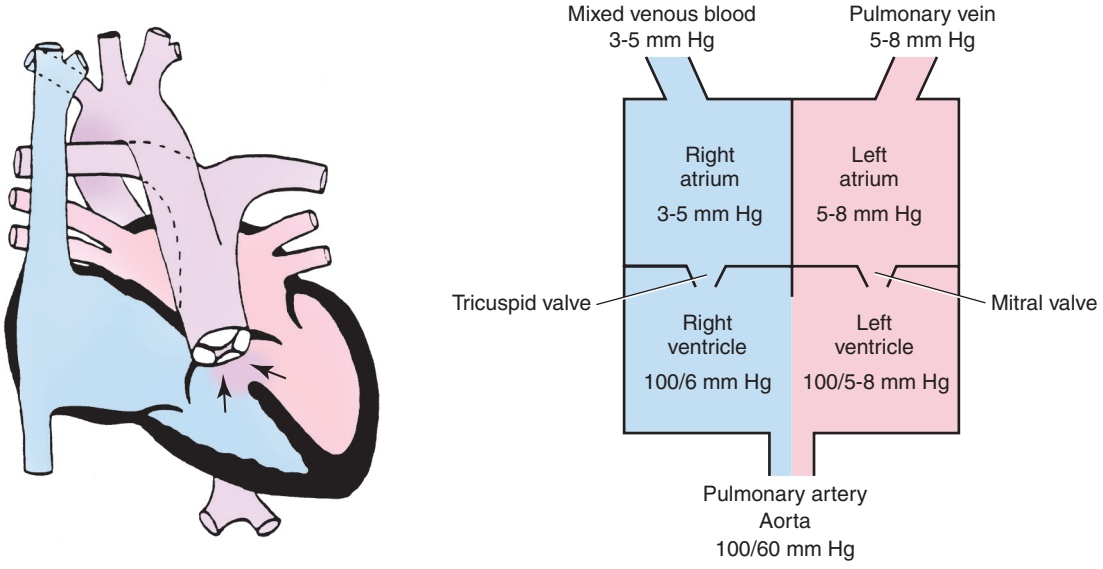


FIGURE 24-16 Truncus arteriosus. A single great artery arises from the ventricles carrying both pulmonary and systemic blood. (From Mullin CE, Mayer DC: *Congenital heart disease: a diagrammatic atlas,* New York, 1988, John Wiley & Sons. This material used by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

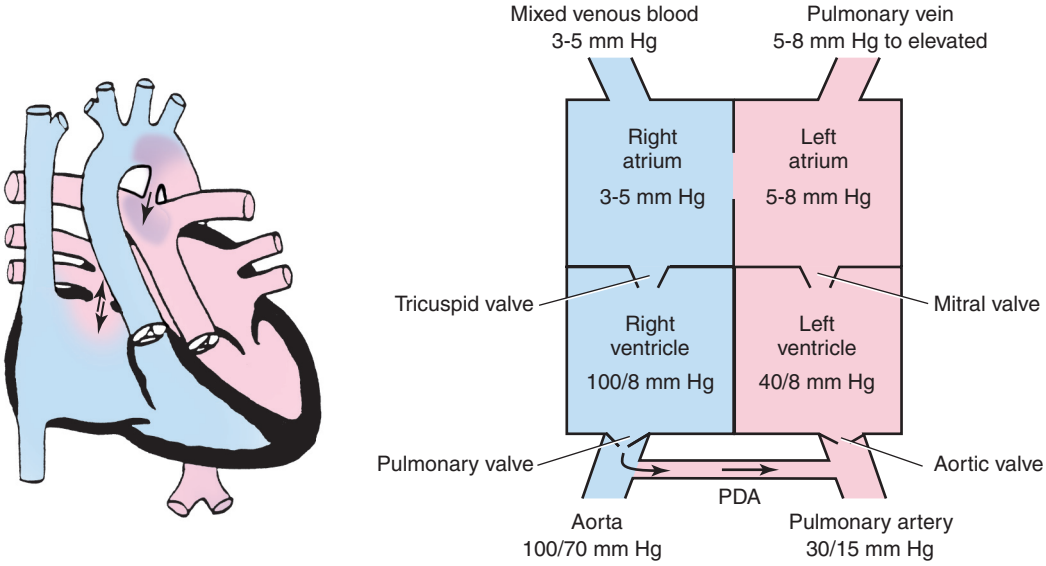


FIGURE 24-17 Transposition of the great arteries. The aorta arises from the right ventricle and the pulmonary artery arises from the left ventricle. A patent ductus arteriosus is necessary to allow pulmonary blood flow. *PDA,* Patent ductus arteriosus. (From Mullin CE, Mayer DC: *Congenital heart disease: a diagrammatic atlas,* New York, 1988, John Wiley & Sons. This material used by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

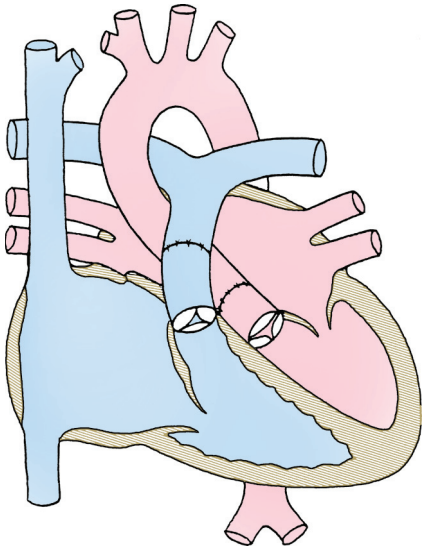


FIGURE 24-18 Arterial switch. The pulmonary artery and aorta are separated from their respective origins and reattached to provide normal pulmonary and aortic blood flow. (From Mullin CE, Mayer DC: *Congenital heart disease: a diagrammatic atlas,* New York, 1988, John Wiley & Sons. This material used by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

the neoaortic root. To switch the positions of the great arteries, the pulmonary artery is usually moved anterior to the aorta (i.e., Lecompte maneuver).[46] After ASO, most infants are stable and can be extubated within 1 to 2 days.

PULMONARY ATRESIA WITH INTACT VENTRICULAR SEPTUM

Pulmonary atresia with intact ventricular septum (PA/IVS) is a condition in which blood flow out of the RV is obstructed because of atresia of the pulmonary valve. The RV is typically hypertrophied, and the RV cavity is often hypoplastic. The left side of the heart receives blood from the right side via an ASD or patent foramen ovale. Pulmonary blood flow is ductal dependent, such that PGE1 is necessary to establish it. Treatment of PA/IVS may involve catheter-based dilation of the pulmonary valve and subsequent weaning from PGE.[47-51]

CLINICAL MONITORING OF PATIENTS WITH CARDIAC ANOMALIES

HEMODYNAMIC MONITORING

Because infants and children with congenital heart disease are at risk of compromised oxygen delivery and blood flow, invasive monitoring is frequently performed. The respiratory therapist should have a familiarity with such monitoring, including norms and common pitfalls, which is the purpose of this section. Much of the rich hemodynamic information comes from an arterial line, an end-hole catheter placed into a major artery commonly in the hand, foot, or groin. When attached to a transducer, this provides a beat-to-beat measurement of arterial blood pressure. The systolic blood pressure is that in the arteries during ventricular systole, the diastolic during ventricular diastole, and the mean blood pressure is time-averaged pressure. A decrease in blood pressure based on the arterial catheter, particularly in concert with other congruent signs, such as loss of plethymograph on the pulse oximetry tracing, should be considered a true sign and not assumed to be "artifact" or arterial spasm in patients in the

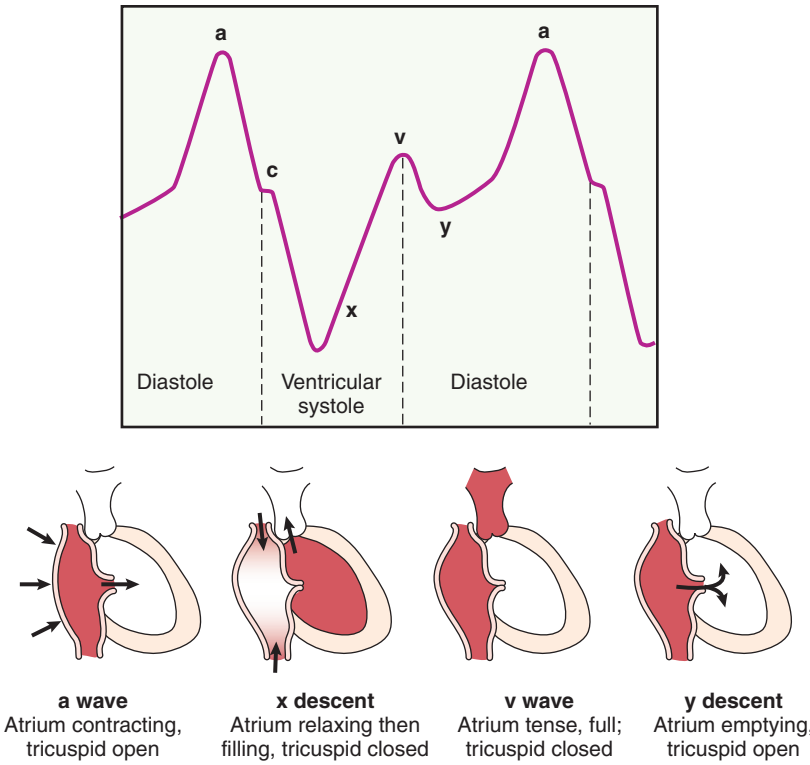


FIGURE 24-19 Central venous pressure tracing, which includes the *a wave*, caused by contraction of atria; the *c wave*, caused by ventricular contraction against closed tricuspid valve; *x descent*, caused by ventricular contraction and pulling of tricuspid valve away from the right atrium; *v wave*, caused by atrial filling; and *y descent*, caused by opening of the tricuspid valve and emptying of the right atrium.

cardiac intensive care unit. A narrowing of pulse pressure (the difference between systolic and diastolic pressure) below 10 to 15 mm Hg is suggestive of a low stroke volume, which may be related to poor ventricular function, impaired venous return (e.g., because of a fluid collection around the heart), hypovolemia, or loss of atrioventricular synchrony, among other reasons.

Another frequently measured pressure is the central venous pressure (CVP, Figure 24-19), which represents the pressure inside the systemic venous system (the largest reservoir of blood in the body). This pressure represents the pressure head filling the atrium and ventricle and is related to but distinct from the concept of ventricular preload. Preload can be defined in several ways, but in essence it is defined as the ventricular end-diastolic volume. The relationship between end-diastolic volume and pressure is the definition of ventricular compliance, which is altered in patients with diastolic dysfunction. The impact of positive pressure ventilation on diastolic filling should be appreciated. Because the venous system operates at low pressure, intrathoracic pressure changes can have a profound impact on venous return. Specifically, positive pressure ventilation can change the pericardial pressure, which represents the downstream pressure that venous blood must overcome to enter the heart, from −5 cm H_2O to +10 cm H_2O (or more, whatever the mean airway pressure is). In diseased hearts that are preload dependent, including in patients with myocarditis, this change can have a profound effect on ventricular filling and stroke volume. In some cases, patients at risk for positive pressure–related decrements in preload can be treated with vasoconstrictors to decrease venous capacitance of the systemic veins, or with administration of volume. In most such cases, ventilation at the lowest possible mean airway pressure is required to minimize the effects of ventilation on ventricular preload. This is particularly true during an acute intubation in the intensive care unit, in which setting a discussion surrounding the susceptibility of the ventricle to alterations in preload should take place before anesthetic induction.

PULSE OXIMETRY AND COOXIMETRY

Pulse oximetry is a fundamental monitoring device in children with congenital heart disease. All pulse oximeters function based on absorbance spectroscopy. The pulse oximeter emits light in the red and infrared spectrum on a tissue, and oxyhemoglobin and deoxyhemoglobin absorb light differently at certain wavelengths, which can be used to quantify the relative quantity of each. Of course, hemoglobin also exists in capillaries and veins, and the pulse oximeter uses changes in absorbance based on pulsatility to identify which fraction of the signal is arterial and which is not. Because of this technique, the pulse oximeter also provides a plethysmogram, displayed on almost all bedside

monitors, that is a vital piece of information—its amplitude indicates the confidence in the signal, and therefore the oximetry reading. A blunted plethysmogram should diminish confidence in the oximetry reading, which often varies widely when signal strength is low. Most often, signal strength is low because of either probe malposition or poor perfusion, low stroke volume, or elevated SVR.

In the cyanotic range, pulse oximetry readings of Spo_2 correlate poorly with the gold standard, Sao_2 from arterial blood gas.[52] The arterial blood of patients with heart disease must be interpreted using cooximetry, an expanded form of absorbance spectroscopy in which the sample is exposed to 168 wavelengths (rather than 2-4 wavelengths used by standard pulse oximeters). Spo_2 may be used as a trend monitor, but in critically ill patients, low Spo_2 is not sufficiently accurate to be actionable.[53,54]

CAPNOGRAPHY

Capnography should be used whenever possible in mechanically ventilated children with congenital heart disease. $ETCO_2$ correlates well with $Paco_2$, with a normal gradient of 2 to 5 mm Hg between the two.[55] Decreased $ETCO_2$ may be caused by endotracheal tube dislodgement or obstruction, air trapping, decreased pulmonary blood flow, low cardiac output, or hyperventilation. Elevated $ETCO_2$ is associated with hypoventilation, fever, or malignant hyperthermia. Increases in the gradient between $Paco_2$ and $ETCO_2$ is indicative of increased dead space, lower pulmonary blood flow, high airway pressures leading to alveolar overdistention, and pulmonary embolism.

Capnography is useful in a number of specific scenarios when caring for critically ill children. Capnography may be used immediately after intubation to distinguish between endotracheal and esophageal tube placement.[56] Continuous $ETCO_2$ readings allow real-time monitoring of ventilation and serve an important patient safety function by relaying data on proper endotracheal tube placement. The magnitude of the $ETCO_2$ tracing may be used as a surrogate of efficacy of cardiopulmonary resuscitation (CPR).[57,58] Finally, in children with a BTS, a precipitous drop in $ETCO_2$ may indicate a loss of pulmonary blood flow as a result of shunt thrombosis.

Key Points

- Shortly after birth, several physiologic changes occur, including closure of the ductus arteriosus, decrease in pulmonary vascular resistance, and closure of the foramen ovale, but some of these intrauterine shunts may persist after birth.
- *Shunt* refers to blood deviating from its normal flow pattern and may be right to left or left to right in different cardiac defects.
- There are a number of different classification schemes for congenital heart defects, including classification by presence or lack of cyanosis, shunt type, or lesions that result in obstructed blood flow, and miscellaneous structural lesions, including those with abnormal valve anatomy or function.
- In understanding the various congenital heart defects, one must understand both the anatomy of each lesion and its underlying physiology.
- Pulmonary vascular resistance may be altered by changes in pH, oxygenation, and mean airway pressure.
- In heart lesions where there is mixing of pulmonary and systemic blood, therapeutic maneuvers often target a balance in the ratio of pulmonary to systemic blood flow (Q_P/Q_S).
- Positive-pressure ventilation may negatively affect pulmonary blood flow or cardiac output in children with a number of heart defects, particularly those who have undergone a bidirectional Glenn or Fontan procedure.

Assessment Questions

See Evolve Resources for the answers.

1. Normal transition to extrauterine life depends on the pulmonary vascular system:
   - **A.** Remaining in a steady state of balance with the hepatic blood flow
   - **B.** Changing from low pulmonary vascular resistance to high pulmonary vascular resistance
   - **C.** Changing from high pulmonary vascular resistance to low pulmonary vascular resistance
   - **D.** Maintaining a patent ductus arteriosus
2. Which of the following affects pulmonary vascular resistance?
   - **A.** Changes in Pao_2
   - **B.** Changes in $Paco_2$
   - **C.** Changes in pH
   - **D.** All of the above
   - **E.** None of the above
3. What are the two categories that have typically been used to classify congenital cardiac defects?
   - **A.** Right-sided versus left-sided
   - **B.** Atrial versus ventricular
   - **C.** Cyanotic versus acyanotic
   - **D.** Simple versus complex
   - **E.** Above versus below the diaphragm
4. The patent ductus arteriosus connects which two vessels?
   - **A.** Superior vena cava and pulmonary artery
   - **B.** Aorta and pulmonary artery
   - **C.** Pulmonary artery and pulmonary vein
   - **D.** Coronary arteries and aortic arch
   - **E.** Ductus venosus and right atrium

5. What is the therapeutic goal of subambient oxygen therapy?
   - **A.** Increase the pulmonary vascular resistance
   - **B.** Balance blood flow between the vena cava and the right atrium
   - **C.** Decrease pulmonary vascular resistance
   - **D.** Increase diastolic blood pressure
6. True or false:
   The purpose of managing pulmonary vascular resistance in the presence of cardiac defects is to ensure the desired balance between systemic and pulmonary blood flow.
7. Tetralogy of Fallot consists of which four concomitant conditions?
   - **I.** Truncus arteriosus
   - **II.** Left ventricular hypertrophy
   - **III.** Right ventricular hypertrophy
   - **IV.** Overriding aorta
   - **V.** Interrupted aortic arch
   - **VI.** Pulmonary stenosis
   - **VII.** Ventricular septal defect
   - **VIII.** Right ventricular outflow tract obstruction
     - **A.** I, II, III, V
     - **B.** III, IV, VI, VII
     - **C.** V, VI, VII, VIII
8. True or false:
   In complete transposition of the great arteries, the aorta and the pulmonary artery circulation run in series.
9. For which condition is positive pressure most likely to have a negative impact on pulmonary blood flow and cardiac output?
   - **A.** Unrepaired truncus arteriosus
   - **B.** Total anomalous venous return
   - **C.** Situs inversus
   - **D.** Bidirectional Glenn
10. Increasing gradients between $ETCO_2$ and $PaCO_2$ in patients with congenital cardiac defects are often the result of:
    - **A.** Loss of calibration
    - **B.** Ventilation–perfusion mismatch
    - **C.** Equipment malfunction

REFERENCES

1. Gilboa SM, Salemi JL, Nembhard WN, Fixler DE, Correa A. Mortality resulting from congenital heart disease among children and adults in the United States, 1999 to 2006. *Circulation*. 2010;122(22):2254-2263.
2. Boneva RS, Botto LD, Moore CA, Yang Q, Correa A, Erickson JD. Mortality associated with congenital heart defects in the United States: trends and racial disparities, 1979-1997. *Circulation*. 2001;103(19):2376-2381.
3. Marelli AJ, Ionescu-Ittu R, Mackie AS, Guo L, Dendukuri N, Kaouache M. Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010. *Circulation*. 2014;130:749-756.
4. Warnes CA, Liberthson R, Danielson GK, et al. Task force 1: the changing profile of congenital heart disease in adult life. *J Am Coll Cardiol*. 2001;37(5):1170-1175.
5. Hermes-DeSantis ER, Clyman RI. Patent ductus arteriosus: pathophysiology and management. *J Perinatol*. 2006; 26(suppl 1):S14-S18, discussion S22-S23.
6. Wyllie J. Treatment of patent ductus arteriosus. *Semin Neonatol*. 2003;8:425.
7. Frank LH, Bradshaw E, Beekman R, Mahle WT, Martin GR. Critical congenital heart disease screening using pulse oximetry. *J Pediatr*. 2013;162(3):445-453.
8. Jones LJ, Craven PD, Attia J, Thakkinstian A, Wright I. Network meta-analysis of indomethacin versus ibuprofen versus placebo for PDA in preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 2011;96(1):F45-F52.
9. Terrin G, Conte F, Oncel MY, et al. Paracetamol for the treatment of patent ductus arteriosus in preterm neonates: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed*. 2016;101:F127.
10. Cockerham JT, Martin TC, Gutierrez FR, Hartmann Jr AF, Goldring D, Strauss AW. Spontaneous closure of secundum atrial septal defect in infants and young children. *Am J Cardiol*. 1983;52(10):1267-1271.
11. Mahoney LT, Truesdell SC, Krzmarzick TR, Lauer RM. Atrial septal defects that present in infancy. *Am J Dis Child*. 1986;140(11):1115-1118.
12. Radzik D, Davignon A, van Doesburg N, Fournier A, Marchand T, Ducharme G. Predictive factors for spontaneous closure of atrial septal defects diagnosed in the first 3 months of life. *J Am Coll Cardiol*. 1993;22(3):851-853.
13. Holzer R, Hijazi ZM. Interventional approach to congenital heart disease. *Curr Opin Cardiol*. 2004;19:84.
14. Bartakian S, Fagan TE, Schaffer MS, Darst JR. Device closure of secundum atrial septal defects in children <15 kg: complication rates and indications for referral. *JACC Cardiovasc Interv*. 2012;5(11):1178-1184.
15. Kimball TR, Daniels SR, Meyer RA, et al. Effect of digoxin on contractility and symptoms in infants with a large ventricular septal defect. *Am J Cardiol*. 1991;68(13):1377-1382.
16. Hijazi ZM, Hakim F, Haweleh AA, et al. Catheter closure of perimembranous ventricular septal defects using the new Amplatzer membranous VSD occluder: initial clinical experience. *Catheter Cardiovasc Interv*. 2002;56(4): 508-515.
17. Ghaffar S, Lemler MS, Fixler DE, Ramaciotti C. Trisomy 21 and congenital heart disease: effect of timing of initial echocardiogram. *Clin Pediatr (Phila)*. 2005;44(1):39-42.
18. Newfeld EA, Waldman D, Paul MH, et al. Pulmonary vascular disease after systemic-pulmonary arterial shunt operations. *Am J Cardiol*. 1977;39(5):715-720.
19. Stellin G, Vida VL, Milanesi O, et al. Surgical treatment of complete A-V canal defects in children before 3 months of age. *Eur J Cardiothorac Surg*. 2003;23(2):187-193.
20. Setty SP, Shen I. *Atrioventricular Septal Defects*. 2nd ed. Philadelphia: Mosby; 2006.

21. Nargozian C. The airway in patients with craniofacial abnormalities. *Paediatr Anaesth*. 2004;14:53-59.
22. Aboulhosn J, Child JS. Left ventricular outflow obstruction: subaortic stenosis, bicuspid aortic valve, supravalvar aortic stenosis, and coarctation of the aorta. *Circulation*. 2006; 114(22):2412-2422.
23. McCrindle BW, Blackstone EH, Williams WG, et al. Are outcomes of surgical versus transcatheter balloon valvotomy equivalent in neonatal critical aortic stenosis? *Circulation*. 2001;104(12 suppl 1):I152-I158.
24. Maskatia SA, Ing FF, Justino H, et al. Twenty-five year experience with balloon aortic valvuloplasty for congenital aortic stenosis. *Am J Cardiol*. 2011;108(7):1024-1028.
25. Jonas RA. Coarctation of the aorta. In: *Comprehensive Surgical Management of Congenital Heart Disease*. 2nd ed. CRC Press; 2014:289-310.
26. Rajasinghe HA, Reddy VM, van Son JA, et al. Coarctation repair using end-to-side anastomosis of descending aorta to proximal aortic arch. *Ann Thorac Surg*. 1996;61(3):840-844.
27. Tabbutt S, Ramamoorthy C, Montenegro LM, et al. Impact of inspired gas mixtures on preoperative infants with hypoplastic left heart syndrome during controlled ventilation. *Circulation*. 2001;104(12 suppl 1):I159-I164.
28. Norwood WI, Lang P, Hansen DD. Physiologic repair of aortic atresia-hypoplastic left heart syndrome. *N Engl J Med*. 1983;308(1):23-26.
29. Gaynor JW, Mahle WT, Cohen MI, et al. Risk factors for mortality after the Norwood procedure. *Eur J Cardiothorac Surg*. 2002;22(1):82-89.
30. Akintuerk H, Michel-Behnke I, Valeske K, et al. Stenting of the arterial duct and banding of the pulmonary arteries: basis for combined Norwood stage I and II repair in hypoplastic left heart. *Circulation*. 2002;105(9):1099-1103.
31. Galantowicz M, Cheatham JP. Lessons learned from the development of a new hybrid strategy for the management of hypoplastic left heart syndrome. *Pediatr Cardiol*. 2005; 26(3):190-199.
32. Bacha EA, Daves S, Hardin J, et al. Single-ventricle palliation for high-risk neonates: the emergence of an alternative hybrid stage I strategy. *J Thorac Cardiovasc Surg*. 2006;131(1): 163-171.e2.
33. Wernovsky G, Bove EL. Single ventricle lesions. In: Chang AC, Hanley FI, Wernovsky G, et al, eds. *Pediatric Cardiac Intensive Care*. Baltimore: Williams and Wilkins; 1998:271-287.
34. Genz T, Locher D, Genz S, Schumacher G, Bühlmeyer K. Chest X-ray film patterns in children with isolated total anomalous pulmonary vein connection. *Eur J Pediatr*. 1990;150(1):14-18.
35. Fyler DC, Buckley LP, Hellenbrand WE, Cohn HE. Report of the New England regional infant cardiac program. *Pediatrics*. 1980;65:375.
36. Reddy VM, Liddicoat JR, McElhinney DB, Brook MM, Stanger P, Hanley FL. Routine primary repair of tetralogy of Fallot in neonates and infants less than three months of age. *Ann Thorac Surg*. 1995;60(suppl 6):S592-S596.
37. Parry AJ, McElhinney DB, Kung GC, Reddy VM, Brook MM, Hanley FL. Elective primary repair of acyanotic tetralogy of Fallot in early infancy: overall outcome and impact on the pulmonary valve. *J Am Coll Cardiol*. 2000;36(7): 2279-2283.
38. Pigula FA, Khalil PN, Mayer JE, del Nido PJ, Jonas RA. Repair of tetralogy of Fallot in neonates and young infants. *Circulation*. 1999;100(suppl 19):II157-II161.
39. Stewart RD, Backer CL, Young L, Mavroudis C. Tetralogy of Fallot: results of a pulmonary valve-sparing strategy. *Ann Thorac Surg*. 2005;80(4):1431-1438, discussion 1438-1439.
40. McFaul RC, Mair DD, Feldt RH, Ritter DG, McGoon DC. Truncus arteriosus and previous pulmonary arterial banding: clinical and hemodynamic assessment. *Am J Cardiol*. 1976; 38(5):626-632.
41. Thompson LD, McElhinney DB, Reddy M, Petrossian E, Silverman NH, Hanley FL. Neonatal repair of truncus arteriosus: continuing improvement in outcomes. *Ann Thorac Surg*. 2001;72(2):391-395.
42. Backer CL, Ilbawi MN, Ohtake S, et al. Transposition of the great arteries: a comparison of results of the mustard procedure versus the arterial switch. *Ann Thorac Surg*. 1989; 48(1):10-14.
43. Hazekamp MG, Ottenkamp J, Quaegebeur JM, et al. Follow-up of arterial switch operation. *Thorac Cardiovasc Surg*. 1991; 39(suppl 2):166-169.
44. Martin RP, Qureshi SA, Ettedgui JA, et al. An evaluation of right and left ventricular function after anatomical correction and intra-atrial repair operations for complete transposition of the great arteries. *Circulation*. 1990;82(3): 808-816.
45. Veelken N, Grävinghoff L, Keck EW, Freitag HJ. Improved neurological outcome following early anatomical correction of transposition of the great arteries. *Clin Cardiol*. 1992; 15(4):275-279.
46. Jonas, RA. Transposition of the great arteries. In: *Comprehensive Surgical Management of Congenital Heart Disease*. 2nd ed. CRC Press; 2014:371-394.
47. Akagi T, Hashino K, Maeno Y, et al. Balloon dilatation of the pulmonary valve in a patient with pulmonary atresia and intact ventricular septum using a commercially available radiofrequency catheter. *Pediatr Cardiol*. 1997;18(1):61-63.
48. Colli AM, Perry SB, Lock JE, Keane JF. Balloon dilation of critical valvar pulmonary stenosis in the first month of life. *Cathet Cardiovasc Diagn*. 1995;34(1):23-28.
49. Gibbs JL, Blackburn ME, Uzun O, Dickinson DF, Parsons JM, Chatrath RR. Laser valvotomy with balloon valvoplasty for pulmonary atresia with intact ventricular septum: five years' experience. *Heart*. 1997;77(3):225-228.
50. Justo RN, Nykanen DG, Williams WG, Freedom RM, Benson LN. Transcatheter perforation of the right ventricular outflow tract as initial therapy for pulmonary valve atresia and intact ventricular septum in the newborn. *Cathet Cardiovasc Diagn*. 1997;40(4):408-413.
51. Agnoletti G, Piechaud JF, Bonhoeffer P, et al. Perforation of the atretic pulmonary valve. Long-term follow-up. *J Am Coll Cardiol*. 2003;41(8):1399-1403.
52. Schmitt HJ, Schuetz WH, Proeschel PA, Jaklin C. Accuracy of pulse oximetry in children with cyanotic congenital heart disease. *J Cardiothorac Vasc Anesth*. 1993;7(1):61-65.
53. Malviya S, Reynolds PI, Voepel-Lewis T, et al. False alarms and sensitivity of conventional pulse oximetry versus the Masimo SET technology in the pediatric postanesthesia care unit. *Anesth Analg*. 2000;90(6):1336-1340.
54. Torres Jr A, Skender KM, Wohrley JD, et al. Pulse oximetry in children with congenital heart disease: effects of cardiopulmonary bypass and cyanosis. *J Intensive Care Med*. 2004;19(4):229-234.
55. Hess D. *Capnometry*. New York: McGraw-Hill; 1998.
56. Roberts WA, Maniscalco WM, Cohen AR, Litman RS, Chhibber A. The use of capnography for recognition of esophageal intubation in the neonatal intensive care unit. *Pediatr Pulmonol*. 1995;19(5):262-268.
57. Falk JL, Rackow EC, Weil MH. End-tidal carbon dioxide concentration during cardiopulmonary resuscitation. *N Engl J Med*. 1988;318(10):607-611.
58. Morrison LJ, Deakin CD, Morley PT, et al. Part 8: Advanced life support: 2010 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Circulation*. 2010;122(16 suppl 2): S345-S421.

Pediatric Sleep-Disordered Breathing

25

Brian K. Walsh

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. Describe normal sleep development.
2. Describe normal sleep architecture.
3. Describe the difference between central and obstructive apnea.
4. Describe the difference between sudden infant death syndrome (SIDS) and acute life-threatening events.
5. Name the intervention that altered the incidence of SIDS.
6. Describe the pathophysiology of obstructive sleep apnea.
7. Describe a sleep history and physical examination.
8. Describe the basic measurements made during a sleep study.
9. Name the most common cause of obstructive sleep apnea in children.
10. Name the two most common treatments for obstructive sleep apnea.

Key Terms

acute life-threatening event (ALTE)
apnea of prematurity (AOP)
central sleep apnea (CSA)
continuous positive airway pressure (CPAP)
EEG arousal
electroencephalogram (EEG)
non–rapid eye movement (NREM) sleep
obstructive sleep apnea (OSA)
periodic breathing
rapid eye movement (REM) sleep
sleep architecture
sleep-disordered breathing (SDB)
sudden infant death syndrome (SIDS)

Sleep may be defined as a neurophysiologically distinct state of awareness required for human health. It involves the intersection of developmental, physiologic, homeostatic, and behavioral mechanisms. The function of sleep in mammals is not well understood. Nevertheless, sleep deprivation causes serious neurocognitive deficits and is lethal in animals. The association of disordered sleep and daytime function has long been appreciated. Sir William Osler stated that "chronic enlargement of the tissues of the tonsillar ring is an affection of great importance and may influence in an extraordinary way the mental and bodily development of children. . . . *At night the child's sleep is greatly disturbed; the respirations are loud and snorting, and there are sometimes prolonged pauses, followed by deep noisy inspirations.*"[1] The neurodevelopmental and cognitive consequences of disturbed sleep in childhood are now an area of intense study.

NORMAL SLEEP DEVELOPMENT

Sleep patterns progressively change throughout childhood.[2,3] A normal newborn spends 70% of a 24-hour day asleep. The baby typically has 3- to 4-hour sleep periods with 1- to 2-hour awake periods. In the first few months of life, babies have not yet become fully entrained to a day–night cycle, but a circadian rhythm consolidates by about the eighth week. Critical sleep reorganization occurs between 8 and 12 weeks. **Non–rapid eye movement (NREM)** sleep develops by 6 months, while **rapid eye movement (REM) sleep** decreases. At 6 months, total sleep time is 13 to 14 hours, and sleep episodes are 6 to 8 hours in duration. Seventy percent of infants are sleeping through the night at 9 months. Toddlers' total sleep time decreases further to about 12 to 14 hours. The sleep cycle length is about 60 minutes. Daytime sleep decreases throughout the first year. In preschool-age children, the sleep cycle lengthens to about 90 minutes and total sleep time shortens to 11 to 12 hours. Daytime sleep continues to decrease, and most have given up napping by 4 to 5 years. The sleep pattern in school-age children becomes more stable, and sleep time continues to decrease. Box 25-1 reviews sleep duration by age.

The **electroencephalogram (EEG)** is used to characterize sleep. The EEG undergoes maturational changes

Box 25-1 Sleep Duration by Age

Full-term infant	16-18 hours
1 year	15 hours
2 years	13-14 hours
4 years	12 hours
10 years	8-10 hours
Mid-adolescence	8.5 hours
Later adolescence	7-8 hours

throughout early childhood. The electrical activity recorded at the surface of the scalp is a summation of electrical activity coming from deep brain structures. As the brain develops, the EEG changes rapidly. *In utero* the pattern is discontinuous. Three sleep stages are present in term infants: (1) REM or active sleep, (2) NREM or quiet sleep, and (3) indeterminate sleep. REM sleep predominates in neonates. During this period REM may be observed at sleep onset, a pattern that is quite abnormal in later life. Quiet sleep (NREM) or slow-wave sleep is poorly developed in infants. However, in the first year of life REM sleep duration decreases and NREM sleep duration increases. There is an intermediate EEG pattern that is referred to *indeterminate sleep* because it is distinguishable as neither REM nor NREM. As the child develops, REM sleep continues to decrease until the duration of REM stabilizes at approximately 20% to 25% of sleep time sometime after 2 years of age. REM is a period when brain metabolism is the highest and muscle activity is dramatically decreased. NREM sleep has been referred to as regenerative sleep. NREM sleep continues to increase in duration and peaks between 5 and 9 years and then decreases throughout the rest of life. When fully developed, NREM sleep has four distinct stages, characterized by four EEG wave patterns. Quantification of these EEG stages provides the basis for a description of **sleep architecture.** In light, or stage 1, sleep, alpha-wave activity predominates and slow eye rolling is observed. Stage 1 is approximately 5% of the sleep period. Stage 2 is 45% to 55% of the sleep period. The EEG contains sleep spindles and K complexes, markers of the stage. Stages 3 and 4 together account for approximately 20% of sleep duration. This EEG stage contains slow waves. An additional important pattern is the **EEG arousal.** During an EEG arousal, there is disruption of the quality and duration of the sleep stages but no arousal, to wakefulness. Disruption of the sleep architecture by EEG arousals causes inefficient and nonrestorative sleep.

DISORDERED BREATHING IN INFANTS

Respiration is under both voluntary and involuntary control. There has been a dramatic increase in our understanding of the anatomic, neurochemical, and genetic basis for the control of the rhythm of respiration. Respiratory control matures as the brain matures. A number of features of this development place babies at increased risk of **sleep-disordered breathing (SDB).** Classical models of control of respiration described central chemoreceptors in the medulla of the brainstem and peripheral chemoreceptors in the carotid body. The central receptors respond to pH and carbon dioxide tension, whereas the peripheral receptors respond to hypoxia. These models are currently undergoing modification as new evidence emerges.[4] Infants have respiratory instability and very commonly have brief apneas up to 10 seconds. These pauses are typically REM related. **Periodic breathing,** a breathing pattern also common in infants, may be defined as a pattern of cycles of rapid breathing followed by pauses longer than 3 seconds. Each cycle may occur 2 to 3 times per minute. Brief apneas and periodic breathing decrease in frequency with increasing age. Apnea is defined as a respiratory pause sustained for more than 15 to 20 seconds, or as little as 10 seconds if it is associated with bradycardia or cyanosis. Central apnea occurs when respiratory effort ceases; there is no chest movement and hence no air flow. Diagnosis of central apnea must take into account a multitude of factors. Because infants normally have a more rapid baseline respiratory rate and a reduced respiratory reserve, and therefore less protection from hypoxia, shorter central events can be more clinically significant in this age group. Central apnea can lead to significant physiologic compromise such as bradycardia or color change associated with declining oxyhemoglobin levels.

A number of anatomic and physiologic features place neonates at increased risk for SDB. Infants are near obligate nasal breathers. Nasal obstruction may paradoxically lead to central apnea in neonates or contribute to respiratory obstruction and lead to obstructive apnea. The shape of the chest is more rounded, the diaphragm tends to be flatter, and the rib articulation is less angular. Therefore the rib cage contributes less to overall breathing than in older children. Chest wall compliance is high in infants. Unlike in older children and adults, in whom functional residual capacity (FRC) is maintained passively by chest wall recoil, FRC in neonates must be maintained actively. FRC is further decreased in REM during the period of decreased muscle activity.

Apnea of prematurity (AOP) is observed in infants born prematurely and is common among infants younger than 32 weeks of gestation. The pathophysiology of AOP is not fully understood. It is assumed to be either central or obstructive. Because of the unstable chest wall and immature lungs, **continuous positive airway pressure (CPAP)** is often the first therapy. If the infant continues to have AOP, it may be related to the immaturity of neural control of the cardiorespiratory system, often in conjunction with environmental stimuli, which seems to be the basis of AOP. AOP is often treated with caffeine, which is thought to stimulate the respiratory centers.

In **central sleep apnea (CSA)** there is an absence of respiratory effort and airflow. The American Academy of Pediatrics (AAP) defines CSA as "an unexplained episode of cessation of breathing for 20 seconds or longer, or a shorter respiratory pause associated with bradycardia, cyanosis, pallor, and/or marked hypotonia."[5] CSA in infants and children is often idiopathic, but

Box 25-2 Conditions Associated With Central Sleep Apnea

- Arnold-Chiari type II malformation
- Prader-Willi syndrome
- Ondine's curse (congenital central hypoventilation syndrome)
- Central nervous system pathology (intraventricular hemorrhage, brain anomaly, CNS infection, ischemic infarction)
- Drugs
- Sepsis
- Respiratory infections (RSV, pertussis)
- Gastroesophageal reflux
- Metabolic disorder
- Neoplasm
- Hypothermia
- Idiopathic

CNS, Central nervous system; *RSV,* respiratory syncytial virus.

like AOP, immaturity of the respiratory centers seems to play a role. When significant CSA is present, an underlying cause should be sought, because there are many medical conditions associated with CSA (Box 25-2). Central and obstructive apnea may be present at the same time in a mixed apnea pattern (Figure 25-1). In some conditions, such as heart disease and obesity, central hypoventilation is related to reduced central chemoreceptor insensitivity.

SUDDEN INFANT DEATH SYNDROME AND ACUTE LIFE-THREATENING EVENTS

Sudden infant death syndrome (SIDS) is a devastating event that accounted for 2226 infant deaths in 2009.[6] It is the leading cause of death in the first 12 months of life and the third leading cause of infant death overall in the United States. It is defined as "the sudden death of an infant less than one 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."[6]

SIDS almost always takes place when the infant is presumed to have been asleep, either during the day or at night. However, more than 70% of its victims are found in the early morning hours after the nighttime sleep. The incidence peaks in infants 2 to 4 months of age. This period coincides with significant changes known to occur in sleep organization and in the modulation of brainstem centers involved in respiratory and arousal state control. SIDS is uncommon after 6 months of age, with 90% of victims affected in the first 6 months of life. It is rare after the first birthday.

Many theories have been offered to explain the tragedy of SIDS. Because it is assumed that there must be a cessation of breathing, there has long been a focus on

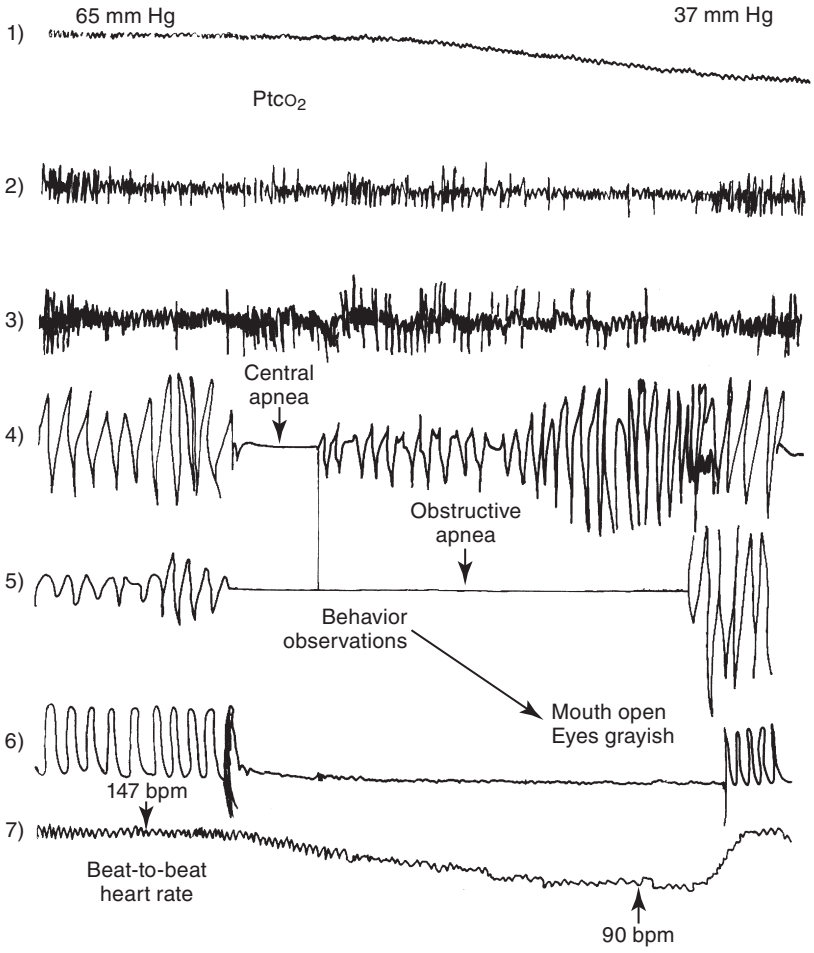


FIGURE 25-1 A 1-minute record from a polysomnogram showing a 37-second mixed apnea. Channel 1 shows a drop in transcutaneous oxygen tension from 65 to 37 mm. Channel 4 shows breathing movements and channels 5 and 6 show airflow. There is an initial cessation of respiratory effort and airflow (central apnea). As effort increases there continues to be no airflow until there is a gasp. Both heart rate and oxygenation fell during this mixed central and obstructive apnea.

apnea as a proximate event. The apnea hypothesis has driven SIDS research for the last 40 years and led to some catastrophic conclusions.[7] Throughout the 1980s an intense search for a predictive model of SIDS was unsuccessful. Abnormalities in cardiac rhythm, control of ventilation, autonomic dysfunction, and faulty arousal have all been a focus of research. More recently it has been suggested that the occurrence of SIDS may not require the susceptible infant to be abnormal, but rather is a consequence of normal neonatal development and physiology placed in the proper environmental context. There is now general agreement that the cause of SIDS is multifactorial.

Although a mechanistic explanation of the cause has been elusive, significant progress has been made in the prevention of SIDS. Risk factors associated with SIDS have been known for decades (Box 25-3). Since the early 1990s numerous epidemiologic studies have pointed to an increased risk of SIDS in infants who sleep in the prone position. It has been estimated that as many as 50% of cases of SIDS may be related to sleep position. In 1992 the AAP made official recommendations with respect to sleep position, and in 1994 the Back to Sleep campaign was initiated in the United States.[8] The movement to aggressively encourage back sleeping has led to a dramatic decrease in the incidence of SIDS worldwide (Figure 25-2).

Box 25-3 Risk Factors for Sudden Infant Death Syndrome

EPIDEMIOLOGIC RISK FACTORS
- Male sex
- African-American race
- Teenage maternal age
- Prematurity
- Winter season
- Low birth weight
- Anemia during pregnancy
- Inadequate prenatal care
- Bottle feeding
- Maternal smoking
- Soft bed covers or loose bedding
- Overheating
- Bed sharing
- Prone sleeping position

MODIFIABLE RISK FACTORS
- Exposure to opioids or cocaine *in utero*

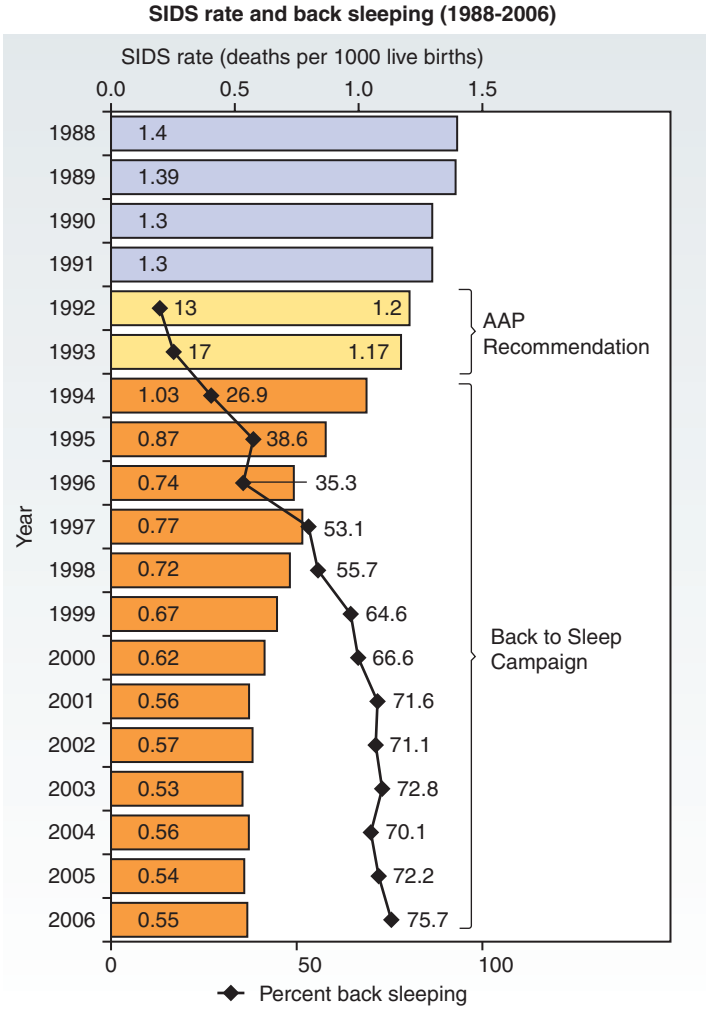


FIGURE 25-2 The sudden infant death syndrome *(SIDS)* rate (deaths per 1000 live births) in the United States from the beginning of the recognition of the importance of sleep position (data from 1988 to 2006). The Back to Sleep campaign began in 1994. The percent of back sleeping is also shown. The SIDS death rate fell 60% as back sleeping increased.

Other risk factors may be modified to reduce the incidence of SIDS. Maternal cigarette smoking during pregnancy has been found to be a major risk factor for SIDS and appears to be dose-dependent. Postnatal exposure to cigarette smoke further increases the risk. Some studies have found breastfeeding to be partly protective against SIDS, but this finding has been inconsistent. Overheating and loose bedding have both been associated with SIDS. Bed sharing has been shown to be a hazardous practice. Overlying remains an important cause of unexplained infant death and should be considered along with other forms of inadvertent suffocation during a death scene investigation. The most effective means of providing a safe sleeping environment is meticulous risk mitigation.[9]

An **acute life-threatening event (ALTE)** is defined as an episode that is frightening to the observer and characterized by some combination of apnea (central/obstructive), color change, marked change in muscle tone (usually marked limpness), choking, or gagging. The ALTE may be idiopathic or have an underlying cause. The phenomenon of ALTE is often discussed in relation to SIDS. However, the relationship between ALTEs and SIDS is poorly understood and increasingly controversial. Indeed, the vast majority of infants who die of SIDS did not have a witnessed episode of apnea until their terminal event. Parental concern may make getting an accurate account of the event difficult at presentation. With a credible story, especially in the presence of cyanosis or change in heart rate or with a resuscitation effort, an admission to the hospital is warranted. Evaluation must include a thorough history, including a family and social history. An accurate description of the event is crucial. A full review of systems and thorough physical examination should help to narrow the very extensive differential diagnosis.[10] The physical examination should examine carefully for bruising and should include a full neurologic examination, including muscle tone and funduscopic examination. The physical examination should include a search for dysmorphic features and abnormalities of the upper airway, chest, and cardiovascular system should be sought. Basic measurements of head circumference, body weight, length, and blood pressure should be made and compared with norms. The parental concern should be assessed and sensitively addressed. The extent of the workup will be determined by this admission data. A heightened index of suspicion must be maintained throughout, because an identifiable cause is found in nearly 50% of cases. Box 25-4 reviews the differential diagnosis of ALTEs.

Home monitoring for apnea in infants at risk remains a controversial subject. In the 1980s and 1990s the prevailing sentiment was that home monitoring made sense, because some patients who had apnea requiring resuscitation subsequently had a recurrence of this life-threatening event. Furthermore, a small number of patients subsequently died of SIDS. Some centers have had a home monitoring program in place for many years and remain committed to monitoring high-risk infants. These include (1) babies who have had a sibling die of SIDS, (2) premature babies who are known to have had significant apnea, and (3) infants who have had an ALTE. Recently the efficacy of this practice has been called into question. In an editorial accompanying the CHIME study,[11] it was stated that "the physiologic basis for such a practice are more in doubt than ever."[12] This study did not support the idea that babies who are thought to be at increased risk of SIDS have more cardiorespiratory events. The AAP has recommended that home monitors should not be used as a strategy to prevent SIDS.[13] It is likely that monitoring will continue in select babies. Individual patients thought to be at high risk may benefit when the caretakers are appropriately trained and compliant in its use. Caretakers in this situation should be trained in cardiopulmonary resuscitation (CPR) as well.

Box 25-4 Differential Diagnosis of Acute Life-Threatening Events

GASTROINTESTINAL (50%)
- Gastroesophageal reflux
- Intussusception
- Volvulus

NEUROLOGIC (30%)
- Seizures
- Intracranial hemorrhage
- CNS anomaly
- Arnold-Chiari malformation
- Hydrocephalus
- CNS infection
- Malignancy

RESPIRATORY (20%)
- Viral infection (e.g., pertussis)
- *Mycoplasma* spp. infection
- Obstructive sleep apnea
- Abnormal respiratory control
  - Breath-holding spells
  - Congenital central hypoventilation
  - Apnea of prematurity

CARDIAC (5%)
- Arrhythmia
- Long QT syndrome
- Wolf-Parkinson-White syndrome
- Cardiomyopathy
- Myocarditis
- Aberrant left coronary artery

METABOLIC (LESS THAN 5%)
- Inborn errors of metabolism (fatty acid defects)
- Sepsis, all causes
- Medications (prescription and nonprescription)
- Nonaccidental trauma
- Accidental suffocation

CNS, Central nervous system.

OBSTRUCTIVE SLEEP APNEA

Obstructive sleep apnea (OSA) is a breathing disorder that occurs in sleep and is characterized by repeated complete or partial obstruction of the upper airway such that gas exchange or sleep integrity is compromised. Multiple factors influence airway patency, including airway geometry, anatomic structures of the upper airway, control of laryngeal muscles, cardiorespiratory control, and neuromuscular factors. Because obstruction does not occur during wakefulness, it is apparent that anatomic features alone do not suffice. The major cause of OSA in children without another predisposing condition (Box 25-5) is adenotonsillar hypertrophy. Anatomic restriction in the airway by the tonsils in combination with altered laryngeal muscle control results in obstruction of the airway. OSA is common in children and its occurrence ranges from 1.2% to 5.7%.[14] In children with a predisposing condition the prevalence is considerably greater. It may occur in children of all ages, but the prevalence peaks between 2 and 8 years of age, which coincides with the time at which the size of the tonsils is at its peak relative to the upper airway size.

Narrowing of the airway during respiration is a normal phenomenon. The caliber of the airway oscillates normally with afferent neural activity from the respiratory centers. During sleep, ventilatory drive is decreased. Upper airway muscle tone decreases, especially during REM. Therefore upper airway resistance increases during sleep. The upper airway may be modeled as a Starling resistor. Upstream (nasal) and downstream (tracheal) pressures determine flow only if the upper airway is patent. The collapsible upper airway will remain patent only if the pressure inside is greater than the pressure outside the airway, known as *Pcrit*.[15] Multiple factors may lead to upper airway pressure approaching Pcrit during respiration and collapse of the airway. These include structural narrowing of the airway, abnormal neuromuscular tone, and possibly genetic and hormonal factors. It is likely that multiple factors work in concert. For example, even though adenotonsillar hypertrophy is a common "cause" of OSA in children, it alone is not a sufficient cause.

The variable changes in upper airway resistance and caliber lead to a continuum of clinical syndromes, which range from primary snoring to frank intermittent occlusion of the upper airway. Primary snoring may affect as many as 10% of children but is not typically associated with disturbance of sleep architecture or gas exchange abnormality. Upper airway resistance syndrome (UARS) is characterized by recurrent respiratory effort—related arousals during sleep. These episodes are not typically associated with gas exchange abnormalities but may be associated with significant daytime symptoms. Obstructive hypoventilation (obstructive hypopnea) may occur in the absence of complete obstruction of the airway and cessation of airflow. These sleep-related events lead to disruption of sleep architecture, degradation of sleep quality, and gas exchange abnormalities that may cause significant daytime symptoms.

Unrecognized and untreated upper airway obstruction is a considerable threat to a child's health. It has long been known that chronic obstruction is associated with substantial morbidity. It became clear in the 1980s and 1990s that childhood OSA was distinct from adult OSA. Features that distinguish childhood from adult OSA are shown in Table 25-1. In otherwise normal children, sleep architecture may be relatively preserved in OSA compared with adults, and excessive daytime sleepiness is less commonly observed. Children with OSA are not typically obese, though they may be. They may have many fewer true obstructions during the night, if any at all. They more typically have intermittent or continuous partial obstruction or UARS. On the other hand, obese children may have a clinical syndrome that is more similar to adult OSA.[16] They may have more excessive daytime sleepiness (EDS), systemic hypertension, left ventricular hypertrophy, insulin resistance, or elevated C-reactive protein (CRP) levels. This form of OSA in children has increased as the incidence of childhood obesity has increased.

Evaluation of the child for SDB begins with a comprehensive history. Symptoms may be volunteered by an observant parent but must also be actively sought by the clinician. A clear description of sleep habits should be obtained. Both nighttime and daytime symptoms should be recorded. Nighttime symptoms may include snoring, respiratory pauses, snorts, mouth breathing, or abrupt awakening. There may also be sweating, restlessness, increased respiratory effort, or extension of the neck. Common medical conditions such as gastrointestinal reflux or asthma may

Box 25-5 Conditions That Predispose to Obstructive Sleep Apnea

- Arnold-Chiari malformation
- Obesity
- Down syndrome
- Nasal obstruction caused by septal deviation, polyps, or masses
- Achondroplasia
- Apert syndrome
- Craniofacial syndromes (Pierre Robin syndrome, Treacher Collins syndrome, Crouzon syndrome)
- Prader-Willi syndrome
- Neuromuscular disease (Duchenne's muscular dystrophy, spinal muscular atrophy)
- Adenotonsillar hypertrophy
- Sickle cell disease
- Macrognathia
- Mucopolysaccharide storage disease

Table 25-1 Features of Childhood and Adult Obstructive Sleep Apnea

	CHILDHOOD	ADULT
Obesity	May be normal or underweight	Common
Snoring	Often continuous	Usually intermittent with respiratory pauses
Excessive daytime sleepiness	Infrequent	Common
EEG pattern	UARS or hypopneas common; may not have cortical arousal	Obstructed pattern with EEG arousals
Sleep architecture	Often preserved	Disrupted
Tonsils and adenoids enlarged	Very common	Uncommon
Sleep state abnormality	REM is most common	REM and NREM
Insulin resistance	Absent	Frequent
Cardiovascular effects	Infrequent	Frequent
Prominent symptoms	Behavioral or neurocognitive; enuresis	EDS, work performance, fatigue, morning headache

EEG, Electroencephalogram; *NREM*, non–rapid eye movement; *REM*, rapid eye movement; *UARS*, upper airway resistance syndrome.

be associated with nighttime symptoms. Upon awakening, the patient may describe dry mouth or headache. Enuresis is relatively common in patients with OSA. Parents and children are often reluctant to volunteer the symptom of enuresis, because the association with SDB may not be known. Snoring is a very common symptom in children and may not be seen as a symptom. As many as 25% of children may snore occasionally and 10% snore habitually.[4] Snoring does not predict the presence of SDB but may be associated with deleterious effects including poor school performance or hypertension. Daytime symptoms include poor school performance, hyperactivity, and inattention or aggressive behavior. Children with the diagnosis of attention deficit/hyperactivity disorder (ADHD) who also snore should have a comprehensive sleep evaluation.

The most common physical findings are limited to the upper airway. The most common finding in a child with OSA is tonsillar hypertrophy. Other findings that may be important are mouth breathing, micrognathia or retrognathia, crowded oropharynx, nasal mucosal edema, nasal septal deviation, and malocclusion. Body weight is important. Obesity is a known risk factor for SDB. However, some children may present with low body weight or even failure to thrive. Other physical findings may be those seen in conditions associated with increased risk for SDB (Box 25-6).

Box 25-6 Clinical Symptoms of Obstructive Sleep Apnea

NIGHTTIME SYMPTOMS
- Snoring
- Paradoxical breathing
- Enuresis
- Sweating
- Dry mouth

DAYTIME SYMPTOMS
- Hyperactivity
- School performance problems
- Daytime sleepiness

The first line of treatment is adenotonsillectomy for those with large tonsils and no other confounding factors.[17] This surgery may be curative in most cases. Patients who are obese or have upper airway abnormalities in addition to tonsillar hypertrophy may have persistent SDB after adenotonsillectomy. For these reasons, careful postoperative follow-up is advisable, especially in children with obesity.[17] CPAP is the treatment of choice in patients who either are not suitable candidates for surgery or have persistent SDB. The effective pressure level is usually determined in a titration sleep study. In recent years the selection of interface options for children has dramatically improved. These include nasal masks or pillows and full-face masks. Most children will adapt to the use of the device with repetition and the help of a well-trained parent. In some cases a bilevel pressure approach may be better tolerated. Patients who hypoventilate, such as those with neuromuscular disease, should be treated with bilevel. The effectiveness of CPAP is dependent on compliance with its use. The introduction of "smart" CPAP devices has improved the ability to ensure compliance. These smart devices have ways of adjusting pressure and often have applications that can provide a summary of use. This summary typically offers how well the child slept, often by quantifying number of apnea events, mask fit, and hours of use. Indeed, some insurance companies now require a threshold level of documented compliance. Compliance with CPAP use in patients with developmental disability is particularly challenging; making it a game or giving them a target (like a total) may improve compliance.

Many medical conditions are associated with increased risk for SDB. Conditions that have decreased oropharyngeal space as a feature include craniopharyngeal syndromes, Down syndrome, mucopolysaccharide storage disease, and Prader-Willi syndrome.

Patients with neurologic disease, most notably Chiari malformation, may be at increased risk for SDB, and patients with neuromuscular disease have an increased incidence of SDB. These patients are less likely to be "cured" with adenotonsillectomy alone. They may require other surgical procedures (e.g., Chiari malformation decompression, mandibular distraction) or treatment with CPAP, BPAP, or even tracheostomy, depending on the severity of the sleep-related gas exchange abnormalities.[18]

LABORATORY ASSESSMENT OF BREATHING IN SLEEP

Definitive evaluation must include an overnight polysomnogram (PSG).[19] Pediatric PSG parameters differ in many respects from the adult PSG (Figure 25-3). Box 25-7 lists the channel recordings that are recommended for a diagnostic PSG. Staging of sleep includes the combined measurement of the EEG to record brain activity, the electrooculogram (EOG) to record bilateral eye movements, and the electromyogram (EMG) to record facial and tibial muscle tone. EEG electrode placement for scoring sleep in children is standardized similarly to that used in adults. Electrodes are placed at EEG positions A1, A2, O1, O2, C3, and C4, and sleep stage is determined by the monopolar derivation C3/A2 or C4/A1. In infants younger than 6 months, an extended EEG montage is preferred. This extended montage should include bilateral EEG electrodes using bipolar channels to more accurately evaluate the two hemispheres of the brain. In this way, EEG features specific to infants, such as *tracé alternant* and delta "brushes," as well as certain epileptiform activity, are better seen. This montage may also provide useful information regarding the maturity of the brain or alert clinicians to potential problems in brain activity. In addition, certain normal features of the infant EEG, such as rudimentary sleep spindles, are better seen using an extended EEG montage that includes frontal leads.

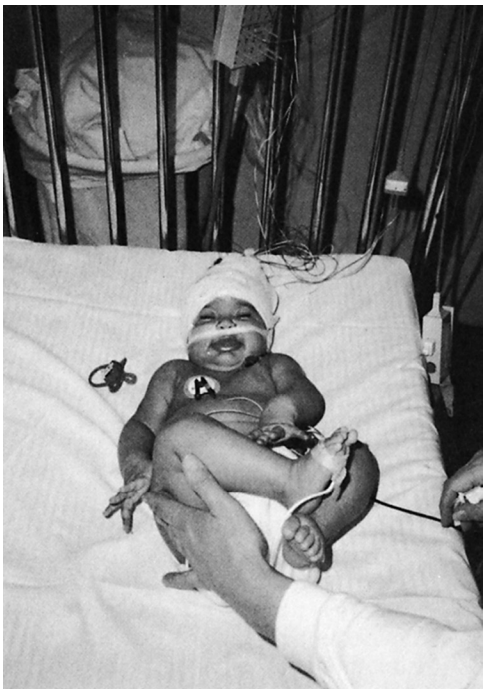


FIGURE 25-3 A baby ready for polysomnography. The head is wrapped with gauze to protect the scalp electroencephalogram electrodes. An electrode to detect eye movement is also covered with gauze. Two eye electrodes are standard. There is a nasal thermistor and a carbon dioxide cannula in place. A strain gauge is attached to the chest to detect breathing movements. A transcutaneous oxygen electrode, electrocardiogram electrodes, and oxygen saturation sensor are also attached.

Box 25-7 Recommended Polysomnogram Channels for a Pediatric Sleep Study

- EEG montage to include four to eight channels
- Electrooculogram
- Electrocardiogram
- Oxygen saturation and waveform
- Redundant measure of airflow (nasal pressure and oronasal thermistor)
- End-tidal P_{CO_2} (peak value and waveform)
- Snore volume
- Measure of respiratory effort (chest and abdominal inductance plethysmography)
- Measure of muscle activity (chin and tibial EMG)
- Video and audio recording
- Time-stamped video
- Body position sensor

EEG, Electroencephalogram; *EMG*, electromyography.

The accurate scoring of sleep stages also requires bilateral EOG sensors to monitor the rapid eye movements that normally occur in REM sleep and the slow eye movements that occur with the onset of sleep. An EMG recording of facial muscle tone assists the clinician in more accurately determining the presence of REM sleep when skeletal muscle tone, particularly the muscles of the face, is normally inhibited.

To comprehensively assess the adequacy of ventilation and differentiate between central and obstructive apnea and their severity, PSGs should also include movements of the chest wall and abdomen, air flow at the nose and mouth, transcutaneous oxygen saturation data (with validating pulse wave from the monitor), and end-tidal carbon dioxide ($ETCO_2$) measures. A pulse waveform is necessary to assess the reliability of oxygenation data, because oxygen saturation monitors can yield artifactual data when the infant is feeding or moving. Capnography, a graphic representation of $ETCO_2$, is recommended, because it can assess both airflow and ventilation simultaneously. Calibrated $ETCO_2$ measurements can effectively detect possible carbon dioxide retention associated with apnea or prolonged hypoventilation.

A standard PSG also includes additional parameters that can provide important information relevant to the patient's electrophysiological status. An electrocardiogram (ECG) monitors cardiac rate and rhythm

and is useful in evaluating the consequences of breathing disorders on heart rhythm. Inductive plethysmography, involving the placement of bands around the rib cage and abdomen, detects respiratory effort and phase relationship, allowing for differentiation between central and obstructive apnea. A PSG may include EMG of the anterior tibialis muscles to identify periodic limb movement disorder, although this disorder is rare in infants and children. As such, leg EMGs are not routinely monitored in children unless clinically indicated.

Although the diagnostic criteria for OSA may vary among institutions, in 2011 practice parameters for respiratory indications were established. To perform PSG, the child is usually sequestered with a parent or caregiver in a sleep lab overnight for monitoring. The demand for PSG testing has outstripped the number of sleep labs available to conduct a study within an appropriate amount of time. To ensure testing in a timely fashion, investigators have explored ways of conducting other tests to either screen or fully diagnose OSA. Recent studies have demonstrated that PSG may be modified to permit home assessment of sleep-disturbed breathing in children.[21] Although the goal standard remains PSG, the standard has been challenged on several fronts, including questionnaires,[22] nocturnal oximetry,[23-25] drug-induced sleep endoscopy,[26] and noninvasive urinary biomarkers,[27-30] that may supplant PSG as the gold standard to diagnose OSA in children.

To assess for the presence of gastroesophageal reflux and its potential cardiorespiratory consequences, continuous esophageal pH measurement can be performed in conjunction with PSG. Video recording with sound is recommended, because it provides invaluable information on sleep behavior, snoring, respiratory effort, and sleep positions associated with a particular respiratory pattern. Finally, the PSG must be performed by a trained technologist who ensures the integrity of the recording, provides descriptions regarding unusual events or behaviors, and makes notations on the recording regarding physiologic changes such as snoring or color changes such as cyanosis. Polysomnographic technologists working with this age group must be certified in pediatric CPR.

Case Study

A 3-month-old female infant is brought to the emergency department by paramedics. They state that they responded to an emergency call and upon arrival found that the mother was distraught and holding the baby. They reported that she had found the baby "not breathing and blue." She had put the baby to bed after a feeding about 1 hour before the event. She could not say how long the episode lasted, but she said she blew in the baby's mouth and the baby started to cry. The baby was full term. The baby's examination is now normal. There is no evidence of foul play. What is the differential diagnosis?

A. Apnea of prematurity
B. Obstructive sleep apnea
C. Congenital central hypoventilation syndrome
D. Near-miss sudden infant death syndrome (SIDS)
E. Acute life-threatening event (ALTE)

This child was admitted to the hospital and underwent a thorough evaluation. The mother stated that she was afraid of SIDS. There is no family history of SIDS. Further history revealed that the baby often slept with the mother in her bed. She stated that the baby was most comfortable "on her tummy." She admitted that she smoked but "only outside." What risk factors must be discussed with this mother?

A. Cosleeping
B. Smoking
C. Prone position sleeping
D. All of the above

See Evolve Resources for answers.

Key Points

- Sleep development: Infants spend the bulk of their day sleeping. Sleep stages are defined by the EEG. The infant has three stages, referred to as *active sleep (REM), quiet sleep (NREM)*, and *indeterminate sleep.* REM sleep predominates sleep time in infants and decreases until about the age of 2 years. NREM sleep time increases in childhood and peaks between 5 and 9 years. NREM sleep has four distinct EEG stages (3 and 4 are now combined). NREM sleep is known as *slow-wave sleep* and has been called *restorative sleep.* Total sleep time progressively decreases throughout childhood to adult levels in adolescence. The distribution of time spent in each stage is quantified during a sleep study and is referred to as *sleep architecture.* Disruption of the sleep architecture leads to daytime symptoms.
- Central sleep apnea: Central sleep apnea occurs when there is a cessation of airflow and no discernible respiratory effort. In infants this may be related to immaturity of respiratory centers. Later in life it may be related to insensitivity of the chemoreceptors responsible for respiratory drive.
- OSA: OSA occurs when there is cessation or limitation of airflow and continued respiratory effort for more than two respiratory cycles. OSA is caused by collapse of the airway. Multiple factors contribute to this collapse, including anatomic structures limiting airflow, laryngeal muscle control, neuromuscular factors, and cardiorespiratory control. Upper airway obstruction occurs in a continuum from snoring to complete apnea. Partial obstruction leads to a limitation of airflow termed *hypopnea.* The most common cause of OSA in children is adenotonsillar hypertrophy. OSA is most often treated with adenotosillectomy. When this treatment

is unsuccessful, CPAP is an effective treatment that maintains airway patency.

- SIDS and ALTE: *SIDS* is defined as "the sudden death of an infant under one 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." It remains the most common cause of death between the ages of 1 month and 1 year. The cause of SIDS remains unknown. Many theories have been advanced. The most important advance arose from epidemiologic data demonstrating that back sleeping dramatically decreases the risk of SIDS. The emphasis on back sleeping has decreased the incidence of SIDS worldwide. There is no test that will predict the occurrence of SIDS. The AAP has recommended that home monitors not be used as a strategy to prevent SIDS.
- An *ALTE* is defined as "an episode that is frightening to the observer and is characterized by some combination of apnea (central and occasionally obstructive), color change (usually cyanotic or pallid but occasionally erythematous or plethoric), marked change in muscle tone (usually marked limpness), choking, or gagging." The relationship of ALTE and SIDS is poorly understood. An identifiable cause may be found in about half the cases.
- Laboratory assessment: The definitive study to assess sleep is the PSG. The diagnostic PSG is performed in an accredited sleep laboratory by trained personnel. Sleep stage is determined using a standard EEG montage that includes bilateral EOG and four EEG leads. Tibial and facial muscle activity is recorded by EMG. In addition, the complete PSG includes the following: nasal airflow, chest and abdominal wall plethysmography, $ETCO_2$, video and audio recording, snore volume, body position sensor, ECG, and oxygen saturation. Sleep stage scoring allows for quantification of sleep architecture. EEG arousal may not be perceived by the patient as an awakening but may still result in disruption of the sleep architecture and daytime symptoms.

Assessment Questions

See Evolve Resources for answers.

1. Which of the following statement is true regarding sleep in infants?
   - **A.** Infant neural development is not yet complete, and infants have not yet developed rapid eye movement (REM) sleep.
   - **B.** Infant sleep is dominated by non–rapid eye movement (NREM) sleep.
   - **C.** Seventy percent of infants sleep through the night by 3 months of age.
   - **D.** The normal newborn spends 70% of a 24-hour day asleep.
2. Which of the following statement is true regarding sleep stages?
   - **A.** During REM sleep in infants, muscle activity is the lowest and therefore metabolic rate is at its lowest.
   - **B.** Newborn infants have immature sleep spindles.
   - **C.** NREM sleep duration peaks between 5 and 9 years of age.
   - **D.** The appearance of REM sleep at sleep onset in the newborn is an abnormal pattern.
3. The mother of a 3-month-old infant arrives at the emergency department with her infant and states that she observed her infant's breathing stop for 8 seconds and then restart. She stated that the baby was also breathing fast right before she stopped breathing. The baby has been eating normally, has no other symptoms, and has a normal physical examination. What is your next action?
   - **A.** Order a complete blood cell count (CBC) and a chest radiograph.
   - **B.** Admit the baby for overnight observation.
   - **C.** Reassure the mother that this is a normal infant breathing pattern.
   - **D.** Arrange for the baby to go home with a home monitor.
4. Infants are particularly susceptible to the development of sleep-disordered breathing (SDB) or respiratory failure. What feature of anatomy or physiology places the baby at increased risk?
   - **A.** Nasal breathing
   - **B.** Chest wall compliance
   - **C.** The angle of rib articulation
   - **D.** The shape of the chest
   - **E.** All of the above
5. Which of the following statements is true?
   - **A.** The peak incidence of sudden infant death syndrome (SIDS) occurs at 6 months of age.
   - **B.** Home monitoring should always be prescribed upon discharge for infants who have experienced an acute life-threatening event (ALTE).
   - **C.** SIDS has been called a diagnosis of exclusion. A full investigation should be undertaken including a full autopsy. An examination of the death scene is optional.
   - **D.** The CHIME study demonstrated conclusively that home monitoring prevents SIDS.
   - **E.** An infant who sleeps in the supine position is at decreased risk of SIDS.
6. What percentage of otherwise normal children who have obstructive sleep apnea (OSA) will present with excessive daytime sleepiness?
   - **A.** More than 75%
   - **B.** 50% to 75%
   - **C.** 25% to 50%
   - **D.** Less than 25%
7. Which of the following statements regarding OSA is/are true?
   - **A.** A complete history is a sensitive indicator of the presence of OSA.
   - **B.** School performance is affected when OSA becomes severe.
   - **C.** The prevalence of OSA is approximately 15%, and the peak incidence is between 2 and 8 years.
   - **D.** OSA may be diagnosed without blood gas abnormalities during the sleep study.
8. Which of the following statements regarding OSA is/are false?
   - **A.** Tonsillar hypertrophy is the most common cause of OSA.
   - **B.** Upper airway obstruction occurs along a continuum from snoring through upper airway resistance syndrome to apnea.
   - **C.** Enuresis may be a presenting symptom of OSA.
   - **D.** A child with ADHD who also snores should be referred to a psychologist.

9. OSA in childhood and adulthood differs in several important ways. Which of the following statements is/are false?
   - **A.** Excessive daytime sleepiness is less common in children than adults.
   - **B.** Adenotonsillectomy is more effective in children than adults.
   - **C.** Sleep architecture is more commonly disrupted in children than in adults.
   - **D.** Obese children with OSA have a phenotype that is similar to adult OSA.
   - **E.** Children tend to have better preservation of REM sleep.

10. The treatment of OSA might include which of the following?
    - **A.** Chiari malformation repair
    - **B.** Tracheostomy
    - **C.** Mandibular distraction
    - **D.** Continuous positive airway pressure (CPAP)
    - **E.** All of the above

REFERENCES

1. Olser W. Chronic tonsillitis. In: *The Principles and Practice of Medicine*. New York: Appleton and Co; 1892:335.
2. McLaughlin Crabtree V, Williams NA. Normal sleep in children and adolescents. *Child Adolesc Psychiatr Clin N Am*. 2009;18:799.
3. Owens J. Classification and epidemiology of childhood sleep disorders. *Prim Care*. 2008;35:533.
4. Gozal D, Kheirandish-Gozal L. Disorders of breathing during sleep. In: Wilmont R et al, eds. *Kendig and Chernick's Disorders of the Respiratory Tract in Children*. 8th ed. Philadelphia: Elsevier Saunders; 2012.
5. American Academy of Pediatrics, Committee on Fetus and Newborn. Apnea, sudden infant death syndrome, and home monitoring. *Pediatrics*. 2003;111(4):914.
6. Mathews TJ, MacDorman MF. Infant mortality statistics from the 2009 period linked birth/infant death data set. *Natl Vital Stat Rep*. 2013;61(8):1.
7. Hymel KP, National Association of Medical Examiners. Distinguishing sudden infant death syndrome from child abuse fatalities. *Pediatrics*. 2006;118:421.
8. Willinger M, Hoffman HJ, Hartford RB. Infant sleep position and risk for sudden infant death syndrome: report of meeting held January 13 and 14, 1994. National Institutes of Health, Bethesda, MD. *Pediatrics*. 1994;93(5):814-819.
9. Trachtenberg FL, Haas EA, Kinney HC, Stanley C, Krous HF. Risk factor changes for sudden infant death syndrome after initiation of Back-to-Sleep campaign. *Pediatrics*. 2012;129:630-638.
10. Hall KL, Zalman B. Evaluation and management of apparent life threatening events in children. *Am Fam Physician*. 2005;71(12):2301-2308.
11. Ramanathan R, Corwin MJ, Hunt CE, et al. Cardiorespiratory events recorded on home monitors: comparison of healthy infants to those at risk for SIDS. *JAMA*. 2001;285(17):2199.
12. Jobe AH. What do home monitors contribute to the SIDS problem? *JAMA*. 2001;285(17):2244.
13. Committee on Fetus and Newborn. Apnea, sudden infant death syndrome, and home monitoring. *Pediatrics*. 2003;111:914.
14. Marcus CL, Brooks LJ, Draper KA, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics*. 2012;130:576.
15. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. *Physiol Rev*. 2010;90:47.
16. Dayyat E, Kheirandish-Gozal L, Gozal D. Childhood obstructive sleep apnea: one or two distinct disease entities? *Sleep Med Clin*. 2007;2:433.
17. Roland PS, Rosenfeld RM, Brooks LJ. Clinical Practice Guidelines: Polysomnography for Sleep-Disordered Breathing Prior to Tonsillectomy in Children. American Academy of Otolaryngology–Head and Neck Surgery; 2011. Available at: www.entnet.org.
18. Halbower AC, McGinley BM, Smith PL. Treatment alternatives for sleep-disordered breathing in the pediatric population. *Curr Opin Pulm Med*. 2008;14:551-558.
19. Beck SE, Marcus CL. Pediatric polysomnography. *Sleep Med Clin*. 2009;4(3):393.
20. Aurora RN, Zak RS, Karippot, et al. Practice parameters for the respiratory indication for polysomnography in children. *Sleep*. 2011;34:379-388.
21. Tan HL, Kheirandish-Gozal L, Gozal D. Pediatric home sleep apnea testing slowly getting there! *Chest*. 2015;148:1382-1395.
22. Walter LM, Biggs SN, Cikor N, et al. The efficacy of the OSA-18 as a waiting list triage tool for OSA in children. *Sleep Breath*. 2016;20:837-844.
23. Pavone M, Cutrera R, Verrillo E, Salerno T, Soldini S, Brouillette RT. Night-to-night consistency of at-home nocturnal pulse oximetry testing for obstructive sleep apnea in children. *Pediatr Pulmonol*. 2013;48:754-760.
24. Villa MP, Pietropaoli N, Supino MC, et al. Diagnosis of pediatric obstructive sleep apnea syndrome in setting with limited resources. *JAMA Otolaryngol Head Neck Surg*. 2015;141:990-996.
25. Van Eyck A, Lambrechts C, Vanheeswijck L, et al. The role of nocturnal pulse oximetry in the screening for obstructive sleep apnea in obese children and adolescents. *Sleep Med*. 2015;16:1409-1412.
26. Kandil A, Subramanyam R, Hossain MM, et al. Comparison of the combination of dexmedetomidine and ketamine to propofol or propofol/sevoflurane for drug-induced sleep endoscopy in children. *Paediatr Anaesth*. 2016;26:742-751.
27. Gozal D, Jortani S, Snow AB, et al. Two-dimensional differential in-gel electrophoresis proteomic approaches reveal urine candidate biomarkers in pediatric obstructive sleep apnea. *Am J Respir Crit Care Med*. 2009;180:1253-1261.
28. De Luca Canto G, Pachêco-Pereira C, Aydinoz S, Major PW, Flores-Mir C, Gozal D. Diagnostic capability of biological markers in assessment of obstructive sleep apnea: a systematic review and meta-analysis. *J Clin Sleep Med*. 2015;11:27-36.
29. Villa MP, Supino MC, Fedeli S, et al. Urinary concentration of 8-isoprostane as a marker of severity of pediatric OSAS. *Sleep Breath*. 2014;18:723-729.
30. Jeong JH, Guilleminault C, Park CS, et al. Changes in salivary cortisol levels in pediatric patients with obstructive sleep apnea syndrome after adenotonsillectomy. *Sleep Med*. 2014;15:672-676.

26 Pediatric Airway Disorders and Parenchymal Lung Diseases

Brian K. Walsh

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. Identify and name upper and lower airway disorders.
2. Recognize the signs of severe or complete airway obstructions that require intervention.
3. Describe the basic intervention and recommended therapy for each of the airway disorders and parenchymal lung diseases.
4. Discuss the different types, and therefore the etiology, of pneumonia.

Key Terms

airway obstruction
aspiration
epiglottitis
lower airway
obstructive apnea
pneumonia
laryngotracheobronchitis
tuberculosis
upper airway

THE PEDIATRIC AIRWAY

Airway disorders may cause severe and at times sudden threats to a child's life. The special susceptibility of children to disorders of the airways stems from several factors. Congenital abnormalities of airway structures tend to cause difficulties early in life. Even when normal anatomy is present, the relatively small size of the pediatric airway puts children at a distinct disadvantage. The inherently narrow trachea, bronchi, and bronchioles can become critically compromised by minimal swelling of the respiratory mucosal lining or by the presence of foreign objects. Children are at increased risk for such narrowing or obstruction because of their susceptibility to respiratory infections and their tendency to engage in risky behaviors, such as placing small objects in their mouths.

Compared with adults, once a child's airway becomes narrowed or obstructed, the pediatric respiratory

system is less able to cope with the resulting ventilation abnormality. In the event of complete **airway obstruction,** children undergo rapid onset of hypoxia, with its resultant neurologic damage or death. Respiratory events are the major reason for cardiac arrest in children. The rapidity of this oxygen desaturation is in part caused by the child's small functional residual capacity and dependency on dynamic compliance combined with an overall increased metabolic rate. Essentially there is minimal oxygen reserve available to supply the child's oxygen requirement. This combination of increased susceptibility to and decreased ability to cope with airway compromise helps explain why children suffer so frequently from airway disorders.

UPPER AIRWAY

Many unique aspects of anatomy must be understood to appropriately support and intervene on behalf of a child during respiratory illness. The **upper airway** consists of all structures connecting the mouth and nose with the glottis. This includes the nose, nasal choanae, nasopharynx, mouth, oropharynx, and structures of the larynx (Figure 26-1). Compared with that of an adult, the anatomy of an infant's airway contains several differences and functional limitations.

The epiglottis is long, floppy, and angled away from the tracheal axis. It shrouds the laryngeal opening because of poor support by the surrounding tissues. Structurally, an infant's larynx is positioned higher in the neck (near C3-4) than is an adult's larynx (at C4-5). Because of this superior location, the tongue base tends to "hide" the larynx from view during direct laryngoscopy. The cricoid cartilage is a nonexpandable cartilaginous ring that is normally the only complete ring of cartilage in the airway. In the pediatric airway, it is the larynx's narrowest portion. With this reduced and fixed dimension, an endotracheal tube (ETT) may pass through the vocal cords and yet not proceed to the subglottic trachea. This already narrowed portion of the airway becomes severely narrowed by even small amounts of edema that develop with diseases such as **laryngotracheobronchitis** (LTB) or trauma (e.g., endotracheal intubation).

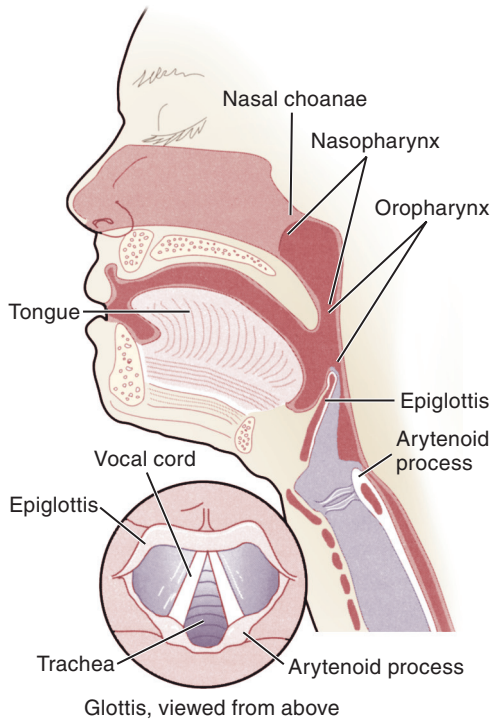


FIGURE 26-1 Normal upper airway structures.

Infants are considered obligate nose breathers until 3 to 6 months of age. Immaturity of coordination between respiration and oropharyngeal motor activity accounts partly for obligate nasal breathing. Also, the infant's tongue is closer to the roof of the mouth and makes mouth breathing difficult. Because the large tongue and small mouth make air passage through the mouth impossible except when crying, patency of the nasopharynx is critical in an infant.

The upper airway and lung do not complete development until approximately 8 years of age. The immature cartilage found in the infant's trachea and bronchi is soft and highly compressible. When the supporting cartilage is excessively flexible, the diagnosis of laryngomalacia or tracheomalacia is applied.

LOWER AIRWAY

The trachea divides into the mainstem bronchi, which in turn divide into smaller divisions called *subsegmental bronchi.* This repeated division continues in the adult to 23 generations (divisions) of smaller and smaller air passages, creating a huge surface area for gas exchange. At birth, however, the infant has only 16 to 17 generations of airways. The terminal generation of airways, the respiratory bronchioles, is present in relatively small numbers, resulting in a small transectional area for gas exchange in the infant. This is in part compensated for by fetal hemoglobin, which has an oxygen affinity superior to adult hemoglobin. Because of the developmentally small airway cross-sectional area, small amounts of inflammation at the level of the respiratory bronchioles can result in severe respiratory embarrassment. In young children, the respiratory bronchioles are commonly attacked by viruses, such as respiratory syncytial virus (RSV), resulting in respiratory failure. The same infection will have little or no respiratory effect on an adult or older child with a larger number of terminal airways.

AIRWAY OBSTRUCTION

Obstruction of the upper or **lower airway** of a child may lead to life-threatening hypoxia or hypercarbia. With the high risk of morbidity comes the need to identify the etiology, recognize the clinical signs and symptoms, and choose the diagnostic methods for and treatment of the many causes of airway obstruction.

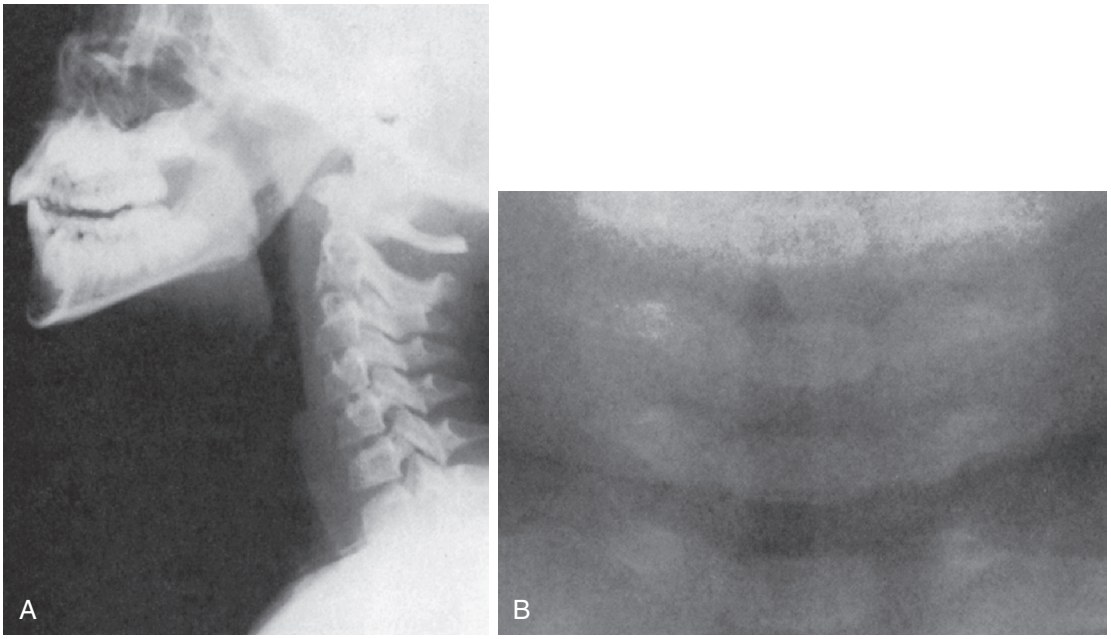


FIGURE 26-2 Normal cervical soft tissue radiographs. **(A)** Lateral view shows a thin epiglottis. **(B)** Anteroposterior view illustrates the "shoulders" appearance of the subglottic trachea.

Radiographic evaluation of the upper airways includes both frontal anteroposterior and lateral views of the head and neck. When performed at the proper angle and exposure, these films are helpful in evaluating the site of upper airway obstruction (Figure 26-2).

Fearing the unfamiliar surroundings of a hospital or clinic, a child may wiggle and scream, further increasing respiratory effort. To be successful in what could be a very difficult examination, the practitioner must proceed with slow and deliberate movements in a kind and gentle manner. However, this does not guarantee cooperation from a frightened and ill child.

A child's narrow airway makes even a small obstruction significant, leading to a marked increase in respiratory effort. Obvious clinical signs of impaired respiratory function are tachypnea, nasal flaring, retractions, cyanosis, and a change in mental state, including a reduced level of consciousness or increased agitation. As a rule, tachypnea and nasal flaring alone suggest a less severe but earlier sign of obstruction than the presence of deep retractions. However, if obstruction is severe, with prolonged respiratory distress, the child may be exhausted and only able to exhibit nasal flaring. In infants, the exhaustion of respiratory muscle leads to decreased dynamic compliance and ineffective respiration, because they have a relatively soft rib cage, leading to increased chest wall compliance. The child's mental state may range from fearful and agitated to lethargic or even unconscious. A child with mild hypoxia tends to have increased levels of agitation, whereas the child with increasing hypoxemia and hypercarbia becomes more lethargic.

Auscultation of the child's upper airway (over the trachea) and lower airway (over the thorax) is vital to determine the extent of air movement and obstruction. Some sounds, such as stridor, may be so prominent that they are audible from outside the patient's room. Stridor is a coarse, vibrating noise generated by airway soft tissue that typically occurs in the presence of a narrowed or obstructed upper airway (extrathoracic). Extrathoracic obstruction of the trachea causes stridor during inspiration. The deeply negative intrathoracic pressure causes the pressure inside the trachea to fall and allows the higher atmospheric pressure (outside the trachea) to collapse the trachea or larynx. This results in the "crowing" sound of stridor. During exhalation, the positive intraairway pressure forces the airway open and eliminates the stridor (Figure 26-3). When airway narrowing is intrathoracic, stridor is present

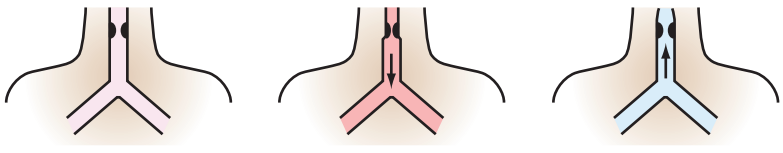


FIGURE 26-3 Obstruction of the upper (extrathoracic) airway. Dynamic motion during the respiratory cycle causes accentuated narrowing during inspiration, resulting in stridor.

during forced exhalation. The positive intrathoracic pressure that occurs with exhalation causes the circumferential tracheal cartilage, and hence the trachea, to collapse. During inspiration, stridor from an intrathoracic airway obstruction is minimized by the radially outward tracheal traction caused by negative intrathoracic pressure.

Auscultation of air movement during inspiration and expiration aids in determining the severity and location of the obstruction. The pitch of the stridor can be used to assess improvement or worsening of the obstruction. Low-pitched sounds signify mild obstruction, whereas a higher pitch indicates that the child is in more distress and is attempting to generate a higher air flow rate. Sounds heard on inspiration but not expiration may indicate a ball-valve obstruction and an accompanying risk for a pneumothorax. Absence of air movement constitutes a true emergency.

UPPER AIRWAY DISORDERS

SUPRALARYNGEAL OBSTRUCTION

Common causes of obstruction above the larynx include congenital lesions, acute inflammatory disorders, and disorders related to abnormal supralaryngeal tissue or airway tone or both (e.g., **obstructive apnea**).

Deep Neck Infections

Deep neck infections are feared complications of upper respiratory and upper gastrointestinal tract infections. Aerobic and anaerobic pathogens are the common cause. They can become rapidly severe, causing airway obstruction and **aspiration,** and quickly spread to adjoining anatomic structures (such as the mediastinum). Antibiotic treatment, airway protection, and surgical intervention are necessary. Peritonsillar and retropharyngeal abscesses are very common examples of these infections and must be differentiated from simple tonsillar enlargement.

Tonsillar Enlargement

A child with an acute illness characterized by fever and sore throat may develop swelling of the oropharyngeal tissues. Inflammation and swelling can progress to airway obstruction. Tonsillitis, or streptococcal pharyngitis, presents as exudative pharyngitis and cervical adenopathy. However, the presence of a cough and nasal congestion increases the likelihood that the infection is viral. A throat culture or rapid streptococcal antigen test is obtained to identify the causative organism. Therapy is routinely restricted to antibiotics unless the swelling is severe.

Peritonsillar Abscess

A peritonsillar abscess commonly forms unilaterally around the tonsillar tissue. It causes unilateral swelling and protrusion of the affected tonsil into the oropharynx with classical deviation of the uvula to the unaffected side. Patients commonly complain about trismus (difficulty opening the mouth), sore throat, torticollis, and muffled or hoarse voice. The diagnosis is made clinically and by culture; if in doubt, frontal anteroposterior and lateral radiographs of the head and neck can aid in the diagnosis. The most likely causative organism is *Streptococcus pyogenes* (group A streptococcus) or *Staphylococcus aureus.*

Retropharyngeal Abscess

Retropharyngeal abscess commonly occurs in children younger than 3 years of age and can cause obstruction from forward displacement of the posterior pharyngeal wall. Infectious agents involved are group A streptococcus, *Staphylococcus aureus,* and, occasionally, anaerobic bacteria. The child often presents with a sore throat, fever, dysphagia, and voice changes. The voice sounds as if the child is attempting to speak without moving the tongue while maximally expanding the oropharyngeal airway. This is described as "hot potato voice." A lateral neck radiograph is obtained to determine the tissue thickness surrounding the abscess. Visualization of the posterior pharynx may reveal a displaced retropharynx. Surgical drainage is the preferred treatment, along with administration of appropriate antibiotics based on culture results of the aspirated material.

Case Study 1

A 14-year-old girl presents to the emergency room complaining of sore throat, fever, and dysphagia. She has no prior health issues and no known sick contact. She says she had been well the day before and noticed her symptoms on awakening in the morning. Physical findings include a mild stridor on auscultation over both apical lung fields and over the trachea. Inspection of the retropharynx is complicated by the patient not being able to open her mouth, but you can see that the uvula is being displaced to the left. She also has problems rotating her head to the left.

What is the most likely diagnosis and what would be your next step in diagnosis?

What is the treatment?

See Evolve Resources for answers.

Periglottic Obstruction

Obstruction of the airway at or just below the level of the glottis typically presents as high-pitched stridor. This region is relatively fixed in diameter, because the noncompliant cartilage surrounding the glottis does not "balloon open" to allow air passage around the obstruction, as easily occurs in the more pliable tissues of the supralaryngeal airway. As a result, progressive obstruction of the periglottic area quickly leads to significant distress with both inspiratory

and expiratory compromise. The most common causes of periglottic obstruction in the pediatric age group are infectious, with **epiglottitis** and LTB representing important causes of respiratory morbidity for this patient population.

Congenital lesions that present as periglottic obstruction are rare and include laryngeal webs and cysts and subglottic hemangiomas. Vocal cord paralysis may be congenital or iatrogenic, caused by birth trauma or inadvertent surgical injury to the recurrent laryngeal nerve. Subglottic stenosis may also be congenital or acquired secondary to local trauma after intubation. A more common and benign congenital cause of upper airway obstruction is laryngomalacia. In this condition, the epiglottis and arytenoid processes are oversized and floppy, causing collapse into the glottis during vigorous breathing. High-pitched stridor is noted during the neonatal period but tends to disappear by the child's first or second birthday.

EPIGLOTTITIS

Epiglottitis is a life-threatening infection that affects both children and adults. It results from bacterial invasion of the soft tissues of the larynx, causing inflammation of the supraglottic structures. This leads to sudden marked swelling of the epiglottis and surrounding tissues and may result in complete airway obstruction and death. Historically, epiglottitis has been a disease of childhood, with little prodrome and rare recurrence. In contrast, adult symptoms are more nonspecific and often clouded by coexistent diseases.

Incidence and Etiology

The most common organism causing epiglottitis has been *Haemophilus influenzae* type B. Before widespread vaccinations with *H. influenzae* type B vaccine, bacterial epiglottitis was a fairly common pediatric illness, seen most often in children younger than 6 years of age. With the advent of widespread vaccination in 1985, the incidence has decreased by more than 95%. Despite the vaccinations and reduced incidence, *H. influenzae* type B still causes 75% of epiglottitis episodes. Although the vaccination program has profoundly reduced the incidence of epiglottitis, multiple isolated cases have occurred in patients with a complete vaccination history. Since the initiation of the vaccination program, patients with epiglottitis now tend to be older, with non–*H. influenzae* type B, principally group A β-hemolytic *Streptococcus,* as the infecting organism. Primary group A β-hemolytic streptococcal epiglottitis can develop as a rare complication of varicella in an otherwise normal host. Noninfectious causes of epiglottitis in children include thermal epiglottitis from aspiration of hot liquid and traumatic epiglottitis from repeated intubation attempts or a blind finger sweep to remove a foreign body from the airway.

Signs and Symptoms

Onset of bacterial epiglottitis is usually abrupt and associated with high fever, severe sore throat, dysphagia with drooling, cough progressing rapidly over a few hours to stridor, muffled ("hot potato") voice without hoarseness, air hunger, and cyanosis. Suprasternal, substernal, and intercostal retractions, along with nasal flaring, bradypnea, and dyspnea, are often displayed. The child assumes a characteristic tripod position of sitting upright with the chin thrust forward and the neck hyperextended (sniffing position). The streptococcal variant of epiglottitis may be associated with a longer prodrome lasting more than 24 hours.

DIAGNOSIS

Diagnosis of epiglottitis must be assumed based on the clinical presentation. Table 26-1 lists the clinical characteristics used in the differential diagnosis of epiglottitis and LTB. Because manipulation or agitation of the child with epiglottitis can trigger complete upper airway obstruction, unnecessary diagnostic

Table 26-1 Differential Diagnosis of Laryngotracheobronchitis and Epiglottitis

	LARYNGOTRACHEOBRONCHITIS	EPIGLOTTITIS
Age	3 months to 3 years	2-6 years
Cause	Viral (parainfluenza, RSV)	Bacterial (*Haemophilus influenzae* type B)
History	Gradual onset (2-3 days) Previous cold symptoms	Acute onset (few hours) Complaint of sore throat
Symptoms	Stridor Barking cough Fever variable Hoarse voice No position preferred Retractions Irritable Does not appear acutely ill	Stridor Minimal cough High fever Muffled voice Prefers sitting upright with chin forward Retractions Drooling Anxiety Appears acutely ill
Radiographic findings	Subglottic narrowing	Swollen epiglottis (thumb sign)

RSV, Respiratory syncytial virus.

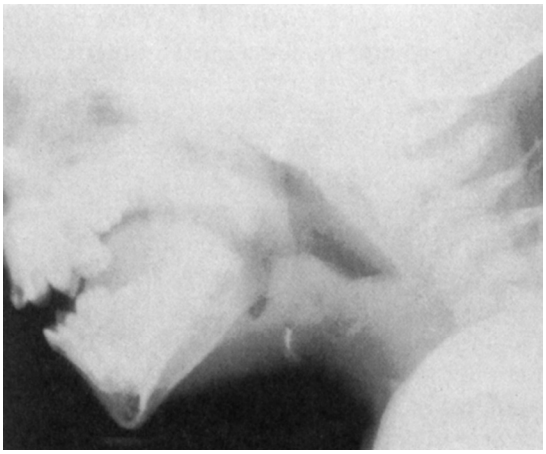


FIGURE 26-4 Epiglottitis. The lateral neck radiograph illustrates the distorted thumb-shaped epiglottic shadow.

procedures are avoided (e.g., arterial blood gas analysis, chest radiography), and every attempt is made to maintain a nonthreatening atmosphere for the child. Until controlled intubation can be achieved (conducted under general anesthesia with a pediatrician, otolaryngologist, and anesthesiologist present), attempts to directly visualize the epiglottis, draw blood, insert intravenous lines, or lay the child flat for an examination are avoided. Instead, the child should be allowed to assume a position of comfort with "blow-by" oxygen therapy provided if necessary. If the clinical history and physical appearance of the child are only mildly suggestive of epiglottitis, more detailed examination or neck radiographs (Figure 26-4), or both, are helpful in confirming the diagnosis.

Treatment

Establishment of a stable artificial airway is the first priority in the treatment of epiglottitis. Placement of an ETT under general anesthesia is a safe way to provide a secure temporary artificial airway. Because there is considerable swelling of the upper airway structures, an ETT one size smaller than the predicted size (based on age) is typically used. Dramatic improvement in respiratory distress is expected after intubation, which bypasses the site of obstruction. Once the ETT is inserted, it must remain in place during the 12 to 48 hours required for the inflamed tissue to shrink in response to therapy.

Treatment of infectious epiglottitis is relatively short, with a 2-day course of ceftriaxone as effective as 5 days of chloramphenicol. This may be adjusted based on patient response and on the results of culture and sensitivity reports from blood and epiglottis swab specimens taken at the time of intubation. Close nursing supervision, constant use of arm restraints, and continuously infused sedatives may suffice to prevent attempts at self-extubation. Mechanical ventilation may be needed for a short time if heavy sedation is required.

Extubation is usually considered within 24 hours when signs of toxicity (e.g., fever) diminish and when an air leak at 20 cm H_2O pressure develops around the ETT. Traumatic epiglottitis often takes several days longer for complete recovery. The physician may choose to directly visualize the epiglottis (by direct laryngoscopy or bronchoscopy) before attempting extubation to ensure that adequate tissue shrinkage has occurred. The child is closely monitored for the return of stridor and other signs of respiratory distress for 12 to 24 hours after extubation.

LARYNGOTRACHEOBRONCHITIS

Incidence and Etiology

LTB, also known as *croup*, is the most common cause of airway obstruction in children between 6 months and 6 years of age. Typically, it occurs in the fall and winter. Parainfluenza virus 1 is the most common cause, resulting in biennial epidemics in the United States during October through February of odd-numbered years. Other much less common infectious causes include influenza viruses, RSV, herpes simplex virus, and *Mycoplasma pneumoniae*.

The viral infection causes a mucosal edema and exudate formation in the glottic and subglottic areas, involving the airways from the larynx to the bronchus—hence the name *laryngotracheobronchitis.* The edema develops over several days, and the resultant airway narrowing becomes severe enough to cause various degrees of airway obstruction. Obstruction is more severe during inspiration because of the deeply negative airway pressure needed to inhale against the edematous airway.

Signs and Symptoms

A child with LTB presents with a gradual prodrome of low-grade fever, malaise, rhinorrhea, and hoarse voice. Over several days, the illness progresses to inspiratory stridor and a "barky" cough, often described as sounding like the bark of a seal. Physical examination reveals nasal flaring; nasal congestion; use of accessory muscles; and suprasternal, subcostal, and intercostal retractions that, along with the stridor, become worse when the child is agitated.

Estimating the severity of the disease can be difficult. The illness usually occurs during cold seasons. Transporting an ill child in moderate distress in an automobile with cold ambient air commonly results in the child being virtually symptom-free on arrival in the emergency department. Inhalation of cold air reduces the swelling and rapidly reduces the respiratory distress. More recent attempts to quantify LTB severity have centered around the presence of pulsus paradoxus and the Croup Score developed by Westley (Table 26-2).[1]

Diagnosis

A lateral neck radiograph, sometimes obtained to help differentiate the disease from epiglottitis, demonstrates

Table 26-2 Croup Scoring System

INDICATORS OF SEVERITY	FINDINGS	CROUP SCORE
Inspiratory stridor	None	0
	At rest, with stethoscope	1
	At rest, without stethoscope	2
Retractions	None	0
	Mild	1
	Moderate	2
	Severe	3
Air entry	Normal	0
	Decreased	1
	Severely decreased	2
Cyanosis	None	0
	With agitation	4
	At rest	5
Level of consciousness	Normal	0
	Altered mental status	5
Total Possible Score 0-17		
< 4 = mild croup	4-6 = moderate croup	7 or greater = severe croup 12 or greater = impending respiratory failure

(Modified from Westley Clinical Scoring System for Croup. Data from Westley CR, Cotton EK, Brooks JG. Nebulized racemic epinephrine by IPPB for the treatment of croup: a double-blind study. *Am J Dis Child*, 132(5):484-487, 1978.)

a large retropharyngeal air shadow without epiglottic swelling. The anteroposterior chest radiograph reveals the classic "steeple sign," a sharply sloped, wedge-shaped, linear narrowing of the trachea. This demonstrates the subglottic tracheal edema that extends from the larynx to the thoracic trachea (Figure 26-5).

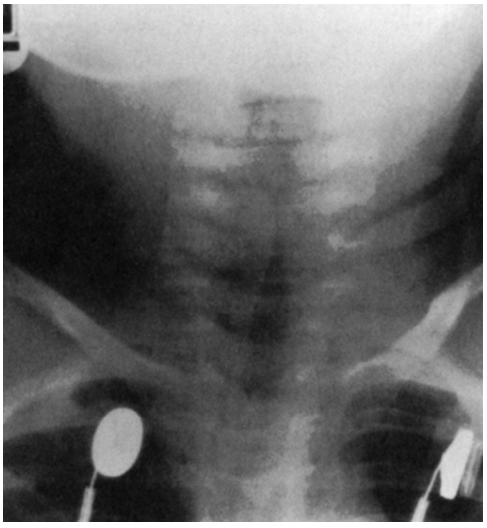


FIGURE 26-5 Laryngotracheobronchitis. The anteroposterior neck radiograph reveals steeply angled subglottic walls ("steeple sign").

Treatment

Treatment of mild cases of LTB is largely supportive—ensuring temperature control, adequate hydration, and humidification of inspired air. Techniques to cool the airway have traditionally used humidified air with water particles large enough to "rain out" onto the upper airway and tracheal mucosa. Cool mist tents (croup tents) were designed to provide continuous humidified air to the trachea. Little, if any, proof of effectiveness exists on the use of this form of humidification, and it has fallen out of favor because of infection control and environmental issues associated with its use.

If increasing respiratory effort, irritability, and inability to engage in play or eating develop, hospitalization may be indicated. Hospital care for a child with LTB is largely symptomatic and centers on careful monitoring for advancing respiratory compromise. Regular assessment of the respiratory rate, degree of retractions, mental status, and air exchange is essential. Oxygen saturation monitoring is useful, but generally desaturation is a late finding. Children requiring an Fio_2 of more than 0.35 are watched closely for evidence of impending respiratory failure.

Nebulized racemic epinephrine is used to induce vasoconstriction of the upper airway. With a 2.2% solution, 0.5 to 1.0 mL of medication is diluted to a 3.0 mL volume with normal saline and given by inhalation with a face mask over a period of approximately 10 minutes. The aerosol is often begun in the emergency department, and the child is evaluated for its effectiveness. A reduction in airway edema usually occurs within 10 to 20 minutes, with a gradual reduction of effect over 2 hours. Although the aerosol may be given as frequently as every 30 minutes, the potential side effects from cardiovascular stimulation and the implied severity of respiratory distress should limit such use to the intensive care unit setting. Reports of a "rebound" effect from persistent use of racemic epinephrine restricted its use to the inpatient setting until recently.[2] In current practice, patients are treated with dexamethasone and racemic epinephrine and discharged from the emergency department to home if they are free of intercostal retractions and stridor after a 2-hour waiting period.[3]

Recommendations for adrenocorticosteroid therapy in patients with LTB have had a long and complicated course. Original proof of effectiveness came with the combined analysis of many studies (metaanalysis) that demonstrated the effectiveness of a single dose of dexamethasone at 0.6 mg/kg given intramuscularly. More recent studies have compared inhaled corticosteroids to oral systemic corticosteroids with and without inhaled racemic epinephrine. Administration of oral dexamethasone at 0.6 mg/kg has been recommended as the least expensive and least invasive way to lower hospitalization rates.

Endotracheal intubation may be necessary if the child becomes exhausted or severe respiratory distress

develops. To avoid traumatizing the inflamed subglottic tissue, the ETT should be at least 1 mm smaller in diameter than that estimated for the child's age. As with epiglottitis, dramatic improvement in respiratory distress is expected after intubation. Attempts at extubation can be made if an air leak develops around the ETT at pressures under 20 to 30 cm H_2O. The child is closely monitored in the 4 to 12 hours after extubation for the return of stridor.

TRAUMATIC AND POSTOPERATIVE LARYNGOTRACHEOBRONCHITIS

Airway obstruction may occur as a sequela of endotracheal intubation. Even the most carefully placed ETT can result in significant injury to the tracheal lining. The cilia in the trachea are easily damaged, especially with aggressive suctioning procedures. Excessively large ETTs lead to necrosis of the tracheal mucosa. An ETT leak of 20 to 25 cm H_2O is recommended to minimize the pressure the ETT applies against the surface of the trachea near the cricoid ring. The value of this leak has been called into question in studies in which the presence of an ETT leak was found to be less predictive of postextubation LTB than the duration of intubation.

Case Study 2

A 2-year-old girl arrives in the emergency room intubated with a 4.0 ETT by emergency medical services (EMS). The mother states the toddler had been ill for several days with a runny nose, fever, and a cough. The night before, the mother had noted that the girl was breathing "funny" and had a barking cough. This morning she refused to drink, had increased difficulty breathing, and was very irritable. She has had multiple episodes of vomiting with coughing, but no diarrhea. After consulting her pediatrician by phone, she had been advised to call an ambulance and have the child transported to the hospital. EMS reports to have found the toddler in respiratory distress and in an altered mental state. Marked stridor was audible and the oxygen saturation was measured at 58%. The child was sedated and paralyzed; intubation with the 4.0 ETT was extremely difficult and required multiple attempts.

What is your differential diagnosis?
What treatment should you recommend?
What complications should you expect?
See Evolve Resources for answers.

LOWER AIRWAY DISORDERS

BACTERIAL TRACHEITIS

Bacterial tracheitis is a medical emergency that can result in complete airway obstruction and death. Patients typically have an antecedent upper respiratory infection or LTB-like symptoms for several days before presenting with severe airway obstruction. Although the slow progression of the disease closely resembles LTB, the fever, toxic appearance, and elevated white blood cell count with an increased percentage of premature white cell forms (bands) all suggest the likelihood of a bacterial disease. Neck and chest radiographs reveal narrowing of a subglottic airway with irregular mucosal surface, without evidence of epiglottic swelling.

Bacterial tracheitis responds poorly to racemic epinephrine and typically requires placement of an artificial airway to manage the copious tracheal secretions. Treatment includes antibiotics to cover for *S. aureus, H. influenzae,* and *S. pneumoniae.* The disease resolves more slowly than epiglottitis, requiring nearly a week before extubation is attempted.

OBSTRUCTION OF THE TRACHEA AND MAJOR BRONCHI

Tracheal narrowing produces either expiratory or biphasic (inspiratory and expiratory) wheezing. The degree and flexibility of the airway narrowing will determine the severity of the wheeze. Because the trachea serves as the final conduit for the removal of secretions, lesions in this area may result in pooling of mucus with rhonchi audible during auscultation. The abnormalities are heard radiating throughout the chest but are best appreciated over the sternal area. It is often difficult to discern where the wheezes or rhonchi originate in a small child. Wheezes or rhonchi that remain equal in pitch across all regions of the chest but are heard loudest around the sternum most likely originate in the trachea. Larger bronchial lesions produce similar manifestations but are more localized to the side of the lesion.

Tracheomalacia

Tracheomalacia is a condition of dynamic tracheal collapse caused by abnormal shape and flexibility of the tracheal cartilage rings. The abnormality can affect either a small section or the entire length of the trachea. Although often idiopathic in origin, there may be identifiable extrinsic causes that led to tracheal wall softening. Common injurious events include neonatal ventilation with high pressures, chronic trauma to the trachea from a malpositioned ETT or aggressive endotracheal suctioning, and external compressive structures, such as a vascular ring.

In most cases of tracheomalacia, the infant or child presents with chronic wheezing that becomes more severe with vigorous breathing. Fortunately, the abnormality tends to improve with time as the child's airway grows, and little intervention is necessary. Severe tracheomalacia may result in complete obstruction and profound episodic hypoxemia, especially during forced exhalation. Repeated airway collapse during exhalation leads to increasingly severe lung hyperinflation. Because exhalation is impaired by airway collapse, once the lung is completely inflated, air movement is no longer possible. This scenario is most

often seen in older infants with a history of prolonged positive-pressure ventilation and severe bronchopulmonary dysplasia (BPD). During severe agitation, these infants become cyanotic and even bradycardic, with little or no air movement despite increased respiratory effort. Treatment options are few, mostly unsatisfactory, and include prolonged continuous positive airway pressure (occasionally fairly high pressure of 10 to 14 cm H_2O) or ventilatory support with a tracheostomy tube in place to distend or "splint open" the airways.

Congenital Tracheal or Bronchial Stenosis

Like tracheomalacia, congenital tracheal or bronchial stenosis may involve extensive or short lengths of the involved airway. The severity of symptoms depends on the degree and length of the stenosis. A common cause of stenosis in a newborn is the formation of a vascular ring. This occurs in infants with congenital malformation of the great vessels of the heart, usually a double aortic arch. With this malformation, the aorta wraps around both the esophagus and trachea. Infants can present with feeding difficulties and uncontrollable wheezing. Surgical correction of the defect can reduce symptoms, although the residual presence of focal tracheomalacia may cause respiratory symptoms to persist postoperatively.

Tracheal stenosis results from complied or nearly complied rings of cartilage. They present as segmental stenosis anywhere in the tracheobronchial tree or as generalized stenosis/hypoplasia. Funnel-shaped lesions are associated with a pulmonary artery sling. This is a very rare anomaly, and outcomes have recently been improved with new surgical techniques.

Intraluminal Obstruction

An acquired cause of airway narrowing is the development of intraluminal obstruction. In children, foreign body obstruction is encountered more commonly than the adult problem of endobronchial tumor. Infectious agents (e.g., *Mycobacterium tuberculosis*) or a neoplasm, classically Hodgkin lymphoma, may cause lymphadenopathy that compresses the airway. The other differential diagnosis to consider is cardiomegaly in patients with congenital heart defects, which especially can compress the left main bronchus because of its anatomic relationship to the heart. The diffuse chronic wheeze associated with these disorders is often confused with asthma. Endobronchial compression is suspected in an infant or child with persistent wheezing who does not respond to bronchodilator therapy. Diagnostic studies to differentiate the cause of wheezing in these patients include barium swallow (for evidence of a vascular ring), bronchoscopy, and computed tomography of the chest. Treatment of intrinsic tracheal and major airway obstruction is often surgical and is directed at widening the narrowed area. Additionally, treatment of the primary cause of the lymphadenopathy, such as Hodgkin lymphoma, is critical.

FOREIGN BODY ASPIRATION

Incidence

A leading cause of accidental death in toddlers is foreign body aspiration. The degree of respiratory sequelae depends on the nature of the material aspirated, whereas the severity of neurologic sequelae depends on the duration of ventilatory compromise. Mobile infants and toddlers are at particularly high risk by virtue of their tendency to place objects in their mouths. Inappropriate toys for a child's age may have loose parts, and certain foods (e.g., nuts, Vienna sausages, hot dogs) are just the right size to become lodged in a child's airway. The preferred location for small enough objects is the right middle lobe bronchi, which has the most direct and straight connection to the trachea. If the child is neurologically intact, these aspiration commonly occurs if the child is startled or falls while harboring such objects in or near the mouth.

Signs and Symptoms

Signs and symptoms of foreign body aspiration vary with the location of impaction and the degree of airway obstruction. They can range from unilateral wheezing or recurrent **pneumonia,** as when peanuts or popcorn obstructs the smaller airways, to immediate occlusion of the upper airway with complete absence of air movement and rapid death from suffocation, as seen in hot dog and balloon aspiration fatalities. It is not necessary for the foreign body to be in the trachea: a big enough object stuck in the esophagus can elicit very similar symptoms of respiratory distress.

Diagnosis

The cause of the obstruction and adequacy of ventilation should be quickly determined. A thorough history of the circumstances surrounding the onset of symptoms helps to determine whether this is a foreign body aspiration or an infectious process. However, a complete history is often difficult to obtain. Examiners must determine, first and foremost, the adequacy of ventilation, followed by the location of the obstruction. Sudden onset of wheezing, particularly if wheezing has never occurred before and is unilateral in nature, should raise suspicion of foreign body aspiration.

Box 26-1 demonstrates locations of foreign body aspiration in children by percentage.[4] Anteroposterior

Box 26-1 Common Locations of Foreign Body Aspiration

- Right lung (including mainstem): 60%
- Left lung (including mainstem): 23%
- Trachea/carina: 13%
- Larynx: 3%
- Bilateral: 2%

(From Ereu S, Balci AE, Dikici B, et al.: Foreign body aspiration in children: experience of 1160 cases. *Ann Trop Paediatr* 23:31, 2003.)

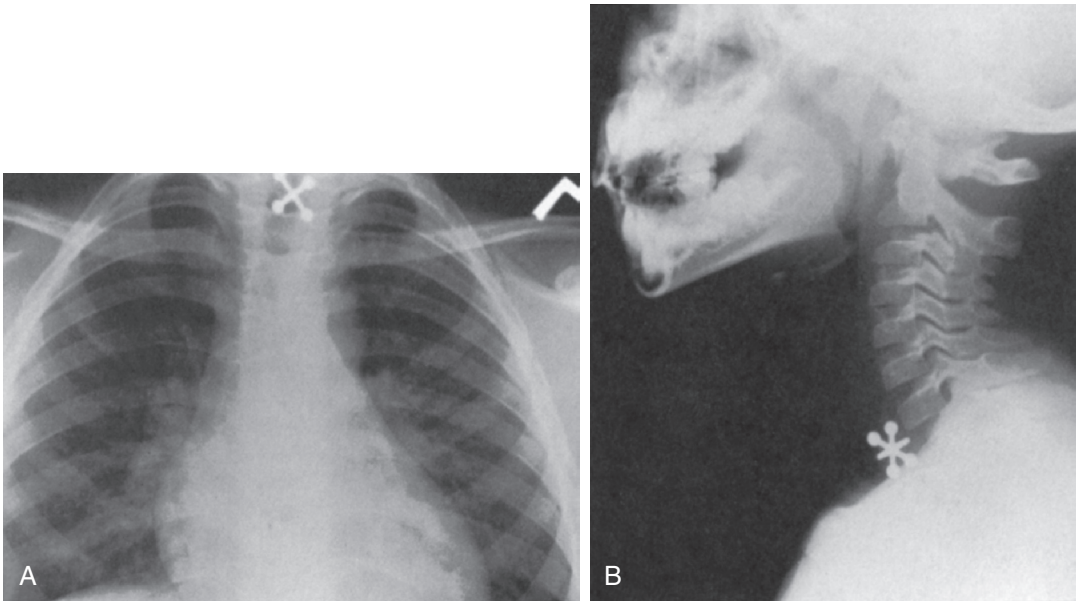


FIGURE 26-6 Foreign body obstruction. Posteroanterior **(A)** and lateral **(B)** chest radiographs reveal an esophageal foreign body that caused respiratory distress from posterior pressure on the trachea.

and lateral neck and chest radiographs are useful if the object is radiopaque. Although the appearance of a radiopaque foreign body on a radiograph is striking, many aspirated materials, such as peanuts and carrots, cannot be detected in this fashion (Figure 26-6). Foreign body aspiration usually occurs at the laryngeal level. Deviation in the airway shape may indicate a foreign body not otherwise visible. Recurrent pneumonia in the same lobe is also suspicious. Asymmetric lung hyperinflation can result from a ball-valve effect of foreign material localized in a major bronchus. This defect is most often apparent on an expiratory film (Figure 26-7).[5] Comparison between expiratory and inspiratory films can also yield the diagnosis but depends greatly on the cooperation of the child.

Fiberoptic laryngoscopy or bronchoscopy is helpful in both finding and retrieving the foreign body. Such a procedures is best done in an operating room and with a rigged bronchoscope. Pulse oximetry is used to determine the need for supplemental oxygen. An end tidal carbon dioxide monitor or arterial blood gas analysis is indicated if hypercarbia is suspected in a child with severe obstruction.

Treatment

The therapy used will vary with the severity of the obstruction. If the child is well oxygenated and ventilated, a controlled therapeutic bronchoscopy or laryngoscopy with appropriate anesthesia is preferred. When foreign body aspiration is suspected and respiratory symptoms are acute, urgent bronchoscopy with removal of the object is necessary. Even if the child appears to be stable, movement of the object to a more critical area can result in sudden clinical deterioration. A child with complete obstruction may require emergent cricothyrotomy to establish a patent airway.

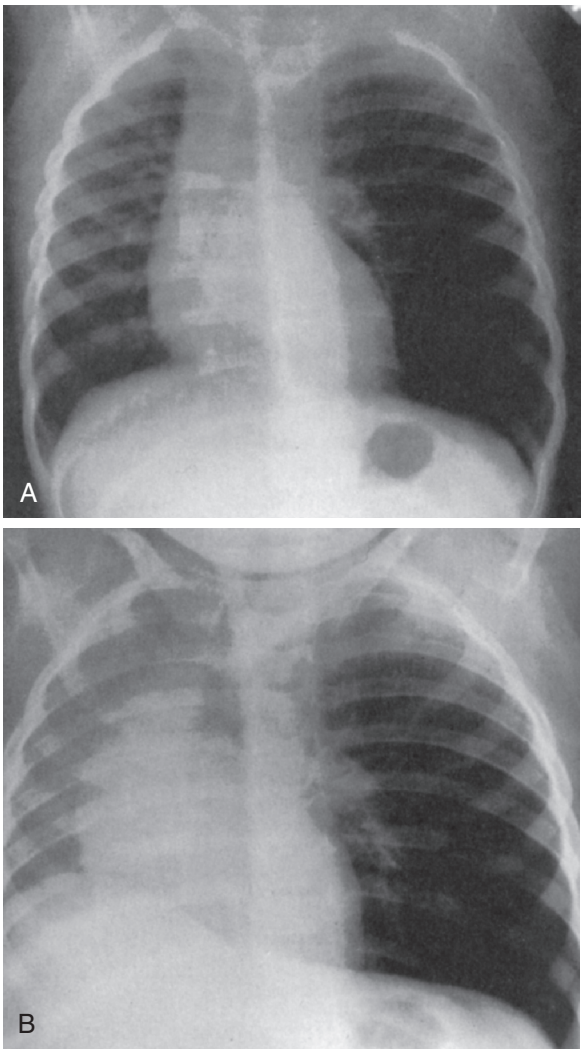


FIGURE 26-7 Foreign body aspiration. Asymmetrical lung volumes **(A)**, accentuated during exhalation **(B)**, indicate an obstructing ball-valve type of lesion in the left bronchus.

Signs of severe or complete airway obstruction that requires intervention include the following:

- Inability to speak or cry audibly
- Weak, ineffective cough
- High-pitched sound or no sound during inhalation
- Increased difficulty breathing, with distress
- Cyanosis
- Universal choking sign (thumb and index finger clutching neck)

No intervention should be taken if the child can cough forcefully or speak. In this case, one should stay with the child, monitoring the situation and providing emotional support. The intervention described here addresses the classical everyday foreign body obstruction scenario. In a hospital setting, the situation may be different and more likely related to causes or complications of medical treatment. In those cases, troubleshooting equipment and suctioning the airway should be the first line of action.

Once the obstruction is relieved, some children will be discharged as soon as they recover from anesthesia. In others, resolution of symptoms may be delayed. Airway edema may develop and require corticosteroid therapy along with careful monitoring to ensure that a progressive obstruction does not ensue. Reactive granulation tissue at the site of impaction along with postobstructive infection may take some time to resolve. A second bronchoscopy may be required because of reaccumulation of secretions.

If intubation and mechanical ventilation are indicated, remembering that these children usually have normal lung function, positive pressure may push the foreign body deeper and it may create an obstructive ventilation pattern. The Fio_2 and minute ventilation requirements are often low and set to obtain normal arterial blood gas values or permissive hypercapnia in extreme situations when removal is difficult. Once patency of the airway is ensured, the patient is weaned from mechanical ventilation. Secondary infection and prolonged intubation are occasional complications.

ATELECTASIS

Etiology and Pathophysiology

Atelectasis is collapsed lung parenchyma and is best compared to a wet sponge that fails to reexpand after being compressed. Many processes can cause atelectasis. Internal or parenchymal disorders that are characterized by an inadequate tidal volume, loss of lung compliance (e.g., acute respiratory distress syndrome), airway obstruction (e.g., mucus plugging), and increased elastance of lung tissue can all result in atelectasis. External forces also lead to compression of lung parenchyma, with the reduction in lung volume resulting in atelectasis. These include chest wall disorders (e.g., kyphosis, flail chest), accumulation of pleural fluid, obesity, and abdominal ascites.

The right middle lobe, which has the poorest collateral air circulation and smallest bronchial opening of the major lung segments, is particularly prone to mucus plugging and collapse. Intubated patients, particularly young infants, have a propensity toward right upper lobe collapse. This is most likely related to their supine positioning and tendency toward obstruction of the right upper lobe bronchus (the most proximal of all the lobar bronchi) by a migrating ETT. Postoperative patients are at particular risk of atelectasis because of an ineffective cough, impaired mucus transport, and the effect of anesthesia. Surfactant deficiency may occur in the child after smoke inhalation or lung contusion, resulting in various degrees of lung collapse. Tracheobronchial suctioning has also been related to atelectasis in children and is believed to result from the negative pressure that the airway is exposed to during the suctioning process.

Signs and Symptoms

Clinical presentation will vary with the cause and severity of the lung volume loss. Clinical history may reveal slow regression of activity and deterioration of pulmonary function, as may be seen with a slowly growing pleural tumor. Conversely, the patient may experience rapid-onset dyspnea and cyanosis from a foreign body aspiration that occludes a large bronchus, leading to airway collapse.

Patients with enough atelectasis to create a severe ventilation–perfusion (V/Q) mismatch exhibit clinical symptoms of cyanosis, tachypnea, nasal flaring, retractions, and grunting. The patient may complain of chest pain on deep inspiration if the pleura is inflamed or there is accompanying pneumothorax.

Arterial blood gas analysis reveals low oxygen saturations, manifesting low V/Q ratios. The $Paco_2$ levels often remain normal in the presence of atelectasis, as a result of the rapid diffusion characteristics of carbon dioxide and close regulation of the $Paco_2$ by an altering respiratory rate.

Diagnosis

Although atelectasis is most often found on a chest radiograph, it may first be suspected during a physical examination. Decreased breath sounds, increased tactile fremitus, tracheal deviation, and an elevated diaphragm may indicate atelectasis; however, many patients with atelectasis are asymptomatic on physical examination. Diagnosis is confirmed with evidence of volume loss on a chest radiograph (Figure 26-8).

Treatment

Treatment of atelectasis is aimed at removing the cause and depends on the individual patient's clinical course. Drainage of pleural fluid or removal of external compressors will allow the lung to reexpand. If the cause is airway obstruction, bronchoscopy or good pulmonary hygiene, including aerosolized bronchodilators

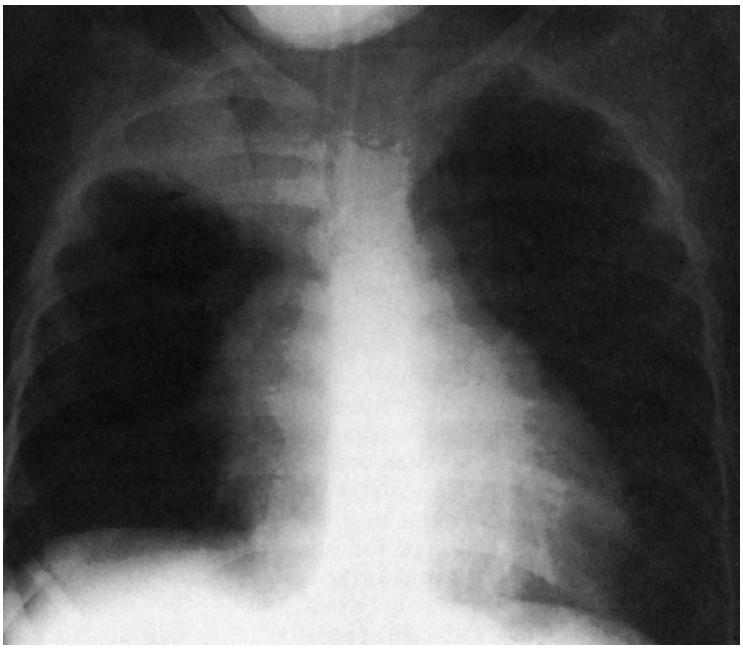


FIGURE 26-8 Anteroposterior chest radiograph with right upper lobe atelectasis.

and chest physiotherapy, will facilitate returned airway patency. In an intubated patient, the use of continuous distending pressure may reverse and prevent further lung collapse. Early mobilization and position changes in postoperative patients, along with encouragement in coughing and deep breathing (e.g., incentive spirometry), are techniques used to prevent and often treat atelectasis.

BRONCHIECTASIS

Etiology and Pathophysiology

Bronchiectasis is defined as irreversible dilation of the bronchial tree. Typically, the segmental and subsegmental bronchi become irregularly shaped and dilated, leading to a loss of the typical funnel configuration that allows smooth central flow of secretions. Additionally, ciliary activity in the area of the dilation is inadequate and further contributes to the difficulty in mobilizing secretions. The secretions become infected as they pool. The lower lobes, particularly the left lower lobe, are most often involved.

A small number of patients may have congenital bronchiectasis, in which there is a defect in the development of bronchial cartilage or developmental failure of the elastic and muscular tissues of the trachea and main bronchi. Most patients acquire the disease, and bronchiectasis develops as a result of airway obstruction or chronic infection. Causes include bronchial obstruction (e.g., foreign body aspiration, mediastinal mass), infection (e.g., measles, pertussis, pneumonia), Kartagener syndrome, and cystic fibrosis (CF).

Signs and Symptoms

Bronchiectasis may occur acutely after an infection or have a more insidious onset in patients suffering from chronic pulmonary diseases such as CF or reflux and aspiration. Patients experience chronic cough, often productive of copious amounts of thick purulent sputum that has a three-layered appearance if left standing for some time, and only occasional hemoptysis. Pulmonary infections are common, with recurrent fever and foul-smelling breath or sputum. Dyspnea on exertion and clubbing of the digits may manifest in some cases. The lower lobes, particularly the left lower lobe, are most commonly involved.

Diagnosis

Bronchiectasis may be suspected on the basis of the clinical history and physical examination. Plain chest radiographs are seldom normal but alone are not definitive in diagnosing the disease. The abnormal pattern of bronchiectasis is seen most strikingly during bronchography. However, this is rarely performed today. Instead, computed tomographic scanning is used to confirm the diagnosis (Figure 26-9). Pulmonary function may be abnormal, with spirometry demonstrating an obstructive pattern. A combined obstructive and restrictive disease pattern may be present in more severe cases.

Treatment

Medical management depends on the severity of the disease. Chest physiotherapy, including postural drainage and percussion is performed, along with adequate hydration to improve the mobilization of pulmonary secretions. Newer concepts favor the idea that low mucus salinity rather than underhydration contributes to mucus retention. This may explain the success and increased use of nebulized hypertonic saline in these patients.

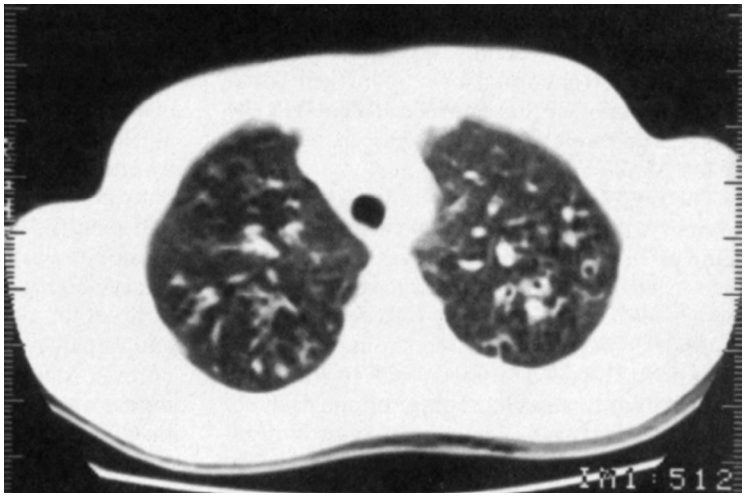


FIGURE 26-9 Widened, thick-walled bronchial tubes (cut in cross-section) in the peripheral lung zones.

Antibiotic therapy is given orally, by nebulization (i.e., tobramycin), or intravenously. The choice of antibiotic is based on the results of the individual patient's sputum culture results. Blind use of broad-spectrum antibiotics in this chronic disease may lead to more resistant colonization. The empiric use of intravenous antibiotics and new mucous-clearing medications and treatments in CF patients has improved outcomes in this particular disease.

In those cases in which the child suffers severe illness (e.g., failure to thrive, severe hemoptysis) despite antibiotic therapy and chest physiotherapy, surgical resection of the bronchiectatic section of lung may be considered. Patients with the disease localized to only one or two lobes are considered better candidates for surgical intervention.

Case Study 3

A 3½-year-old boy is admitted to the intensive care unit (ICU) after heart surgery. He was on cardiopulmonary bypass for 190 minutes, and the operation went well. In the ICU he is sedated and ventilated. A chest radiograph and cultures are obtained on postoperative day 1 for fever. The chest radiograph shows consolidation of the left lower lobe, and it remains the same over the next few days. All cultures are negative, and he is successfully extubated on postoperative day 4. The chest radiographs remain unchanged, and the decision for bronchoscopy is made. Before the bronchoscopy, the plan is to reintubate the child. He is paralyzed, and his baseline oxygen saturation remains at 75% to 79% under bag-mask ventilation. An ETT is placed under good visualization of the vocal cords, but his oxygen saturations fall to 60% to 65% with minimal chest rise and increased resistance to bagging. He is extubated, and it is not possible to bag-mask ventilate him. His oxygen saturations continue to drop, and after a second intubation attempt with good visualization of the vocal cords, he goes into cardiac arrest.

What is your differential diagnosis?

What are your actions?

See Evolve Resources for answers.

ACUTE BRONCHIOLITIS

Etiology and Pathophysiology

The term *acute bronchiolitis* is applied to a condition in infants in which a viral respiratory tract infection results in clinical symptoms of small airway obstruction. In most infants with bronchiolitis, the causative organism is RSV.

RSV is a highly contagious virus and has its greatest impact on young infants. Infants younger than 6 months of age are at particular risk of severe infection, with the peak incidence for hospitalization occurring between 2 and 6 months of age.[6] Bronchiolitis is the number one cause of hospitalization in the United States, and considerable variation exists in the management. Although most cases are mild and do not require hospital admission, epidemics of the infection occur between December and March. Postmortem evaluation of infants with severe bronchiolitis reveals obstructed airway lumina from impacted cellular debris. *In vitro* studies suggest that an intense inflammatory response occurs in the infant's airways and may contribute to increased mucus secretion and transudation of fluid into the airways and airway walls.

Incidence

Acute bronchiolitis is seen most often in infants younger than 1 year of age who were born prematurely, live in a crowded environment, attend day care facilities, and are exposed to passive smoke.[6] Bronchiolitis with RSV infection is particularly devastating to infants with certain at-risk conditions, including premature birth, chronic lung disease (e.g., BPD, CF), congenital heart disease (especially those with pulmonary hypertension), and immunodeficiencies.[6] These infants are at risk of respiratory failure and death.

Signs and Symptoms

Physical findings vary considerably with the patient's age. Infants (younger than 1 year of age) develop

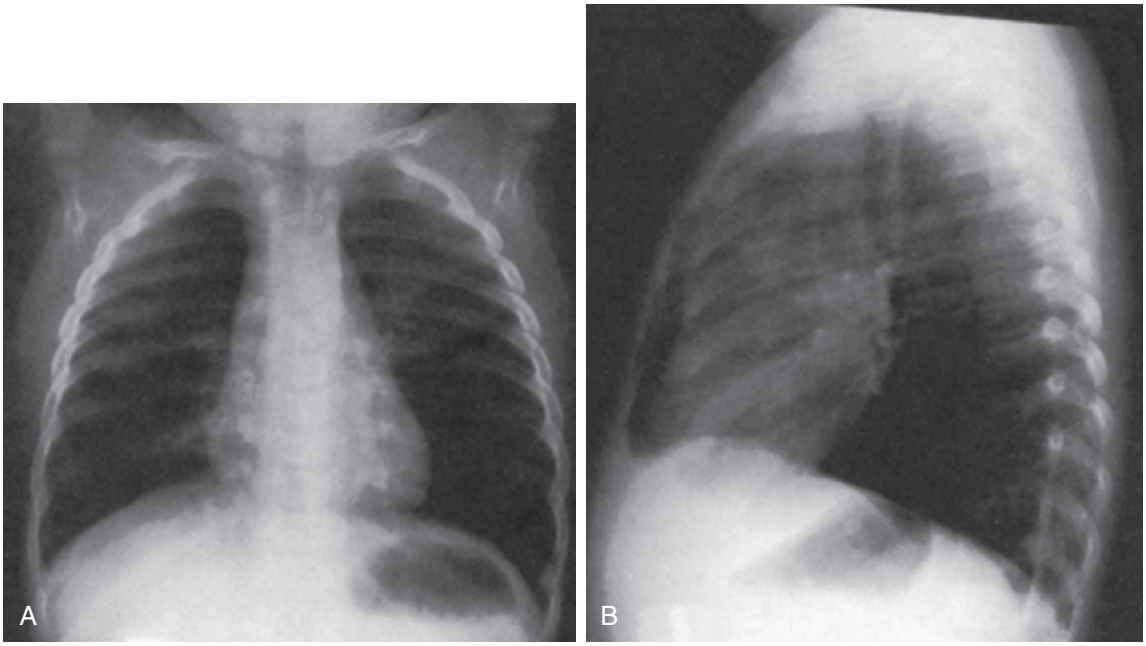


FIGURE 26-10 Severe bronchiolitis. Posterior **(A)** and lateral **(B)** chest radiographs reveal flattening of the diaphragm and widening of the anteroposterior diameter, which is indicative of severe air trapping. Perihilar markings are accentuated.

coryza, cough, respiratory distress, wheezing, and tachypnea. The symptoms of infection usually peak around 48 to 72 hours, and a previously healthy infant can progress from what was thought to be a simple cold to severe respiratory distress during that time. In contrast, the principal symptoms in children older than 2 years of age are profound nasal congestion and productive cough. Chest auscultation reveals diffuse, coarse, "sticky" rales ("Velcro" rales), which may be accompanied by wheezes. A chest radiograph typically reveals intense lung hyperinflation with flattened hemidiaphragms (obstructive), with occasional films showing evidence of collapse or consolidation (Figure 26-10).

Severe, life-threatening apnea is a common symptom in very young infants with bronchiolitis, especially those with cardiorespiratory disease or a history of premature birth or apnea. An infant may also be agitated and have difficulty feeding as a consequence of hypoxia. This may lead to dehydration and respiratory failure. Development of cyanosis usually heralds impending respiratory failure. Arterial Pco_2 rising above 55 mm Hg despite tachypnea indicates impending respiratory failure, and noninvasive respiratory support should be considered. Invasive mechanical support may be required if noninvasive treatment fails to improve gas exchange or apnea occurs.

Diagnosis

Clinical diagnosis of acute viral bronchiolitis is confirmed by identifying the RSV or other respiratory virus. Nasopharyngeal aspirate or nasal lavage provides samples of the virus. Diagnosis is based on the clinical presentation and the results of viral culture and antigen detection assays (i.e., enzyme-linked immunosorbent assays). Clinical history and physical examination form the basis for a diagnosis of bronchiolitis.

Features of the clinical history may include but are not limited to the following:

- Preceding upper respiratory infection or rhinorrhea
- Features of lower respiratory infection
- History of sick contacts

Features of the physical examination may include but are not limited to the following:

- Signs of respiratory distress: tachypnea, retraction, hypoxia, color change, nasal flaring, grunting, apnea, head bobbing, or wheezing
- Signs of dehydration

Although the diagnosis of bronchiolitis is clinically evident, the differential diagnosis is broad and always warrants consideration.

Treatment

Treatment of bronchiolitis is largely supportive, along with careful monitoring. The infection is self-limiting in many patients, and hospitalization is not necessary if symptoms are mild. The infant is monitored for apnea, hypoxia, and dehydration. Care is taken to provide adequate feedings and prevent further respiratory distress.

The decision to hospitalize a child with bronchiolitis involves a multifactorial assessment of the risk factors, clinical symptoms, age, and familial resources. Supportive care with supplemental oxygen, intravenous hydration if needed, and close clinical monitoring is essential. In most cases, low-flow oxygen therapy (typically nasal cannula) is sufficient to reduce the

hypoxia and respiratory distress. Patients with recurrent apnea or respiratory failure may need intubation and mechanical ventilation. Continuous monitoring with pulse oximetry is essential, as well as arterial blood gas analysis for those patients in whom respiratory failure is suspected. Moderate yet persistent hypoxia (Spo_2 88% to 92%) despite oxygen therapy can be an ominous sign of impending respiratory failure, because the patient could be moving from the obstructive (improved functional residual capacity) to the restrictive (atelectasis) phase of disease. In practice, it is very important to ensure patent nares, especially if nasal cannula is used, because RSV typically generates copious amounts of nasal secretions. This is best achieved by frequent and efficient suction of the nares.

Infants with tachypnea, agitation, and cough are at risk of dehydration. In many moderate to severe cases they stop eating because they cannot coordinate the sequence of suck, swallow, and breathe at high respiratory rates. This is a common concern in those patients who experience vomiting with the cough. Intravenous fluids or frequent small-volume feedings are both routes to consider when fluid intake is poor.

The role of bronchodilators in the management of bronchiolitis is controversial. A single inhalation trial using epinephrine or albuterol can be considered for respiratory distress on an individual basis, such as when there is history of asthma, allergy, or atopy.[7] It is recommended to discontinue inhalation therapy if there is no clinical response, such as improved respiratory distress or improved bronchiolitis scores. Nebulized racemic epinephrine demonstrates better short-term improvement in pulmonary physiology and clinical scores, but only in the outpatient setting.[8] However, continuation of inhalation therapy despite documented nonresponse exposes the patient to unnecessary therapy and cost.

Ipratropium bromide and theophylline have not proven to be beneficial as bronchodilators in the treatment of bronchiolitis. Despite the evidence of airway inflammation, use of systemic or inhaled corticosteroids early in the symptomatic phase of the disease does not tend to improve outcome. However, inhaled corticosteroids are sometimes given to reduce short-term morbidity when there is delayed recovery. It is questionable whether these interventions are successful in infants and children with a tendency to have recurrent wheezing or asthma in the future or whether the children with treatment success have some other unknown underlying respiratory physiology or chemistry variety.

Nebulized hypertonic saline (3%) is considered an effective and safe treatment for infants with mild to moderate respiratory distress and has been shown to reduce length of stay.[9] The optimal treatment regimen for nebulized hypertonic saline in acute bronchiolitis in the inpatient setting remains unclear. A randomized controlled trial[9] using hypertonic saline every 2 hours for 3 doses, every 4 hours for 5 doses, and every 6 hours until discharge has shown promising results and is an alternative; however, more evidence is needed on efficacy and dosing regimen. Hypertonic saline therapy significantly reduces bronchiolitis scores (prehypertonic/posthypertonic saline) among patients with mild to moderate bronchiolitis. The first dose of hypertonic saline requires close clinical monitoring for development of acute bronchospasm. A one-time as-needed albuterol order is recommended for the first dose. Acute bronchospasm during or immediately after hypertonic saline therapy is a possible side effect, especially in children with a known or unknown family history of asthma. Given the difficulty in distinguishing between asthma and viral bronchiolitis in infants, the first dose should be monitored closely.

Antibiotics. Antibiotics are not recommended in the absence of an identified bacterial focus.[10] Bacterial infections should be treated in the same manner as when bronchiolitis is not present. Previously healthy febrile children 24 months old or younger with bronchiolitis have a low incidence of meningitis, bacteremia, and urinary tract infections. Physician discretion is required when managing infants younger than 60 days. For infants diagnosed with bronchiolitis and otitis media, practitioners should refer to practice guidelines.[6] If using antibiotics without an identified bacterial focus, the practitioner should exercise caution and consider potential side effects, such as cost to patient and community and increasing bacterial resistance to antibiotics.

Other medications. It is recommended that antihistamines, oral decongestants, and over-the-counter (OTC) cough and cold medications not be used for routine therapy because of potential side effects.[11] The US Food and Drug Administration (FDA) recommends that OTC cough and cold products not be used for children younger than 2 years, because serious and potentially life-threatening side effects can occur.[12]

Ribavirin, a broad-spectrum virustatic agent, continues to play a very limited and contentious role in the treatment of bronchiolitis. It is administered as an aerosol and delivered to the patient through either an oxygen hood, aerosol mask, or ventilator circuit, for 12 to 18 hours per day. Although early studies proclaimed its benefits, concerns remain about its safety, cost, and efficacy. Reported side effects are uncommon; however, precautions are taken to minimize exposure to hospital personnel and family. Ribavirin is expensive to use, and there is no convincing evidence that its use aids in reducing morbidity or mortality. Studies that concluded that there is a reduction in morbidity and mortality among high-risk patients have been criticized, with many centers suggesting that the improvement was caused by improved supportive

care rather than the antiviral therapy. For those who support the use of ribavirin, the majority consider it most beneficial in treating extremely ill patients, those who are immuno compromised, and those requiring mechanical ventilation. Today the role of ribavirin remains controversial, and its use varies significantly among clinicians. There is a renewed interest in this drug with new and easier-to-manage nebulizers on the market such as the Aerogen micropump.[13]

RSV spreads rapidly and is transmitted through touch, with the virus able to survive on hands and other surfaces (e.g., bed rails, toys). RSV prevention is accomplished by strict avoidance of other infected children and careful attention to hand washing. Disease prevention in high-risk patients (e.g., those with BPD or born prematurely) can best be accomplished by passive immunization with immune serum globulin (RSV-IGIV). This passive immunity decreases the incidence of RSV hospitalization by 40% to 65% and the number of hospital days by 50% to 60%.[14] Strict avoidance of air pollutants, especially cigarette smoke, assists in the long-term recovery from bronchiolitis.

Prognosis

The mortality rate of infants in high-risk groups is much improved over the past several years. Recurrence of bronchiolitis episodes is seen in some patients; however, subsequent infections are usually much less severe. Studies have indicated that many patients have recurrent cough and wheeze several years after RSV infection. An increase in bronchial responsiveness is often found later in childhood.

PRIMARY CILIARY DYSKINESIA

Etiology and Pathophysiology

Normal cilia beat in a coordinated fashion, effectively propelling overlying mucus in one direction out of the airway. The upper and lower respiratory tracts are cleared of secretions, inhaled particles, and bacteria. Without the forward thrust of the cilia and coordinated ciliary beating, mucus transport is slowed and there is an accumulation of particles, secretions, and bacteria in the dependent portions of the lungs.

In 1933 Kartagener described a unique clinical triad of situs inversus, chronic sinusitis, and bronchiectasis. This became known as Kartagener syndrome. Subsequent studies found that these patients had defects in the ultrastructure of the cilia that line the mucous membranes of the sinus cavities, lungs, and nose. The syndrome was initially called *immotile cilia syndrome.* However, further studies demonstrated that the cilia in patients with this syndrome are not always immotile but often have uncoordinated or ineffective motility.[15] The term *primary ciliary dyskinesia* (PCD) is used increasingly today.

Signs and Symptoms

Chronic cough, often productive, is the most common presenting feature of PCD. It is most apparent early in the morning and with sleep and exercise. Although the mucopurulent sputum initially clears with antibiotic therapy, with age the patient develops increasingly severe airway obstruction. Physical findings include persistent crackles, although wheezing is relatively uncommon. A chest radiograph may reveal lung hyperinflation and changes consistent with bronchiectasis.

Upper respiratory tract infections are common. Persistent nasal congestion, a common presenting feature, may progress to chronic nasal drainage with radiographic evidence of sinusitis. Chronic otitis media, with or without chronic effusions, often occurs and requires prolonged use of transtympanic ventilation tubes.

A right-to-left reversal of the position of the heart and intestinal structures, known as *situs inversus,* is seen in approximately 50% of patients with PCD. Isolated dextrocardia may also be found. The accepted explanation for the association of situs inversus with the ciliary defect is that normal rotation of chest and abdominal organs depends on properly functioning embryonic cilia during closure of the thoracic and abdominal cavities. Because similar functional defects are found in both mucosal cilia and sperm flagella, the abnormal cilia motility affects male fertility, and males are nearly always sterile.

Diagnosis

Diagnosis can be made rapidly by microscopic evaluation for ciliary motility in specimens taken from the paranasal sinuses, nose, or tracheal mucosa. Light and electron microscopy of bronchial mucosal cells reveal abnormal cilia numbers with abnormal structures. Patients with PCD have defects in the dynein arms, radial spokes, and nexin links. Cilia with an inadequate number of out-dynein arms may be immotile or may have some disorganized rigid movement. Absence of radial spokes and alteration in the figuration of the microtubules in the cilia are other ultrastructural changes.

Treatment

Treatment of PCD focuses on reducing the volume of pooled respiratory secretions in the lung. Chest physiotherapy for airway clearance is essential and is used with exercise and aerosolized β_2-agonists. Children with PCD have evidence of obstructive pulmonary disease. The obstruction is best minimized by exercise before physiotherapy, instead of relying on β_2-agonist therapy. Because coughing is one of the few mechanisms available for removing secretions, antitussive therapy is contraindicated.

Nebulized recombinant human DNase (Pulmozyme) is indicated for treatment of cystic fibrosis. It

reduces sputum viscosity, improves pulmonary function, and results in a small reduction in acute respiratory exacerbations. It has been found to be beneficial in the treatment of PCD. Aerosolized or intravenous antibiotics directed by bacterial antibiotic sensitivities, in combination with chest physiotherapy (CPT) and mucolytic therapy, are believed to reduce the progression of obstructive pulmonary disease. Although rarely necessary, surgical excision of the pulmonary segments is considered when suppurative disease is poorly controlled and localized to a single area.

PNEUMONIA

Lower respiratory tract infections are a leading cause of morbidity and mortality in the pediatric population. They most often affect children younger than 2 years of age. These children typically experience the greatest number of complications. Gram-positive cocci, particularly group B streptococcus and *S. aureus*, along with gram-negative enteric bacilli, are the source of most neonatal pneumonias. Children between 1 month and 5 years of age are the most common victims of viral pneumonia. RSV and parainfluenza viruses types 1, 2, and 3, along with adenovirus, are the most common infectious viral agents. However, *Chlamydia pneumoniae, H. influenzae, S. pneumoniae,* and *S. aureus* are occasional bacterial agents in this age group. *S. pneumoniae* is the major cause of bacterial pneumonia in children older than 5 years, whereas *M. pneumoniae* and *C. pneumoniae* are more common in school-age children and young adults. Box 26-2 lists the infectious causes of pneumonia in the pediatric population.

VIRAL PNEUMONIA

Respiratory Syncytial Virus

Nearly 80% of all pneumonias in the pediatric population have a viral etiology, with RSV occurring most often. RSV commonly affects children younger than 2 years, although it has been found in older immunocompromised children and in children with chronic lung disease. Outbreaks occur annually during the winter and are rarely seen during the spring and summer. RSV often causes bronchiolitis, but pneumonia can develop.

The first symptoms noted are usually coryza and nasal congestion, followed by cough, fever, and malaise. Retractions, nasal flaring, tachypnea, wheezes, and rhonchi are common. The chest radiograph typically shows hyperinflated lungs with patchy infiltrates and/or atelectasis (most often involving the right upper lobe). Dehydration can develop as a result of tachypnea, cough, and decreased feeding. Diagnosis is confirmed with rapid immunofluorescent detection of RSV antigen in nasal washings or enzyme-linked immunosorbent assays of nasal secretions. Test methods are relatively inexpensive.

Box 26-2 Infectious Causes of Pneumonia

VIRUSES
- Respiratory syncytial virus
- Parainfluenza types 1, 2, and 3
- Influenza virus
- Adenovirus
- Rhinovirus
- Cytomegalovirus
- Epstein-Barr virus
- Herpes simplex virus

MYCOPLASMA
- *Mycoplasma pneumoniae*
- *Ureaplasma urealyticum*

BACTERIA
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Staphylococcus aureus*
- *Streptococcus agalactiae*
- *Legionella pneumophila*
- *Mycobacterium tuberculosis*

PROTOZOA
- *Pneumocystis carinii*

FUNGI
- *Histoplasma capsulatum*
- *Coccidioides immitis*
- *Candida* spp.
- *Blastomyces dermatitidis*
- *Cryptococcus neoformans*

RICKETTSIAE
- *Coxiella burnetii* (Q fever)

CHLAMYDIA
- *Chlamydia pneumoniae*
- *Chlamydia trachomatis*
- *Chlamydia psittaci*

PARASITES
- *Ascaris lumbricoides*

Hypoxemia and hypercarbia are complications of RSV pneumonia and may mandate supplemental oxygen for an extended period. Supportive care is aimed at monitoring the severity with pulse oximetry. Patients may experience progressive hypoxemia and respiratory failure, necessitating intubation and mechanical ventilation. There may be further progression to advanced respiratory failure, despite maximal ventilatory support. Those patients may require extracorporeal membrane oxygenation (ECMO).

Parainfluenza Virus Types 1, 2, and 3

The parainfluenza viruses are the second-most common cause of LTB and pneumonia. Type 3 is the most common cause in children younger than 5 years of age and occurs year-round with no seasonal peak. Clinical presentation is similar to that described for RSV. Chest radiographs typically reveal patchy or

interstitial infiltrates. Diagnosis is confirmed with rapid antigen testing or viral isolation from a nasal washing. Therapy is supportive, with supplemental oxygen and additional hydration provided as needed. Parainfluenza virus is not to be confused with influenza virus, which has a very narrow seasonal peak.

Influenza Virus

Although influenza virus may cause pneumonia, it occurs predominantly in very young and very old patients. Yearly epidemics occur during the late winter and early spring. Clinical symptoms consist of rapidly developing fever, malaise, and myalgia. Duration of the illness is usually shorter than that of RSV and the parainfluenza viruses. Although rare, a rapid pneumonia may result in death within 2 days of onset. Diagnosis and treatment are similar to those of RSV and parainfluenza virus infections. Vaccines are provided annually and are recommended for high-risk children with chronic cardiopulmonary and immunologic disorders. Chest radiographs typically reveal interstitial or patchy alveolar infiltrates.

Adenovirus

Although it occurs year-round, adenoviral pneumonia is most often seen in the late summer and early fall. It occurs most often in children younger than 2 years of age. It is easily confused with bacterial illnesses because it mimics their symptomatology: rapid onset, high fever, leukocytosis, and chest radiograph consistent with pneumonia. Additional findings may include lymphadenopathy and conjunctivitis. A chest radiograph reveals patchy or interstitial infiltrates.

Certain adenoviral types (i.e., 3, 7, 21) are associated with a high mortality rate because of the overwhelming sepsis and cardiovascular collapse that occur. Diagnosis is confirmed with rapid antigen testing or viral isolation from a nasal washing. Therapy is supportive, and no specific treatment is available. Close monitoring for bacterial superinfection is suggested. New viruses are being isolated, and their implications will become clearer over time.

BACTERIAL PNEUMONIA

Incidence

Although the incidence of bacterial pneumonia is less than that of viral pneumonia, it has a higher mortality rate. It may occur as a secondary problem to a primary viral pneumonia, as is often seen with pneumonia from influenza virus. Certain other factors known to increase the risk of bacterial pneumonia include compromised immune function, recurrent aspiration from gastroesophageal reflux, malnutrition, day-care attendance or school-aged sibling, exposure to passive cigarette smoke, and congenital abnormalities of the airway (e.g., tracheoesophageal fistula). Bacterial pneumonia is seen throughout the year, with peak incidence in the winter and early spring.

Etiology

Bacterial agents that cause pneumonia vary considerably throughout the pediatric age group. In the neonatal patient, the offending bacteria are most often contaminants from the mother's genital tract and include group B streptococcus, *Escherichia coli, Listeria monocytogenes,* and *Chlamydia trachomatis.* Infants older than 4 to 6 weeks tend to develop pneumonia from *S. pneumoniae, H. influenzae,* and *S. aureus.* Less likely organisms include *Bordetella pertussis, M. pneumoniae,* and *C. pneumoniae.*

Bacterial pneumonia develops when the intrinsic host defenses are decreased, either by another disease process (e.g., viral infection) or when the anatomic protective mechanisms are destroyed (e.g., primary ciliary dyskinesia). Therefore any microorganism colonizing the upper respiratory tract has the potential to cause pneumonia if it evades these defenses.

Signs and Symptoms

There are no symptoms that distinguish a bacterial pneumonia from a viral pneumonia in children, although children with bacterial pneumonia tend to present with more severe symptoms of fever and distress. Prodromal symptoms are often nonpulmonary and include headache, fever, malaise, and abdominal pain. Productive cough, with sputum often swallowed, and chest pain during inspiration (pleuritic pain) are common complaints. Physical examination usually reveals nasal flaring, accessory muscle use, intercostal and subcostal retractions, tachypnea, and shallow breathing. Crackles, decreased breath sounds, increased fremitus, and dullness to percussion are often found during auscultation and examination of the chest.

Diagnosis

The chest radiograph is an important diagnostic tool when evaluating a child with suspected bacterial pneumonia. Although bacterial pneumonia is commonly manifested as an alveolar consolidation, lobar and interstitial infiltrates are often found, as is pleural effusion. It has been suggested that certain radiographic findings vary among the various bacterial agents involved and may help determine the etiology.

An elevated total band count (>1500 total bands) is common in the presence of bacterial pneumonia. Increased C-reactive protein levels and erythrocyte sedimentation rates provide supporting, albeit not specific, evidence of inflammation. Blood culture is the most helpful test to give absolute confirmation of bacterial disease, but it is positive in only 25% of patients with *S. pneumoniae* pneumonia and 33% of patients with *S. aureus* pneumonia. Similarly, latex particle agglutination and countercurrent immunoelectrophoresis studies are insensitive in most cases of pneumonia. When pleural fluid is present in significant quantities, sampling for Gram stain and culture will yield specific

bacterial diagnosis in 65% to 80% of patients. Bronchoalveolar lavage fluid obtained during a bronchoscopy can be used for atypical presentations. Lung tissue may be obtained for culture through an open-lung biopsy, transthoracic needle aspiration biopsy, or percutaneous lung puncture.

Precise microbiological diagnosis is not always obtained, even though bacterial pneumonia is suspected. There are several reasons why clinicians may take an empiric approach to treatment. Many of the diagnostic procedures are much too invasive for any but the sickest patients. Some procedures use instruments (e.g., bronchoscope, suction catheter) that pass through the contaminated pharynx or upper airway. Although it is difficult to obtain a sputum specimen in children younger than 8 years of age, when it is obtained the flora in the upper airway contaminates the sputum, making the diagnosis questionable.

Treatment

Standard initial treatment of bacterial pneumonia varies considerably according to the patient's age and immunologic status, time of year, and local antibiotic sensitivity patterns. The need for hospitalization is often determined by the severity of the symptoms. When the cause is identified, antimicrobial therapy is determined and is usually given for 7 to 14 days by the parenteral route, although the clinical symptoms and history of underlying disease often guide empiric therapy. Neonatal pneumonia is routinely treated with intravenous antibiotics. The patient is monitored with pulse oximetry and arterial blood gas analysis when indicated. Supplemental oxygen is provided if hypoxia occurs, and mechanical ventilation is provided if there is respiratory failure.

Streptococcus Pneumoniae

The most common cause of bacterial pneumonia is pneumococcus. The clinical picture differs with age. The infant presents initially with a sudden fever and diarrhea or vomiting. Signs of respiratory distress, including nasal flaring, tachypnea, grunting, and retractions, appear along with restlessness and cyanosis. The classic clinical presentation of the older child is that of rapid-onset respiratory distress, high fever, shaking chills, headache, pleuritic pain, and cough with rust-colored sputum. The chest radiograph usually reveals lobar or segmental alveolar consolidation, which may be accompanied by a pleural effusion or empyema. Sputum reveals sheets of gram-positive diplococci and many white blood cells. The clinical diagnosis can be made based on these findings. However, in reality the clinical presentation is rarely this clear, and treatment of suspected bacterial pneumonia includes pneumococcal coverage.

Pneumococcal pneumonia can be rapidly fatal without appropriate therapy. Penicillin is the antibiotic of choice; erythromycin is used for penicillin-allergic individuals. Although penicillin resistance in the United States is rare, it is increasingly common in Europe and Africa. Therefore, treatment should be guided by antibiotic susceptibilities when an organism is recovered. Other antibiotics that have successful activity against *S. pneumoniae* include cephalosporins, chloramphenicol, clindamycin, and vancomycin.

Haemophilus Influenzae

Before the use of vaccination against serotype b, this gram-negative rod was a common cause of pneumonia in children. Infection occurs most often in children younger than 5 years of age. The chest radiograph is highly variable and can exhibit any pattern from a bronchiolitic-type picture with hyperinflation to patchy infiltrates to segmental or lobar consolidation. Pleural effusion is present in about one-third of patients. Positive blood culture results or positive results on urine antigen screen confirm diagnosis. Empiric therapy is usually with a cephalosporin. Other potentially therapeutic drugs effective against all *H. influenzae* isolates include trimethoprim-sulfamethoxazole, clarithromycin, azithromycin, chloramphenicol, and amoxicillin–clavulanate.

Staphylococcus Aureus

Pneumonia caused by *S. aureus* ("staph") is a virulent, aggressive disease that can be rapidly fatal, particularly in infants younger than 1 year of age. This organism is commonly found on the skin and mucosa, with 20% to 30% of the population carrying bacteria in the nose. Pneumonia is often seen in debilitated patients who often have associated skin infections. It is common to have a history of an antecedent viral infection, particularly influenza.

The severity of clinical symptoms varies, with the typical presentation being an upper respiratory tract infection, fever, cough, and respiratory distress. The clinical course in the neonate is often rapidly progressive and is associated with a high mortality rate shortly after the onset of symptoms. The chest radiograph usually reveals large consolidation that can progress rapidly to a "whiteout" of the lung. Pleural effusion and empyema as well as a pneumothorax often complicate the clinical picture. While resolving, areas of consolidation often progress to pneumatoceles, which are round, air-filled areas of lung destruction that are easily visible on the radiograph. The pneumatoceles may contain fluid and change rapidly in number and size, leading to a mediastinal shift.

Diagnosis is by positive blood, skin abscess, or pleural fluid culture results. Therapy is with antistaphylococcal penicillins such as nafcillin and oxacillin. Susceptibility testing is imperative to exclude the possibility of methicillin-resistant *S. aureus* spreading throughout the general community, which requires treatment with vancomycin.

ATYPICAL PNEUMONIA

The major pathogens of pneumonia that are commonly missed by the tests listed previously cause atypical pneumonia. In the neonate, those agents include the uncommon viral diseases rubella, varicella-zoster, and cytomegalovirus and the even rarer nonbacterial agents *Toxoplasma, Treponema pallidum,* and *C. trachomatis.* In the older child, *M. pneumoniae, C. pneumoniae,* and *M. tuberculosis* cause atypical pneumonia.

Mycoplasma Pneumoniae

M. pneumoniae commonly causes community-acquired pneumonia that is seen year-round but peaks in the late summer and early fall. Although it occurs in all age groups, it is most often a disease of school-aged children and young adults. The incubation period is 2 to 3 weeks, and it presents as a viral upper respiratory infection. Clinical onset is insidious, with a gradual development of malaise, fever, and cough, which are the most prominent symptoms. Cough is nonproductive or productive with blood-tinged sputum. Chills, pharyngitis, headache, nausea, vomiting, diarrhea, and chest pain are also associated with this infection. Crackles are heard most often during auscultation, with occasional wheezing, although there may be no abnormal findings at the beginning of the illness. The clinical and radiographic findings are often out of proportion to the clinical severity; hence the common lay description "walking pneumonia" is often applied to this infection. The chest radiograph usually reveals bronchopneumonia with patchy infiltrates.[16] The complete blood cell count is usually normal; however, a cold hemagglutinin assay with a titer of 1:64 is highly suggestive of infection with *M. pneumoniae.*

Without treatment, the illness resolves in 2 to 4 weeks. Oral erythromycin for 10 to 14 days provides optimal therapy, and the patient usually becomes afebrile within 48 hours. Azithromycin has also shown efficacy and is widely used as a 5-day therapy course.

Chlamydia Pneumoniae

Infected respiratory droplets most likely transmit *C. pneumoniae.* Primary infection occurs most often in school-aged children and young adults. Only a small portion of patients infected are clinically symptomatic, yet some patients experience severe illness leading to death. Most infections with *C. pneumoniae* are mild and commonly coincide with other bacterial pathogens. Illness is characterized by pharyngitis, followed several days later by cough. Fever is often present early in the illness but does not persist. Wheezing is often heard on auscultation. In fact, this infection has a strong correlation with recent-onset asthma.

Host factors appear to influence the severity of this illness. Immunocompromised patients with acquired immunodeficiency syndrome, malignancy, primary immune deficits, or sickle cell disease may have severe or frequent infections. *C. pneumoniae* is a common cause of acute chest syndrome in children with sickle cell disease and may also act as a trigger for acute asthma.[17]

C. pneumoniae is difficult to isolate, even in tissue cultures, and requires special handling of the culture sample. Because of the long delay in serologic diagnosis, empiric antibiotic therapy is commonly used. Infection with *C. pneumoniae* is treated with tetracycline or erythromycin for 10 to 14 days, although a prolonged course of 21 days is not uncommon.

VENTILATOR-ASSOCIATED PNEUMONIA

A patient who is receiving mechanical ventilatory support is at risk of developing pneumonia. New onset of pulmonary infiltrates can occur, stemming from a multitude of causes, including atelectasis, infection, spontaneous or catheter-related pulmonary emboli, or acute lung injury. The pathogenesis appears to involve the microaspiration of oropharyngeal organisms. Clinical and radiographic criteria for diagnosing ventilator-associated pneumonia are unreliable.

The development of ventilator-associated pneumonia (VAP) increases hospitalization stay by 30% but does not change mortality rates. In pediatric patients undergoing mechanical ventilation, polymicrobial aerobic and anaerobic floras are isolated from pulmonary specimens. Predominant aerobic bacteria are *Pseudomonas aeruginosa* and *Klebsiella pneumoniae;* predominant anaerobic bacteria are *Prevotella, Porphyromonas, Peptostreptococcus, Fusobacterium,* and *Bacteroides fragilis.*[18]

To better establish the diagnosis of VAP, Gram stain of bronchoalveolar lavage fluid is obtained through a fiberoptic bronchoscope. Bronchoalveolar lavage fluid is considered positive for VAP when the following conditions occur:

1. Polymorphonuclear neutrophils are greater than 25 per optic field at a magnification ×100.
2. Squamous epithelial cells are less than 1%.
3. One or more microorganisms are seen per optic field at a magnification of 1:1000.

Gram stain of bronchoalveolar lavage fluid is 77% sensitive and 87% specific, with a positive predictive value of 71% and a negative predictive value of 90%.[19] Although bronchoalveolar lavage samples acquired through bronchoscopy are used to diagnose VAP, quantitative cultures of endotracheal aspirates are easier and less expensive to obtain. Persistence of significant numbers of pathogens in quantitative cultures of endotracheal aspirates occurred in 82% of the samples. This quantitative culture of endotracheal aspirates is reproducible and may be useful in the diagnosis of VAP.[20]

Multiple forms of therapy have been attempted to minimize the risk of developing VAP, including routine hand washing, closed airway suctioning, oral care, and elevating the head of bed. Some studies

suggest that the use of heat and moisture exchangers is a cost-effective clinical practice associated with fewer late-onset hospital-acquired VAP and results in improved resource allocation and utilization for adults.[21] However, other studies conclude that their use does not affect the frequency of VAP and could potentially lead to mucus plugging. Decreasing the frequency of ventilator circuit changes from three times per week to once per week had no adverse effect on the overall rate of VAP, thus prompting institutions to change ventilator circuits as needed and convincing most experts that the ventilator has nothing to do with VAP. In fact, some experts are calling for a name change, suggesting that this phenomenon be called *endotracheal tube–associated pneumonia (EAP),* because it appears that the ETT has more to do with VAP than the ventilator. Scheduled changes in antibiotic class for empiric treatment of VAP have been demonstrated to lower the incidence of bacteremia associated with antibiotic-resistant gram-negative bacteria.

Box 26-3 Cutoff Size of Induration for Positive Mantoux Tuberculin Skin Test

5 MM
- Contacts of infectious cases
- Abnormal chest radiograph
- HIV-infected and other immunosuppressed patients

10 MM
- Foreign-born persons from areas of high prevalence
- Low-income populations
- Residents of prisons, nursing homes, institutions
- Intravenous drug users
- Other medical risk factors
- Health care workers
- Locally identified high-risk populations
- Infants

15 MM
- No risk factors

HIV, Human immunodeficiency virus.
(Modified from Starke JR, Jacobs RF, Jereb J: Resurgence of tuberculosis in children. *J Pediatr*120:839, 1992.)

TUBERCULOSIS

INCIDENCE AND ETIOLOGY

Tuberculosis (TB) is the most common infectious cause of death throughout the world. Although the frequency declined in the 1980s and early 1990s, the disease is again increasing in incidence and severity. It is a chronic bacterial disease caused by infection with *M. tuberculosis.* This organism is a very hearty and virulent bacterium that resists inactivation by drying, heat, and sunlight. Patients infected with *M. tuberculosis* are usually medically underserved, poverty stricken, or immunocompromised. Most children do not develop clinical disease unless disease resistance declines as a result of malnutrition, fatigue, or chronic illness.

TRANSMISSION

Transmission is airborne, occurring through the inhalation of viable respiratory droplets in an enclosed space (e.g., room, hospital). The pathogen is rapidly killed by ultraviolet light in the outside air. The household contact for an infant or child is usually an adult; rarely is there child-to-child transmission. The incubation period lasts from 2 to 10 weeks, at which time a skin test becomes positive, manifesting a delayed-type hypersensitivity (Box 26-3).

SIGNS AND SYMPTOMS

Most infants and children who become infected with *M. tuberculosis* never develop TB and remain asymptomatic. They may continue with few if any clinical symptoms or manifest nonspecific signs of fever, weight loss, and failure to thrive. Most patients develop cough and wheezing, with crackles and rhonchi heard in some cases. Chest radiography in these individuals reveals focal or diffuse infiltrates. Many cases of pulmonary infection with *M. tuberculosis* are caused by reactivation and are characterized by focal findings on chest radiography in patients with chronic respiratory and systemic symptoms.

DIAGNOSIS

Diagnosis in adults is based on identification of stains of gastric or respiratory washings that have bacteria uniquely resistant to acid decoloration ("acid fast"). In children, because of the low number of bacilli, 3 consecutive days of gastric washings may increase the sensitivity of this test. More commonly, the diagnosis of TB is based on a positive skin test (Mantoux skin test) in a patient with an appropriate clinical picture and radiographic findings. Proper interpretation of these skin tests is critical and is based on the probability of disease using a combination of risk factors, clinical findings, and the size of induration resulting from the skin test (see Box 26-3). Differential diagnosis includes asthma, foreign body aspiration, tumor, sarcoidosis, and all pulmonary pathogens.

TREATMENT

Treatment of TB in children focuses on early diagnosis, identification of the primary case that spread the disease to the child, and long-term antituberculosis medications. For the patient with active disease, multiple medications are indicated for an extended period. These include isoniazid, rifampin, pyrazinamide, and ethambutol. Corticosteroid therapy can be safely used in conjunction with antituberculosis drug therapy to lower the inflammatory response to the infection, reduce the size of enlarged lymph nodes, and accelerate the resorption of fluid when a large pleural effusion has developed.

Case Study 4

A 13-month-old infant born prematurely at 24 weeks of gestation with resolving bronchopulmonary dysplasia (BPD) is brought to his pediatrician for a 2-day history of decreased appetite, runny nose, and increased cough. It is February. His oxygen saturation, vital signs, and examination are unremarkable, and the decision is made to discharge him home with close follow-up. Two days later his oxygen requirement is up to 1 L/minute via nasal cannula (from 0.25 L/minute), and he exhibits increased respiratory distress. Oxygen saturation is decreased to 80%, and he is afebrile. He is admitted to the hospital with decreased oral intake and respiratory distress. A rapid respiratory syncytial virus (RSV) test is positive, and his chest radiograph shows infiltrates in the right middle lobe and left upper lobe.

What is the likely diagnosis? What therapy would you recommend?

See Evolve Resources for answers.

RSV infections demonstrate the difficulty of distinguishing between bacterial and viral pneumonias. In the case of a child with underlying lung disease such as BPD, this may lead to a more conservative and widespread use of antibiotics. Multiple studies in the recent literature have established the importance of neutrophils in many respiratory diseases, including RSV bronchiolitis,[22,23] and attempted to use bronchoalveolar lavage (BAL) samples and cell counts as clinical markers in conjunction with cultures.[24] They have demonstrated the predominance of neutrophils in viral infections of the airway and other lung diseases.[25] More interesting is the observation that neutrophilic inflammation can be correlated to the extent of lung injury. Currently we lack medical treatments targeting neutrophils in the airway, but the development of such treatments is under way. It remains to be seen how effective they might be in the treatment of RSV, bronchiolitis, and similar pulmonary diseases associated with neutrophilic inflammation and if BAL examination has a future value in the routine testing of pediatric patients with lung diseases.

SICKLE CELL DISEASE

INCIDENCE AND ETIOLOGY

Sickle cell disease is an autosomal-recessive inherited disorder of the hemoglobin structure and is the most common inherited disease of the African-American population. Defective hemoglobin S converts from a soluble hemoglobin molecule contained in the red cells to a gelatinous state in the presence of low oxygen, low pH, rapid temperature changes, or hypernatremic dehydration. This gelatinous state causes the red cells to "sickle," resulting in a variety of complications, including acute chest syndrome, cardiomegaly and left ventricular failure, splenectomy, and renal disease. Pulmonary complications are the primary cause of illness and death in patients with sickle cell disease.

PATHOPHYSIOLOGY

A complex interaction between the abnormal cells and vascular endothelium results in a hypercoagulable state. Recent reports indicate that high levels of endothelin-1, an endothelial-derived vasoactive mediator, are present during vasoactive crises. An abnormality of the vascular endothelium may contribute to the development of acute chest syndrome. The red blood cells are more rigid, resulting in increased viscosity of blood, which causes plugging of the blood vessels.

The pulmonary effects that occur most often in patients with sickle cell disease include pneumonia, acute chest syndrome, pulmonary vascular injury, pulmonary infarction, and sickle cell chronic lung disease. Bacterial pneumonia is a common cause of hospitalization, and pulmonary vascular injury can cause sudden death if the occlusion is in a large vessel.

SIGNS AND SYMPTOMS

Acute chest syndrome is the leading cause of death in sickle cell disease and presents as pleuritic or chest wall pain and dyspnea. The chest radiograph often reveals pulmonary infiltrates, often located in the lower lobes, as well as atelectasis and pleural effusion. Young children ages 2 to 4 years old who present with acute chest syndrome have fever, cough, and a negative physical examination, with little or no pain. Adults are often afebrile, complaining of severe dyspnea, chills, and severe pain along the ribs, sternum, abdomen, and back.

Reports in the 1970s suggested that sickle cell disease was caused by a bacterial infection; however, more recent studies suggest that bacterial infection is found in only 3% to 14% of patients, whereas *Mycoplasma* and/or *Chlamydia* infections are found in approximately 15%. Children younger than 5 years of age tend to have a milder disease course that is usually triggered by infection. Risk of death is four times higher in adults with acute chest syndrome than in children and most likely related to the higher incidence of fat embolism from bone marrow infarction. Aplastic crisis in young children with sickle cell disease is typically associated with acute human parvovirus B19 infection. Infection with this pathogen may also be related to acute chest syndrome. Pneumonia and pulmonary infarction can occur simultaneously and are sometimes difficult to differentiate. Fever and chills are seen more often with pneumonia, with fever resolving slowly. Acute pulmonary symptoms with tachypnea and pleuritic chest pain are more suggestive of pulmonary infarction. In some cases, pneumonia causes hypoxemia that leads to pulmonary infarction.

Sickle cell chronic lung disease occurs most often during the teenage years and may develop after multiple episodes of acute chest syndrome. Hypoxemia is present as a result of pulmonary fibrosis and a reduction in diffusion and pulmonary perfusion. Parenchymal lung injury and an increase in pulmonary vascular resistance cause progressive dyspnea and cor pulmonale. Diffuse interstitial markings and edema are common findings on the chest radiograph.

TREATMENT

Empiric therapy includes antibiotics for gram-positive encapsulated organisms of *Streptococcus, Staphylococcus,* and *Salmonella.* Erythromycin is used to provide coverage for the pathogens *M. pneumoniae* and *C. pneumoniae.* Antibiotics are quickly instituted because the infections, especially pneumococcal pneumonia, can become life-threatening.

Adequate hydration is an essential therapeutic modality and is used cautiously to avoid pulmonary edema. Red blood cell transfusions are provided to improve the hemoglobin's ability to transport oxygen and reduce the incidence of acute chest syndrome, myocardial ischemia, and sickle cell chronic lung disease. Bronchodilators for bronchiole constriction, deep breathing, and coughing can help prevent or reverse atelectasis (incentive spirometry) decreasing pulmonary vascular resistance, and adequate pain control can be an important adjuvant. Supplemental oxygen is used when indicated, but depending on the case can foster additional sickling. In cases of impending respiratory failure, mechanical ventilation is instituted.[26] Successful treatment of acute chest syndrome with high-frequency ventilation or venovenous ECMO has been reported in patients experiencing life-threatening acute chest syndrome despite maximum conventional ventilation support.

PREVENTION

Acute Chest Syndrome

The treatment of recurrent acute chest syndrome is aimed at preventing repeated vascular and parenchymal insults, which constitute the greatest risk for the development of sickle cell chronic lung disease. Chronic transfusion programs aim to decrease the sickle cell amount to less than 30%, a level that will prevent recurrence of acute chest syndrome. The risks involved are transfusion-associated infections and iron overload. Hydroxyurea was shown to be clinically effective in reducing acute chest syndrome recurrence and vasoocclusive crises by 50%, but the long-term effects of this treatment are uncertain, and frequent peripheral blood count monitoring is necessary. Antibiotic prophylaxis with penicillin is recommended for patients between 4 months and 3 years of age, as well as routine polyvalent pneumococcal vaccine for children and adults.

RECURRENT ASPIRATION SYNDROME

ETIOLOGY

Neurologically impaired patients, those with abnormal anatomy of the gastrointestinal tract or airways, and patients with gastroesophageal reflux are often diagnosed with recurrent aspiration syndrome. The patient aspirates respiratory secretions or stomach contents. The low pH of the stomach contents results in a chemical pneumonitis and inflammatory response in the airways. The patients and their families suffer through multiple hospitalizations for pneumonia and airway hyperreactivity. Children who are treated for frequent asthma exacerbations, yet have negative responses to allergens, benefit from evaluation for recurrent aspiration. Infants with gastroesophageal reflux are at particular risk for pneumonia.

DIAGNOSIS

Diagnosis is based on clinical and radiographic findings. Barium swallow may reveal a tracheoesophageal fistula or other malformation that requires surgical intervention. Bronchoscopy with bronchoalveolar lavage can reveal pathogens normally found in the gastrointestinal tract as well as provide visual confirmation of inflamed airways.

TREATMENT

The cause and severity of the disease determine treatment. Fundoplication, a surgical tightening of the gastroesophageal junction, may alleviate gastroesophageal reflux. Appropriate antibiotic coverage is necessary to control infection. Inhaled corticosteroids are indicated to control and reduce the airway damage that occurs from chronic inflammation. Prevention of recurrent aspiration is paramount to obtain a long-term positive outcome. Prognosis in uncontrolled recurrent aspiration syndrome is guarded because of chronic reinjury of the respiratory parenchyma. Respiratory and cardiac insufficiency may develop over time. Accurate and early diagnosis, prevention, and prophylaxis may reduce the severity of the injury and improve the patient's quality of life.

DIFFUSE INTERSTITIAL LUNG DISEASE

Pediatric diffuse interstitial lung disease (DLD) represents a spectrum of rare diffuse parenchymal lung diseases prevalent in children. Because of the similarity of symptoms, it is often difficult to differentiate from more common lung diseases, and DLD may be underdiagnosed. DLD consists of a diverse group of rare disorders of the lung parenchyma and interferes with gas exchange. Classification of DLD is based on both clinical characteristics and histopathology and recognizes disorders that are only seen in neonates (Table 26-3).

ETIOLOGY

The etiology of DLD of the neonate is often grouped into four categories: (1) disorder of lung development,

Table 26-3 Classification of DLD

CATEGORY	ENTITIES
Disorders of Neonates	
Diffuse developmental disorders	• Acinar/alveolar dysgenesis • Congenital alveolar dysplasia • Alveolar capillary dysplasia
Lung growth abnormalities	• Pulmonary hypoplasia • Chronic neonatal lung disease (BPD) • Structural changes related to chromosomal abnormalities
Specific conditions of unknown or poorly understood etiology	• Neuroendocrine cell hyperplasia of infancy • Pulmonary interstitial glycogenosis
Surfactant dysfunction disorders and related abnormalities	*SFTPB*, *SFTPC*, *ABCA3*, *NKX2.1/TTF1*, lysinuric protein intolerance; pulmonary alveolar proteinosis
Disorders of Children	
Disorders of the normal host (immunocompetent)	• Infectious/postinfectious processes • Related to environmental agents • Aspiration syndromes • Eosinophilic pneumonia • Acute interstitial pneumonia • Nonspecific interstitial pneumonia • Idiopathic pulmonary hemosiderosis
Disorders of the immunocompromised host	• Opportunistic infections • Related to therapeutic intervention • Related to transplantation or rejection syndromes
Disorders related to systemic disease processes	• Immune-mediated • Anti-GBM antibody • Nonspecific pulmonary manifestations • Collagen-vascular disease • Storage diseases • Sarcoidosis • Langerhans cell histiocytosis • Malignant infiltrates
Vascular disorders masquerading as ILD	• Arterial hypertensive vasculopathy • Congestive vasculopathy and venoocclusive disease • Lymphatic disorders • Pulmonary edema • Thromboembolic disease
Unclassified	Captures cases of diffuse lung disease that cannot be classified for any reason. Common reasons include end-stage disease, nondiagnostic biopsies, or inadequate biopsy material.

BPD, Bronchopulmonary dysplasia; *GBM*, Glomerular basement membrane; *ILD*, interstitial lung disease.

(2) pulmonary interstitial glycogenosis, (3) neuroendocrine cell hyperplasia of infancy, and (4) genetic disorders of surfactant dysfunction.[27]

Forms of DLD of the child include aspiration syndromes, bronchiolitis obliterans, and hypersensitivity pneumonitis.[28] Immunocompromised hosts are prone to DLD. In addition to the risk of infections some DLDs are related to therapeutic intervention, such as chemotherapy and/or radiation injuries or drug reactions, especially connective tissue diseases. Last is DLD of which there is no specific cause, labeled *idiopathic DLD.*

DIAGNOSIS

DLD is diagnosed by a systematic approach and based on age at presentation, clinical characteristics, radiologic features, and histopathology. Although this classification is important to recognize, it does not often provide a specific diagnosis, but instead a framework. A number of systemic disorders may be associated with DLD.

TREATMENT

The cause and severity determine the treatment. Largely the treatment is supportive, because there is no definitive treatment for many of the rare DLDs. Some interventions like oxygen therapy, mechanical ventilation, or even ECMO are performed in the acute phase to get to a diagnosis, whereas others like steroids, surfactant, or antibiotics are symptom-based therapies or therapies based on other more common diseases.

Key Points

- Establishment of an artificial airway in patients with epiglottitis is the first priority and should be performed in the safest place possible. It is often done in the operating room with surgical assistance on standby.
- Patients with upper airway obstructions tend to have normal lung compliance and function. Improper ventilator management can complicate drastic measures such as intubation or tracheostomy.
- Because crying can cause additional respiratory distress in patients with upper airway disorders, it is imperative to keep parents involved to reduce stranger anxiety or irritability.
- Most airway disorders and lung diseases can be classified into four pathologic categories: obstructive, restrictive, infectious, or vascular. Some patients have a combination of diseases, but understanding the primary culprit can assist with choosing the most appropriate therapy.

Assessment Questions

See Evolve Resources for the answers.

1. Where do you find the narrowest portion of the pediatric airway that may compromise endotracheal intubation?
   A. Vocal cords
   B. Oropharynx
   C. Cricoid cartilage
   D. Epiglottis
   E. Trachea
2. What is not a sign of respiratory distress in an infant?
   A. Nasal flaring
   B. Retractions
   C. Irritability
   D. Lethargy
   E. Crying
3. A child presents with high fever, severe sore throat, dysphagia with drooling, cough progressing rapidly over a few hours to stridor, muffled ("hot potato") voice without hoarseness, air hunger, and cyanosis. Severe intercostal retractions, along with nasal flaring, bradypnea, and dyspnea, are present. The child assumes a characteristic tripod position of sitting upright with the chin thrust forward and the neck hyperextended. Bacterial epiglottitis is suspected. What is the next necessary action?
   A. Visualize the upper airway
   B. Obtain upper airway radiographic imaging
   C. Call supporting services
   D. Lay the child flat and provide blow-by oxygen
   E. Secure an intravenous line for sedation
4. What is the right estimated endotracheal tube (ETT) size for a 6-year-old boy, using a cuffed ETT?
   A. 4
   B. 4.5
   C. 5
   D. 5.5
   E. 6
5. You are in a restaurant and a child at the table next to yours starts to cough violently. He looks about 5 years old and is eating French fries when he suddenly turns red, starts to cough, and falls to the floor. His parents are nervously patting his back and trying to lift him up from the floor. What intervention needs to be done?
   A. Perform the Heimlich maneuver
   B. Open his airway with the tongue-jaw lift
   C. Finger swipe the oropharynx
   D. Leave the child on the floor and monitor
   E. Push the parents out of the way and perform efficient back blows
6. What is bronchiectasis?
   A. Irreversible dilation of the bronchial tree
   B. Pus accumulation in the airway
   C. An airway immediately placed before an emphysema
   D. A condition only found in cystic fibrosis patients
   E. Restrictive lung disease
7. Which infant is especially at risk for severe or life-threatening respiratory syncytial virus (RSV) bronchiolitis infections?
   A. Immunocompromised infant
   B. Premature infant
   C. Infant with congenital heart disease
   D. Infant with bronchopulmonary dysplasia (BPD)
   E. All of the above
8. Which combination of pneumonia and causative pathogen is incorrect?
   A. Viral pneumonia; parainfluenza virus type 3
   B. Bacterial pneumonia; *Escherichia coli*
   C. Atypical pneumonia; *Mycoplasma pneumoniae*
   D. Bacterial pneumonia; *Streptococcus pneumoniae*
   E. Atypical pneumonia; methicillin-resistant *Staphylococcus aureus* (MRSA)
9. Which signs suggest acute chest syndrome in a patient with sickle cell disease?
   A. Fever
   B. Rib pain
   C. Pleuritic pain
   D. Tachypnea
   E. A, C, and D
10. The major culprit for ventilator-associated pneumonia (VAP) appears to be what?
    A. Ventilator tubing
    B. Ventilator circuit
    C. Endotracheal tube
    D. Droplet transfection from hospital personnel
    E. Routine antibiotic usage

REFERENCES

1. Westley CR, Cotton EK, Brooks JG. Nebulized racemic epinephrine by IPPB for the treatment of croup: a double-blind study. *Am J Dis Child*. 1978;132:484.
2. Kairys SW, Olmstead EM, O'Connor GT. Steroid treatment of laryngotracheitis: a meta-analysis of the evidence from randomized trials. *Pediatrics*. 1989;83:683.
3. Cherry JD. Clinical Practice. Croup. *N Engl J Med*. 2008; 358(4):384-391.
4. Ereu S, Balci AE, Dikici B, Doblan M, Eren MN. Foreign body aspiration in children: experience of 1160 cases. *Ann Trop Paediatr*. 2003;23:31.
5. Kenna MA, Bluestone CD. Foreign bodies in the air and food passages. *Pediatr Rev*. 1988;10:25.
6. Ralston Sl, Lieberthal AS, Meissner HC, et al. Clinical practice guidelines: the diagnosis, management and prevention of bronchiolitis. *Pediatrics*. 2014;134:e1474.
7. American Academy of Pediatrics. Subcommittee on diagnosis and management of bronchiolitis. *Pediatrics*. 2006;118(4): 1774.
8. Numa AH, Williams GD, Dakin CJ. The effect of nebulized epinephrine on respiratory mechanics and gas exchange in bronchiolitis. *Am J Respir Crit Care Med*. 2001;164(1):86.
9. Kuzik BA, Al-Qadhi SA, Kent S, et al. Nebulized hypertonic saline in the treatment of viral bronchiolitis in infants. *J Pediatr*. 2007;151:266-270.
10. Spurling GKP, Fonseka K, Doust J, Del Mar C. Antibiotics for bronchiolitis in children. *Cochrane Database Syst Rev*. (1), 2009.
11. Vassilev ZP, Chu AF, Ruck B, Adams EH, Marcus SM. Adverse reactions to over-the-counter cough and cold products among children: the cases managed out of hospitals. *J Clin Pharm Ther*. 2009;34(3):313.
12. U.S. Food and Drug Administration. An Important FDA Reminder for Parents: Do Not Give Infants Cough and Cold Products Designed for Older Children. Available at: http://www.fda.gov/Drugs/ResourcesForYou/SpecialFeatures/ucm263948.htm.
13. Walsh BK, Betit P, Fink JB, Pereira LM, Arnold J. Characterization of ribavirin aerosol with small particle aerosol generator and vibrating mesh micropump aerosol technologies. *Respir Care*. 2016;61(5):577.
14. Wandstrat TL. Respiratory syncytial virus immune globulin intravenous. *Ann Pharmacother*. 1997;31:83.
15. Leigh MW. Primary ciliary dyskinesia. In: Chernick V, Boat TF, Kendig EL, eds. *Disorders of the Respiratory Tract in Children*. Philadelphia: WB Saunders; 1998:819-826.
16. Fernaldl GW. Infections of the respiratory tract due to Mycoplasma pneumoniae. In: Chernick V, Boat TF, Kendig EL, eds. *Disorders of the Respiratory Tract in Children*. Philadelphia: WB Saunders; 1998:526-531.
17. Hammerschlag MR. Chlamydia trachomatis and Chlamydia pneumoniae infections. In: Chernick V, Boat TF, Kendig EL, eds. *Disorders of the Respiratory Tract in Children*. Philadelphia: WB Saunders; 1998:978-987.
18. Brook I. Pneumonia in mechanically ventilated children. *Scand J Infect Dis*. 1995;27:619.
19. Prekates A, Nanas S, Argyropoulou A, et al. The diagnostic value of Gram stain of bronchoalveolar lavage samples in patients with suspected ventilator-associated pneumonia. *Scand J Infect Dis*. 1998;30:43.
20. Bergmans DC, Bonten MJ, De Leeuw PW, Stobberingh EE. Reproducibility of quantitative cultures of endotracheal aspirates from mechanically ventilated patients. *J Clin Microbiol*. 1997;35:796.
21. Kirton OC, DeHaven B, Morgan J, Morejon O, Civetta J. A prospective, randomized comparison of an in-line heat moisture exchange filter and heated wire humidifiers: rates of ventilator-associated early-onset (community-acquired) or late-onset (hospital-acquired) pneumonia and incidence of endotracheal tube occlusion. *Chest*. 1997;112;1055.
22. Emboriadou M, Hatzistilianou M, Magnisali Ch, et al. Human neutrophil elastase in RSV bronchiolitis. *Ann Clin Lab Sci*. 2007;37:79.
23. McNamara PS, Ritson P, Selby A, Hart CA, Smyth RL. Bronchoalveolar lavage cellularity in infants with severe respiratory syncytial virus bronchiolitis. *Arch Dis Child*. 2003;88: 922.
24. Chang AB, Faoagali J, Cox NC, et al. A bronchoscopic scoring system for airway secretions—airway cellularity and microbiological validation. *Pediatr Pulmonol*. 2006;41: 887.
25. Simpson JL, Grissell TV, Douwes J, Scott RJ, Boyle MJ, Gibson PG. Innate immune activation in neutrophilic asthma and bronchiectasis. *Thorax*. 2007;62:211.
26. Bunn HF. Pathogenesis and treatment of sickle cell disease. *N Engl J Med*. 1997;337:762.
27. Kurland G, Deterding RR, Hagood JS, 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;188:376.
28. Vece TJ, Young LR. Update on diffuse lung disease in children. *Chest*. 2016;149:836.

27 Asthma

Brian K. Walsh

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. Explain the pathophysiology of asthma.
2. Treat asthma using an evidence-based approach.
3. Identify the five components of asthma.
4. Explain how to improve the efficacy of the medications used to treat asthma.

Key Terms

asthma
asthma action plan
asthma education
asthma triggers
β_2-agonist
corticosteroids

Asthma is the most common chronic childhood disease, affecting more than 6 million children, and prevalence continues to increase. It is the most common reason for pediatric hospitalizations and the most common cause of absence from school. Hospitalization rates have remained stable over the past 10 years, but this has not been consistent through all childhood age groups. The highest incidence of asthma occurs in children 4 years of age or younger.[1] Although the number of asthma patients has climbed, the death rate is decreasing. Improvements in the science behind asthma care have led to increased awareness among patients and physicians about the disease's underlying causes, but widespread misunderstanding still exists.

In 1991, to improve awareness of the causes and treatments of asthma in America, the National Heart, Lung, and Blood Institute's (NHLBI) National Asthma Education and Prevention Program (NAEPP) released its first set of asthma management guidelines. In 2007, they released the Expert Panel Report 3, which is available to caregivers and patients. The report provides guidelines for management of asthma based on the expert panel review with an emphasis on evidence-based practice of medicine.[2] There is a wealth of information on the NHLBI as well as the Centers for Disease Control and Prevention,[3] including two videos that demonstrate how to control and prevent asthma exacerbations within a clinic visit[4] and how to control asthma during travel.[5] New or updated guidelines are forthcoming, so practitioners should reference the latest guidelines. This chapter references the 2007 Expert Panel Report 3.

PATHOGENESIS OF ASTHMA

DEFINITION

Asthma is an immune-mediated process in which an environmental or infectious agent triggers a hypersensitive immunoglobin E–mediated allergic reaction causing mast cell degranulation, histamine release, and activation of proinflammatory cytokines. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, chest tightness, breathlessness, and coughing, especially at night or in the early morning.

PATHOPHYSIOLOGY

Asthma is characterized by the triad of chronic airway inflammation, bronchial hyperresponsiveness, and hypersecretion of mucus (Figure 27-1). Airway obstruction is the consequence of these pathologic mechanisms. There are six significant components to airway obstruction:

1. Inflammation
2. Acute bronchoconstriction
3. Airway edema
4. Mucous plugging
5. Airway hyperresponsiveness
6. Airway remodeling

The obstruction can result in increasingly difficult air entry, air trapping, atelectasis, ventilation–perfusion abnormalities, hypoxia, fatigue, and hypercarbia. Approaches to therapy are directed toward blocking the inflammation and preventing and relieving bronchospasm and remodeling.

Airway Inflammation

The understanding of the pathogenesis of airway inflammation in asthma continues to grow as the function and interaction of inflammatory mediators are revealed. Inflammation results from the introduction or activation of specific mediators in the airway. There is evidence that inflammatory findings (e.g., eosinophilic airway inflammation, hypergranulation of mast cells, increased IgE levels, and increased allergic response) result in part from an inappropriate activation of CD4+ T cells, which results in release of inflammatory cytokines.

In some individuals, neutrophils appear to be the primary mediator of cytokine release and inflammation. These individuals appear to be less responsive to steroids and bronchodilators and are more likely to experience remodeling of their airways. No matter what the underlying pathology is, inflammation and the resulting swelling of airway mucosa can affect the airway caliber and decrease airflow. We now know that airway inflammation is persistent and that early intervention with antiinflammatory medications may help to slow the course of the disease, but any successful response usually requires weeks to achieve, and in some instances may be incomplete.

After Dr. Hunt and colleagues' discovery in 2000 that exhaled breath condensate (a noninvasive marker of airway lining pH) is acidic during acute exacerbations of asthma,[6] there is an evolving concept that this acidity appears to go hand in hand with inflammatory lung disease such as asthma. Acidification of the airway lining fluid is known to cause important respiratory symptoms. Likewise, bronchoconstriction occurs when the airway lining fluid is acidified.[7] Furthermore, acidification inhibits ciliary motility, increases mucous viscosity, alters nitrogen oxide reactivity and oxidative processes, and enhances eosinophilic and neutrophilic inflammation.[7] These consequences of airway acidification reflect precisely the pathophysiology of acute asthma. A recent publication asserts that nebulized β-agonists such as albuterol (discussed later in this chapter) are poorly transported across the alveolar epithelium when the airway lining fluid is acidic,[8] providing one potential explanation for the clinical failure of β-agonists in the management of chronic bronchitis and in many acutely ill asthma patients.

The Path of Inflammation in Allergic Asthma

Asthma has been shown to be predominantly allergic in nature in children. IgE has been identified as a key molecule in mediating allergic asthma. Allergic disease starts with a sensitization phase, in which an allergen on the airway mucosa is processed by an antigen-presenting cell (APC), such as a dendritic cell. The dendritic cell travels to regional lymph nodes and acts as a key antigen-presenting cell, causing the release of interleukins that cause naïve T cells to differentiate into Th2 cells. The Th2 cells then release interleukin 4 (IL-4), which enhances the production of IgE by stimulating B cells to differentiate into IgE. IL-4 also stimulates the differentiation of more naïve T cells to Th2 to further this process. IgE binds to high- and low-affinity receptors on mast cells, basophils, and eosinophils. These cells contain inflammatory mediators. The IgE produced is specifically sensitive to the allergen (antigen) that started the process. When the

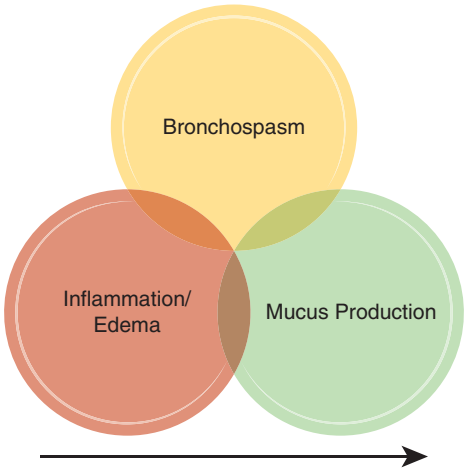


FIGURE 27-1 Asthma pathophysiology.

allergen is reintroduced into the system (on mucosa or in the bloodstream), it will bind to the IgE attached to mast cells, eosinophils, and basophils. This will result in cross-linking that causes a calcium influx and resulting degranulation that releases the inflammatory mediators within the cells that cause allergy and asthma symptoms.[9]

There are three phases of inflammation. The first phase involves the preformed mediators that are released with degranulation: histamine, heparin, and tryptase. These mediators result in airway smooth muscle contraction, vasodilation, increased vascular permeability, and mucous secretion. The resulting injury to airway cells attracts other mediators such as cytokines (leukotrienes, interleukin (IL)-4, IL-5, IL-13, tumor necrosis factor (TNF) α, and eosinophils, to name a few), resulting in a late phase that occurs 4 to 8 hours after the immediate response. Persistent inflammation can lead to a remodeling phase that results in airway smooth muscle hypertrophy, hyperplasia, increased angiogenesis, and collagen deposition. This last phase will result in a decline in lung function and irreversible obstructive lung disease.

The Definition and Role of T Cells: The Th1/Th2 Paradigm

T helper cells, Th1 and Th2, cross-regulate each other and regulate immune responses. There continues to be considerable interest in the role of immune response in airway inflammation. It has become clear that a bias toward the production of Th2 cells results in increased atopy and asthma. Th2 cells produce IL-4, which enhances IgE synthesis; IL-5, which stimulates eosinophil production; IL-9, which increases mast cell production; and IL-13, which increases mucus production and airway hyperresponsiveness. Th1 cells produce interferon-γ and IL-2, which aid in the defense of infection. It is believed that newborns are skewed toward a Th2 response through exposure to infections and other environmental stimuli. When the Th2 response triggers, the Th1 response is activated, and a balance between the Th1 and Th2 responses occurs.[10] The "hygiene hypothesis" suggests that because of immunizations and increased use of antibiotics, children are not exposed to the stimuli to drive the Th1 response, and the cytokine pattern then favors the Th2 response in susceptible individuals, which will cause the production of more IgE and thus increase atopy and risk for asthma.

Airway Hyperresponsiveness

Hyperresponsiveness is an exaggerated bronchoconstricting response to stimuli. The level of hyperresponsiveness is often correlated with the severity of constriction created by a bronchoprovocation test (such as a methacholine challenge). Exposure to certain allergens causes an IgE-dependent release of mediators from mast cells. These mediators include histamine, tryptase, leukotrienes, and prostaglandins. They directly contract airway smooth muscle, giving rise to acute bronchoconstriction or airway hyperresponsiveness. Other "triggers" of airflow obstruction include aspirin and nonsteroidal antiinflammatory drugs, exercise, cold air, irritants, gastroesophageal reflux, respiratory infections, and psychological stress. When reduction of airway inflammation is achieved, better control of asthma should be expected.

Airway remodeling is the permanent structural change that occurs in the airway. It is associated with progressive loss of lung function and may not be prevented or be fully reversible by current therapeutic interventions. The processes of repair and remodeling in the airway are not well understood, but it is certain that these processes are key to explaining why asthma remains persistent and in some cases resistant to therapy. Features of airway remodeling include inflammation, mucous hypersecretion, subepithelial fibrosis, airway smooth muscle hypertrophy, and angiogenesis.[2] Inflammatory mediators stimulate hyperplasia of mucous glands, resulting in more and chronic mucus production. The excessive mucus secretion and plugging of the airway may act to reduce the diameter of the airway and further limit airflow. Activation of inflammatory mediators also results in increased vascular permeability and leakage, with activation of structural cells such as epithelial tissue, mucous glands, and blood vessels. Repeated inflammatory episodes result in airway mucosa thickening and eventual fibrosis.

RISK FACTORS FOR DEVELOPMENT OF ASTHMA IN CHILDREN

Asthma is a dynamic disease. Its progression will vary over time regardless of the age of the patient. Although the etiology of asthma is not well defined, there appear to be risk factors associated with its onset and persistence. Asthma is more prevalent in prepubescent boys but more common in girls after puberty. It is more common among inner-city and African-American and Hispanic children in the United States; however, there is disagreement as to whether racial and ethnic background is a risk factor or if poverty has the greater impact. Currently available data from genetic studies of asthma suggest a strong genetic component. However, the exact mode of inheritance is unknown. Low-birth-weight infants as well as children born to young mothers or mothers who smoke during pregnancy tend to have an increased incidence of asthma. Other theories have emerged to suggest that asthma develops in children when there is a predominant T2 cell response (as opposed to a predominant T1 cell response) when exposed to various triggers. It has been proposed that this shift results from early exposure to certain viruses or the lack of exposure to early childhood diseases, as well as from the overuse of antibiotics.

ALLERGIC RESPONSE: ATOPY

Atopy seems to be the strongest identifiable predisposing factor for developing asthma, with atopic dermatitis often preceding its onset. Infants who become sensitized to food allergens early in life have an increased risk for developing asthma. Most children with asthma are atopic, but not all atopic children develop asthma. Inhaled allergens are believed to be the most important factor in the onset of asthma in children predisposed to atopy.

ENVIRONMENTAL TRIGGERS

There are several significant indoor environmental triggers. Once an aggravating agent is identified, it is essential that that the household undergo intervention that could remediate or eliminate it. If the child is sensitive to warm-blooded animals, the suggested interventions include removing the pet from the home or, if this is not possible, keeping the bedroom door closed so that the animal does not have access to the child's room.

Tobacco smoke is closely linked with increased asthma prevalence and morbidity, and therefore it is important that the patient and others who live in the household refrain from smoking. Smoking cessation measures are suggested. If there are smokers in the home, it is important that all smoking take place outside the home.

Cockroach exposure is another concern that affects patients who live in the inner city. Cockroach antigens are commonly found in the bedrooms of children who are sensitized. It is important that the family practice a routine that includes not leaving food exposed or the garage open. Poison baits, boric acid, and traps are also important tools that can reduce or eliminate the cockroach problem. Of course, in using these interventions it is important to make sure that the child is not able to access baits or poisons.

Molds are another common trigger in the home. Once identified, it is essential that the mold be cleaned out and the area dried. This can be a particular problem in humid environments or where there are plumbing leaks that are left unattended.

House-dust mites are another trigger. To manage this problem, it is recommended that mattresses and pillows be encased in allergen-impermeable covers. It also is advisable that the bedding be washed in water that is warmer than 130° F. Other suggested steps are to reduce humidity in the home to less than 40%, remove carpeting from the bedroom, avoid lying on upholstered furniture, and not carpet over concrete flooring. It is important to not expose stuffed toys to dust but rather keep them covered and consider frequent washing as well. It appears that exposure to any environmental allergen, if it is intense and persistent, may lead to sensitization in atopic children and then be associated with chronic asthma.

Much research has been devoted to the relationship between wheezing illnesses in infants and the development of asthma. Respiratory syncytial virus is the most common viral respiratory tract pathogen isolated from infants who wheeze. Many infants with severe infection with respiratory syncytial virus develop recurrent wheezing and asthma later in life.

NATIONAL ASTHMA EDUCATION AND PREVENTION PROGRAM GUIDELINES (REPORT 3)

PURPOSE

The National Asthma Education and Prevention Program (NAEPP) was formed by the National Institutes of Health in the late 1980s to assist in the promotion of **asthma education** to the public, health care professionals, and patients. The most significant undertaking of this organization has been the development and dissemination of the *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma,* published in 2007 and also known as "the Asthma Guidelines." The recommendations in the latest version are also evidence-based, which allows for a document that has been under the scrutiny of the Expert Panel. All sets of guidelines have been written by a science-based committee of experts from all medical disciplines, all based in the United States.

The stated purpose of the guidelines is to serve as a comprehensive tool in the diagnosis and management of asthma. The NAEPP states that the report, which is not an official regulatory document, should serve as a guide, and that a patient's specific history must be considered when implementing its guidelines. Despite massive public promotion directed to the medical community, the response to the report has been mixed. Disagreement by primary care physicians with components of the guidelines has often led to poor compliance, whereas other physicians remain unfamiliar with the guidelines. Asthma specialists tend to be more familiar with the guidelines and receptive to their use. Getting the guidelines into the hands of all providers who interact with asthma patients and influencing them to use the guidelines to guide therapy remains the goal of the NAEPP. It is also essential that the clinician, patient, and family members understand and abide by the goals of optimal management (Box 27-1).

Box 27-1 Goals of Asthma Management

1. Prevent chronic asthma symptoms and minimize asthma exacerbations using the least aggressive therapy that is sufficient.
2. Maintain normal activity levels, including exercise and other physical activities; avoid missing school activities.
3. Maintain normal or near-normal pulmonary function.
4. Prevent recurrent asthma exacerbations and minimize the need for emergency department visits or hospitalizations.
5. Provide optimal pharmacotherapy with minimal or no adverse effects.
6. Meet the patient's and family's expectations of and satisfaction with asthma care received.

DIAGNOSIS

Children who present with chronic or episodic cough, wheezing, difficulty breathing, or chest tightness may have asthma. The diagnosis of asthma cannot be established until alternative diagnoses are excluded. There should be evidence of airflow obstruction that is at least partially reversible and episodic symptoms of airflow limitation or airway hyperresponsiveness. The NAEPP guidelines recommend a detailed medical history, physical examination, and spirometry to determine reversible disease. It is also important to determine the severity, control, and responsiveness to therapy to determine the patient's current asthma status. Once a diagnosis has been made, it is important that the clinician use methods (e.g., testing for allergies and determining IgE levels) to identify precipitating factors.

MEDICAL HISTORY

A detailed medical history is essential in identifying the symptoms, triggers, and severity of asthma. A diagnostic history includes recurrent wheezing, chest tightness, shortness of breath, and cough, with nocturnal symptoms being common. Symptoms that occur or worsen with various stimuli (e.g., allergens, respiratory infections, emotional expressions, menses, viral infections, exercise, weather changes) or follow a seasonal pattern are highly suggestive of asthma.

A thorough history includes descriptions and frequency of previous exacerbations, hospitalizations, number of emergency department visits or unscheduled office visits, amount of school missed because of symptoms, and response to previous therapy. It is also important to determine whether symptoms are episodic or persistent. A history of allergic disorders (including family history), premature birth, and sinus and respiratory infections is often linked to asthma.

PHYSICAL EXAMINATION

A physical examination of the upper respiratory tract, chest, and skin is essential for the diagnosis of asthma, as well as to rule out other disorders. However, examinations may be completely normal between acute exacerbations, and the medical history is a stronger factor in supporting a diagnosis of asthma. Symptomatic children may present with audible wheezing and prolonged expiration, cough, increased nasal secretions, hyperexpansion of the thorax, retractions, use of accessory muscles, and tachypnea. Examination of the upper airways may show evidence of allergic disease (e.g., allergic shiners, edematous nasal mucosa, postnasal drip). Atopic dermatitis is typical in the presentation of asthma; however, digital clubbing is rarely found in asthma and raises the suspicion of cystic fibrosis. Many physical examination findings lead to consideration of a diagnosis other than asthma.

PULMONARY FUNCTION TESTING

Pulmonary function testing is used to help confirm the diagnosis of asthma, estimate the severity of airway inflammation, and follow the response to changes in therapy. Because all pulmonary function tests are essentially effort dependent, children must be old enough to correctly perform the test and provide maximum effort. Some children can perform an acceptable expiratory maneuver at 4 years of age, whereas others are unable to accomplish this until they are 7 or 8 years of age. If effort or technique is poor, results are not helpful in the diagnosis or treatment of asthma and should not be used.

Typical spirometry measurements in the diagnosis of asthma include the total volume of air exhaled forcefully from a maximal inhalation (forced vital capacity [FVC]), the volume of air exhaled during the first second of FVC (forced expiratory volume in 1 second [$FEV_{1]}$), and the FEV_1/FVC ratio. Other measurements, including the flow in the middle portion of FVC (FEF_{25-75}), are often reported. FEF_{25-75} is also known as *maximum midexpiratory flow.* It is sensitive to small changes in airway caliber and decreases with increasing obstructive disease; however, it is highly variable. Airway obstruction is indicated when FEV_1 is less than 80% of the predicted value and FEV_1/FVC values are less than 65% (or below the lower limit of normal).

The diagnosis of asthma requires that the airway obstruction be reversible. Spirometry measurements are performed before and after inhalation of a short-acting bronchodilator (e.g., albuterol). Significant reversibility is established when there is a greater than 12% increase in the postbronchodilator FEV_1 measurement.

Pulmonary function tests are performed at the time of initial diagnosis and after treatment has been initiated or changed. It is also performed periodically to document optimal pulmonary function values. If the patient demonstrates deterioration in pulmonary status, additional testing is warranted. It is recommended that children who require long-term control medication for asthma and are capable of performing the tests have pulmonary function tests performed at least annually.

EXHALED NITRIC OXIDE

Nitric oxide (NO) is known as a biological mediator in humans and is produced by the lungs and presented in exhaled breath. Fraction of exhaled nitric oxide (F_{ENO}) is a quantitative, noninvasive, simple, and safe method of measuring airway inflammation in patients with asthma. It is specifically used in the diagnosis and treatment of eosinophilic airway inflammation. Many clinicians today use F_{ENO} to determine the eosinophilic response to corticosteroids, unmasking of otherwise unsuspected nonadherence to therapy, and routine monitoring. According to the ATS Clinical Practice Guidelines, a patient with a low F_{ENO} level of

less than 25 parts per billion (ppb) is considered less likely to respond to corticosteroids than a person with a high FENO level of more than 50 ppb who is symptomatic. Intermediate is considered between 25 and 50 ppb.[11]

BRONCHOPROVOCATIONAL CHALLENGES

Airway responsiveness can be assessed using pharmacologic (e.g., histamine, methacholine) and nonpharmacologic (e.g., exercise, cold air hyperventilation) challenges. Methacholine and histamine are the most common pharmacologic agents used for bronchoprovocational challenge. The challenge is performed in a medical facility with a physician and resuscitative equipment present.

Methacholine Challenge

During a methacholine challenge, carefully increased doses of methacholine are nebulized and delivered directly to the patient through a face mask or mouthpiece. The patient's FEV_1 is measured after inhalation of each concentration until there is a 20% decrease in FEV_1 or until all nine concentrations have been delivered. A 20% decrease in FEV_1 is considered a positive challenge. This demonstrates the presence of bronchial hyperresponsiveness and is highly associated with asthma. When the test is completed, the bronchoconstriction may be relieved with inhalation of a quick-relief bronchodilator.

Methacholine challenge is safe and reproducible in children. However, it is recommended that the patient's FEV_1 be greater than 70% of predicted before performing the challenge. Patients with well-documented asthma should not be challenged. A negative bronchoprovocational challenge may be useful in ruling out asthma.

Exercise Challenge

Exercise tolerance tests are performed using a variety of forms of exercise, including treadmill running, free running, and bicycle ergometry. Most children are exercised until their heart rate reaches at least 170 beats per minute or more than 85% of the predicted maximum heart rate for their sex and age for 5 to 8 minutes. FEV_1 is measured immediately after and at 5-minute intervals for 20 to 30 minutes after exercise has stopped. A decrease in FEV_1 of 15% or more from the pretest baseline indicates a positive response and exercise-induced bronchospasm (EIB). When comparing the results of exercise challenges with pharmacologic challenges, exercise testing has been observed to be less sensitive and a poorer screening test for bronchial hyperresponsiveness.

DIFFERENTIAL DIAGNOSIS

Asthma is the most common cause of recurrent or persistent wheezing, cough, and dyspnea in children. However, several diseases and conditions produce similar signs and symptoms and may imitate an asthma exacerbation. Whether it is the first exacerbation for the child or further assessment of a patient with "difficult-to-manage" asthma, other causes of wheezing and airway obstruction must be considered. This is of particular importance in infants and young children whose small airways are more easily obstructed. The differential diagnosis of conditions that cause wheezing and airway obstruction varies with the age of the child. A thorough history, including response to prior treatment, physical examination, and data from additional tests, can help differentiate other disorders. Box 27-2 lists respiratory conditions that can produce asthma-like symptoms.

Box 27-2 Respiratory Conditions That Mimic Asthma

- Upper airway disorders
- Allergic rhinitis and sinusitis
- Vocal cord dysfunction
- Tonsillar/adenoid hypertrophy
- Laryngeal web
- Laryngeal papillomatosis
- Laryngotracheomalacia
- Tracheobronchomalacia
- Tracheoesophageal fistula
- Subglottic stenosis
- Tracheal stenosis
- Bronchial stenosis
- Vascular ring
- Enlarged lymph nodes or tumor
- Foreign body aspiration
- Lower airway disorders
- Acute viral bronchiolitis
- Bronchiolitis obliterans
- Bronchopulmonary dysplasia
- Cystic fibrosis
- Primary ciliary dyskinesia
- Mediastinal cysts or tumors
- Pulmonary embolism
- Aspiration syndromes
- Aspiration bronchitis
- Aspiration pneumonia
- Gastroesophageal reflux
- Hypersensitivity pneumonitis
- Allergic bronchopulmonary aspergillosis
- Cardiac disease
- Large left-to-right shunts
- Congestive heart failure
- Cardiomyopathy
- Myocarditis
- Hysterical symptoms
- Psychogenic cough
- Hyperventilation syndrome

MANAGEMENT OF ASTHMA

After the diagnosis of asthma has been made, the NAEPP guidelines suggest a stepwise approach to classifying the severity of asthma and initiating treatment. For classifications beyond mild asthma, daily control medication is recommended and the amount of medication is increased, described as a "step-up," as the need for treatment increases. When the asthma is under control, the amount of medication is decreased and described as a "step-down." The treatment prescribed is determined by classification of disease severity. Although asthma morbidity and mortality have increased in the United States, for most children with asthma, proper disease management helps to provide a normal lifestyle.

The pharmacologic management of asthma requires the use of long-term control and short-term relief medications. Identification, avoidance, and control of factors that worsen asthma symptoms are as essential to asthma management as the use of medication. Regular monitoring and assessment of asthma severity have been proven to aid in control of the disease. Finally, management of a chronic illness such as asthma requires patient and family involvement in developing a treatment plan and understanding the illness.

PHARMACOLOGIC THERAPY

Long-Term Control Medications

Pharmacologic management involves using medications to control and relieve symptoms. Any medication that is taken to provide ongoing control of asthma is classified as a long-term control medication. Long-term control medications are taken daily to achieve and maintain control of persistent asthma.

Antiinflammatory agents. Antiinflammatory agents are still considered the most effective long-term treatment for chronic inflammation in asthma. They block late-phase reactions to allergens, reduce airway hyperresponsiveness, and inhibit antiinflammatory cell migration and activation.[2] They are considered first-line agents for children with mild to moderate asthma. Although the potency of their antiinflammatory activity is less documented than that of inhaled corticosteroids, they have few adverse effects.

Inhaled **corticosteroids** are the most consistently effective controller medication for asthma and are considered first-line therapy for its treatment. Their advantage over oral corticosteroids is that they are clinically effective without having significant side effects. Oral corticosteroid-dependent patients have been able to decrease or discontinue their use of oral corticosteroids when appropriate inhaled corticosteroid therapy is initiated.

Although there is much less risk of developing adverse events with inhaled compared with systemic corticosteroids, the potential for side effects remains.

Box 27-3 Side Effects of Long-Term Use of Systemic Corticosteroids

- Adrenal suppression
- Growth suppression
- Muscle myopathy
- Aseptic hip necrosis
- Hyperglycemia
- Increased risk of infection
- Skin atrophy and striae
- Psychological disturbances
- Easy bruising
- Fluid retention
- Hypertension
- Osteoporosis
- Peptic ulcer
- Cataracts
- Acne
- Weight gain
- Obesity
- Hirsutism
- Glaucoma
- "Moon" facies
- "Buffalo hump"

Dysphonia, voice change, reflex cough, and oral candidiasis occur most often with higher doses, although these manifestations can occur at any dose. Use of spacers or holding chambers along with rinsing after inhalation may reduce these effects. Questions remain about the clinical significance of all side effects, particularly regarding growth suppression in children. Until more data are obtained, the NAEPP guidelines recommend that children be maintained on the lowest dose of inhaled corticosteroid tolerated with close monitoring of linear growth and development.

Systemic or oral corticosteroids are often required during an asthma exacerbation. However, daily or every-other-day use, along with high doses of an inhaled corticosteroid, is necessary in some patients with very severe disease. The side effects of long-term regular use of systemic corticosteroids are significant and are listed in Box 27-3. Once asthma control is achieved, efforts are made to wean the patient from oral corticosteroids.

Long-acting β2-agonists. Salmeterol and formoterol are long-acting inhaled **β2-agonists** (LABAs) available in the United States. Salmeterol is available alone as a dry-powder discus. It is also available in a dry-powder discus in combination with the corticosteroid fluticasone. Formoterol is available in a dry-powder inhaler device alone and as combination therapy and most recently in a liquid form for nebulization. The biggest difference between the two long-acting bronchodilators is their onset of action. Salmeterol can take from 30 to 90 minutes to have peak effect, whereas formoterol begins to work in 3 to 5 minutes. Evidence on the use of LABAs in asthma has demonstrated that the addition of LABAs to the treatment of asthma not well controlled on low- or medium-dose inhaled corticosteroids improves lung function and decreases symptoms more effectively than the use of inhaled corticosteroid (ICS) therapy alone.[2] Concerns were raised regarding the use of these medications when a large clinical trial comparing daily salmeterol with placebo added to usual asthma therapy demonstrated an increased risk of asthma-related deaths in those on salmeterol.[12] This resulted in the Food and Drug Administration (FDA)

placing a black box warning on all asthma medications containing a LABA. These studies resulted in the Expert Panel 3 recommending that the option of increasing the ICS dose be given equal weight to the decision to add a LABA for uncontrolled asthma symptoms. It is also not recommended that LABAs be used in the treatment of acute asthma symptoms or as monotherapy for long-term control.

Methylxanthines. Although theophylline was at one time a prominent component of daily asthma treatment, its role has changed dramatically over the past 10 years. It is listed as an alternative but not preferred adjunct therapy to ICS. With the current focus on antiinflammatory therapy for asthma, along with its narrow therapeutic window and need for close monitoring of serum levels, theophylline has limited use in the pharmacologic management of asthma in children.

Leukotriene modifiers. Leukotrienes are potent proinflammatory mediators that promote bronchospasm, mucus production, and airway edema. Leukotriene modifiers are the first new class of medicines for asthma treatment in 20 years. Leukotriene action is modified by agents that either inhibit production of the leukotrienes or block their action. These agents are still relatively new, and studies are needed to determine their role in pediatric asthma care.

Zileuton is the only approved agent that inhibits the production of leukotrienes; however, suggested dosing is four times daily, and there have been reports of elevated liver function tests in patients taking the medication. Therefore it has a limited role in pediatric asthma care. The Expert Panel Report recommends that this classification of medication be considered as an alternative but not a preferred therapy in the management of mild persistent asthma. It does recommend its use as an adjunct therapy with inhaled corticosteroids for patients 12 years of age and older.[2]

Cromolyn sodium and nedocromil. Stabilized mast cells can interfere with chloride channel function. They are used as an alternative but not preferred. They can also be used as preventive treatment before exercise or unavoidable exposure to known allergens.[2]

Immunomodulators. Omalizumab, the only drug that specifically binds circulating IgE, is indicated for moderate to severe asthma in patients older than 12 years who have had a positive skin test or positive *in vitro* test for aeroallergens, who have a quantitative IgE level between 30 and 700 IU/L, and whose asthma is not controlled on ICS therapy. Omalizumab is dosed based on the quantitative IgE level and the person's weight. Injections of 150 to 375 mg are given subcutaneously one to two times monthly. Omalizumab can significantly reduce exacerbations in patients with atopic asthma.[13]

Quick-Relief Medications

Medications in the quick-relief category are short-acting β2-agonists, anticholinergic agents, and systemic corticosteroids. These medications are used to relieve acute airway obstruction. All patients with asthma need a quick-relief medication, preferably a short-acting β2-agonist, to take as needed for acute symptoms.

Short-acting β-agonists. With a rapid onset of action of 5 to 15 minutes and a 4- to 6-hour duration of action, short-acting β-agonists are the treatment of choice for acute episodes of bronchospasm. They are often referred to as "rescue" medications and are most effective when inhaled. They are used only on an as-needed basis and not as part of the regularly scheduled medication regimen. Increased use of these agents, particularly more than one canister per month, is an indication of inadequate asthma control and increasing severity. The most common side effects are tremor, palpitations, and tachycardia. Although acute respiratory symptoms are relieved, short-acting β2-agonists have no antiinflammatory action. They are used to prevent EIB.

Anticholinergics. Ipratropium bromide is the anticholinergic agent approved for use in the United States. It is available alone in a metered-dose inhaler (MDI) and nebulizer formulation. Given alone, it is a less potent bronchodilator than short-acting β2-agonists. The combination of ipratropium bromide and albuterol is marketed in an MDI and a nebulizer unit-dose preparation.

Systemic corticosteroids. Patients with acute exacerbations often receive 3- to 10-day bursts of prednisone or methylprednisolone. The bursts are primarily used to hasten recovery and prevent recurrence of symptoms. The dose of corticosteroid is tapered as symptoms resolve. However, if the symptoms return within 1 month or if the bursts are frequently required, changes are likely required in the long-term control medication regimen.

Delivery Systems

Asthma medications are usually given through inhalation in an aerosol form. The medications are administered by a metered-dose inhaler, a dry-powder inhaler, or liquid small-volume nebulization.

Valved holding chambers are simple, inexpensive tools that have been developed for use with metered-dose inhalers. Their purpose is threefold:

1. To slow aerosol velocity
2. To minimize particle impaction in the oropharynx
3. To enhance deposition in the lower respiratory tract

Their use in children is recommended to reduce the problem of coordinating actuation of the metered-dose inhaler with the inhalation. Studies have demonstrated that the decrease in pharyngeal deposition results in improved drug efficacy and reduction in

local side effects. It is imperative that patients and parents or caregivers are instructed in the proper use of all inhalers, nebulizers, masks, and valved holding chambers. See Chapter 11 for more details of delivery devices.

CONTROL OF ASTHMA TRIGGERS

Most children with asthma have an allergic component to their disease, or **asthma triggers.** If asthma is to be managed adequately, the allergens and irritants that worsen symptoms must be identified and controlled. The most common allergens implicated in chronic asthma are listed in Box 27-4. Exposure to allergens and irritants may significantly increase bronchial hyperresponsiveness, whereas reduced exposure to allergens can decrease asthma symptoms.

Box 27-4 Allergens Associated With Asthma

- House-dust mites
- Pet allergens
- Cat
- Dog
- Guinea pig
- Rabbit
- Rodent
- Rat
- Mouse
- Cockroach
- Indoor mold
- *Aspergillus*
- *Penicillium*
- Outdoor mold
- *Alternaria*
- *Cladosporium*

Identification of Allergens

Because childhood asthma is often exacerbated by allergen exposure, it is helpful to identify the allergens. Allergy skin testing, along with a thorough history and physical examination, is one method an allergist uses to determine which allergens may be aggravating a child's asthma. Another common test used to determine what allergens are responsible for allergic disease is the radioallergosorbent (RAST) test.

Avoidance and Control Measures

It is nearly impossible for a child with asthma to avoid exposure to all offending allergens and irritants, but it is possible to minimize exposure to them. This begins with teaching the child and family to recognize the triggers and use measures to control and avoid them. Box 27-5 lists control measures for environmental factors that often exacerbate asthma in children.

Role of Immunotherapy

Allergen avoidance can produce changes in asthma disease activity and bronchial hyperresponsiveness, but often there are no practical means of avoiding exposure to all allergens. Allergen immunotherapy, or "allergy shots," should be considered for asthma patients when the following conditions are met:

1. There is clear evidence of a relationship between asthma symptoms and allergen exposure.

Box 27-5 Environmental Control Measures

HOUSE-DUST MITES

- Kill with hot water (>130° F) and dry cleaning.
- Enforce bedroom dust control.
- Encase pillows, mattresses, and box springs in zippered allergen-impermeable covers.
- Wash sheets and blankets weekly in hot water.
- Replace wool bedding with cotton or synthetics.
- Avoid feather or down bedding.
- Remove stuffed toys, wall hangings, and other "dust-catchers."
- Hot-water wash or freeze stuffed toys weekly.
- Vacuum and dust weekly wearing a mask; vacuum with a double-thick bag and HEPA filter.
- Keep heating, ventilation, and air conditioner filters clean.
- Remove carpeting; wash rugs; avoid heavy curtains and blinds.
- Keep clothing in closets with doors closed.
- Clean with damp cloths.
- Reduce indoor humidity.
- Replace upholstered furniture with wood, vinyl, or leather.

ANIMAL DANDER

- Remove animal from house or restrict animal to washable area (may take 4 to 6 months to remove cat allergens).
- Banish animal from bedroom.
- Close bedroom door and vents.
- Use a HEPA or electrostatic filter in bedroom.
- Remove carpets and minimize upholstered furniture and other allergen reservoirs.

COCKROACHES

- Hire a professional exterminator.
- Use poison baits.
- Store food and garbage in sealed containers.
- Perform meticulous regular cleaning.
- Eat only in the kitchen/dining room.

INDOOR MOLD

- The kitchen, bathroom, and basement are the most common sites.
- Leaky pipes, shower curtains, refrigerator drip pans, garbage pails, and window edgings are major sources.
- Wrap plumbing to eliminate condensation.
- Use commercial fungicides and bleach solution.
- Reduce humidity to less than 45% with dehumidifiers, air conditioning, and increased ventilation.
- Avoid humidifiers and vaporizers.
- Close windows, especially in the bedroom.
- Remove moldy items.
- Repair water leaks.
- Dry clothing and shoes before placing them in the closet.
- Limit houseplants and remove them from the bedroom.
- Avoid live Christmas trees.

NONALLERGEN IRRITANTS

- Avoid tobacco smoke and passive smoke in the home and closed cars.
- Avoid wood stoves, kerosene heaters, cleaning products, and perfumes.

HEPA, High-efficiency particulate air.

2. The patient is symptomatic during a major portion of the year.
3. Symptoms are difficult to control with pharmacologic therapy.

The value of immunotherapy in children with asthma remains controversial. Evidence suggests that it can be safely given to children with asthma and that life-threatening reactions are uncommon when the process is prescribed and supervised by an appropriately trained physician. However, the risk of anaphylaxis remains, and the injections must be administered in a health care facility where personnel, medication, and emergency equipment are immediately available to treat a systemic reaction. The patient waits 20 to 30 minutes after each injection, because this is the interval of highest risk for a systemic reaction. It is also suggested that the immunotherapy be delayed when the child has an acute illness or asthma exacerbation. Allergen immunotherapy is typically given every 7 to 28 days for 3 to 5 years, with a positive effect often seen within 1 year of therapy.

PEAK FLOW MONITORING

Using a peak flow meter to monitor peak expiratory flow rate (PEFR) is an important tool in asthma management when it is accompanied by a written action plan. It can be performed in children as young as 3 to 4 years old. Monitoring assists children and parents or caregivers in recognizing changes in respiratory status, affording them the chance to make necessary interventions. Although lung function measurements such as peak flow or spirometry may be useful in the management of asthma, many children may be unable to perform or have difficulties performing maneuvers during an asthma exacerbation.[14] Therefore the use of peak flow is not as strongly supported in the assessment of hospitalized patients with acute asthma exacerbations.

Peak Flow Meter

The peak flow meter is a comparatively inexpensive monitoring tool that measures PEFR (Figure 27-2). It is used only for ongoing monitoring and not to diagnose asthma. Different brands of peak flow meters are available, and it is possible to get a slightly different peak flow value when using a different meter. Because there is variation between different brands, it is important to use the same peak flow meter or model for long-term monitoring. Box 27-6 lists the steps in performing a peak flow maneuver. Patients are asked to bring their peak flow meter to their physician's office to check the accuracy of the meter and to recheck for proper technique. When a quick-relief medication is taken because of an increase in asthma symptoms, it is suggested that a peak flow reading be obtained before and after taking the medication.

FIGURE 27-2 Child with peak flow meter.

Box 27-6 How to Use a Peak Flow Meter

1. Make sure the meter reads zero or the indicator is at the bottom of the numbered scale.
2. Stand up (unless there is a physical disability). Remove any food or gum from your mouth.
3. Take as deep a breath as possible, filling your lungs completely.
4. Place the meter in your mouth, behind your teeth, and close your lips around the mouthpiece. Do not let your tongue block the mouthpiece.
5. Blow out as hard and as fast as you can in a single blow. Do not cough into the meter.
6. The force of your breath moves the indicator on the peak flow meter. The number opposite the indicator is your peak flow.
7. Write down the peak flow number obtained.
8. Repeat the steps two additional times. Record the highest of the three attempts (not the average) in your diary or on your peak flow chart.

Peak Flow Diary

Keeping a diary or chart of the readings is, for many patients, an important part of their treatment plan. Graphs for plotting peak flows are often included with the peak flow meter and can be photocopied for additional use. There are also smartphone apps that can help parents and children track their progress. With daily peak flow monitoring, a patient may see a drop in the peak flow before severe symptoms are felt and may begin early treatment or seek medical help. This may prevent asthma exacerbations from occurring or lessen the seriousness of an episode by medicating at the first sign of low peak flow readings. The physician reviews the peak flow diary at each office visit.

Personal Best Reading

There are predicted "normal" peak flow values that are determined by height, age, gender, and race. However, it is necessary to determine a child's "personal best" peak flow reading. This is defined as simply the highest or best measurement obtained when the patient is free of symptoms and asthma is under control. To determine the personal best reading, the patient

Box 27-7 Traffic Light Zone System

GREEN ZONE: PEAK EXPIRATORY FLOW IS GREATER THAN 80% OF PERSONAL BEST NUMBER
- Good control of asthma is indicated.
- The patient is relatively symptom-free.
- Quick-relief medication is not indicated.
- Long-term control medication is the only medication indicated.
- If peak flow is constantly in the green zone with minimal variation, the physician may consider changing or decreasing daily medication.

YELLOW ZONE: PEAK EXPIRATORY FLOW IS 50% TO 80% OF PERSONAL BEST NUMBER
- "Cautious" zone; asthma is worsening.
- There is less-than-optimal control of asthma.
- Asthma symptoms may be increased, with awakening at night.
- Quick-relief medication is needed (usually a short-acting β2-agonist).
- Increase in daily maintenance therapy may be needed.

RED ZONE: PEAK EXPIRATORY FLOW IS LESS THAN 50% OF PERSONAL BEST NUMBER
- "Danger" zone; exacerbation is severe.
- Asthma is poorly controlled.
- Asthma symptoms are serious and possibly life-threatening.
- Immediate intervention is required (usually a short-acting β2-agonist).
- Depending on the physician's direction and the patient's response to quick-relief medication, the patient may be directed to seek emergency care.

records peak flow readings at least once a day for 2 to 3 weeks. The best peak flow reading will usually occur in the early afternoon.

Peak Flow Zone System

Once a patient's personal best peak flow has been established, every effort is made to maintain the peak flow values within 80% of this number. One peak flow monitoring system uses a zone system to indicate asthma severity and guide patients to an appropriate response. As illustrated in Box 27-7, green, yellow, and red zones are established. The zones are broad guidelines designed to simplify asthma management.

Asthma Action Plan

All patients with asthma should be provided with an approved management plan, or **asthma action plan,** with information that patients can immediately refer to should they become symptomatic. However, more important than the action plan itself is that they understand the action plan fully. Based on the patient's current peak flow reading and the personal best number, the plan provides the patient with appropriate actions to take when symptoms arise or peak flow values drop. Included are detailed instructions specifying when to begin quick-relief medications, when to increase daily medications, and when to contact a physician or seek emergency care. Also identified are the specific medications to be given, the route of administration, the dose to be administered, and the frequency of dosing. Reminders to recheck the peak flow reading are included. It is helpful to have the physician's name and phone number on the plan along with the phone number of a close relative or neighbor.

Patients are instructed to take the action plan and peak flow meter with them when traveling. If the patient attends school, a copy of the plan is provided for the school to be used by the teacher or school nurse in the event of an exacerbation or to prevent EIB while at school.

PATIENT AND FAMILY EDUCATION

For any asthma disease management program to be successful, there must be an active partnership between patients, their families, and health care providers. This partnership is critical when the patient has a chronic disease such as asthma. Patient and family education begins at diagnosis and is a continual process, with the ultimate goal being to improve self-management.

It is unlikely that the patient's physician has the time to devote to a complete and comprehensive regimen of education; therefore all members of the health care team need to work together to reinforce the same message. A comprehensive asthma education program, which should be provided to patients with asthma, includes a system of well-trained health care providers who specifically address barriers to learning and test the comprehension of the parents and child; includes the community in which the child lives; and uses age-specific teaching methods (including technology when appropriate) to accomplish the NAEPP objectives (Figure 27-3):

1. Self-monitoring to assess level of asthma control and signs of worsening asthma
2. Using an asthma action plan
3. Taking medication correctly (proper inhaler technique and use of devices)
4. Avoiding environmental factors that worsen asthma

A successful partnership keeps the lines of communication open. Asking open-ended questions can lead to the patient and family being freer in discussing concerns, fears, and expectations regarding asthma care. Perception of the disease and beliefs about treatment are influenced by earlier experience, education, personality characteristics, socioeconomic status, cultural background, and the available support system. It is important to be sensitive to the cultural background of the patient and family. Ethnic beliefs can often affect the way the patient and family view asthma and its treatment. For example, some cultures view an illness as either a "hot" or a "cold" disease. Many in the

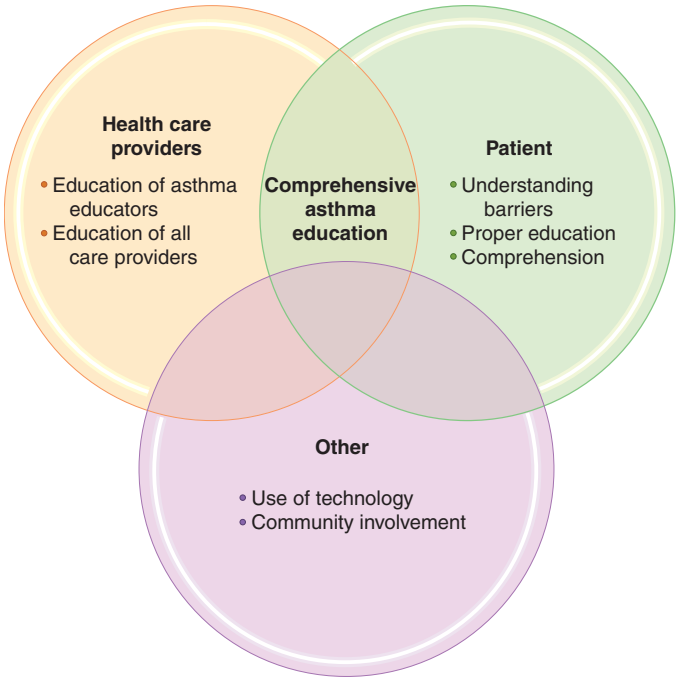


FIGURE 27-3 A comprehensive asthma education program includes all stakeholders in the successful outcome of improved self-management of the patient.

Hispanic population believe that asthma should be treated with a "hot" remedy such as hot tea. Often there is no harm in the belief, and the caffeine may even help; however, there may be times when the clinician must intercede in the interest of patient safety.

Asthma Disease Process

Key points concerning the disease process include a basic understanding of what asthma is and what can trigger asthma episodes. Often drawings of a normal airway contrasted with one with asthma help patients visualize what is occurring in their own lungs.

Medication Skills

It is imperative that patients (depending on age) and families understand the names of their medications, proper dosing, when and how to take each medication, and the side effects of each. Providing written instructions for each medication assists in understanding and adherence to the treatment regimen. Proper inhaler technique is taught and then reviewed at each subsequent physician visit. It is stressed that the long-term control medications are preventive in nature and are to be taken even if the patient is symptom free. Patients often discontinue use of their controller medications, only to develop an asthma exacerbation within 3 to 4 weeks.

Identification and Control of Triggers

Patients and their families need information to discern what triggers their asthma and ways to avoid the triggers. Although all triggers may not be totally avoidable, the patient and family are urged to take all necessary measures to avoid them and learn to monitor which variables influence their symptoms.

Self-Monitoring Techniques

Patients must learn to monitor and recognize signs and symptoms of worsening asthma. Education in the proper use of a peak flow meter and how to follow an asthma action plan is an essential component of asthma education. Reinforcing appropriate behavior includes reviewing peak flow monitoring, inhaler technique, and implementation of the action plan. Review of the action plan at each visit has been shown to improve patient compliance and decrease the chance for confusion. In addition to reviewing the action plan, the physician will modify it as the child gets older so the patient can assume more of not only the monitoring but treatment as well.

MANAGING ASTHMA EXACERBATIONS IN THE EMERGENCY DEPARTMENT

Patients presenting to the emergency department have often had previous emergency admissions and hospitalizations for treatment of severe asthma. Often these patients have no primary care physician and rely on symptomatic control and emergency departments as their primary source of medical care. Along with inadequate use of corticosteroids, these characteristics are associated with an increased risk for fatal asthma.

ASSESSMENT

The intensity and progression of the asthma exacerbation can vary and will determine the intensity of treatment in the emergency department. It is essential that a primary classification of severity be determined in the emergency department. On admission, a physical examination is performed along with measurement of oxygenation and air flow. A pulse oximeter is used to measure oxygen saturation. Continuous monitoring of oxygen with a pulse oximeter is crucial to prevent desaturation.

A peak flow meter or spirometer can provide assessment of the severity of airway obstruction from inflammation and bronchospasm. If a child who normally uses a peak flow meter is unable to perform the maneuver during an attack, severe air flow obstruction is considered and intensive medical therapy is indicated.

β2-AGONISTS

One of the first lines of therapy is with β2-agonist agents. The Expert Panel Report 3 recommends that the patient receive three treatments given every 20 to 30 minutes by either nebulization or MDI. If there is an inadequate response to this, continuous nebulization of albuterol may be initiated. In severe exacerbations, the addition of ipratropium bromide to β2-agonists

should be considered. Adverse effects typically seen with the use of β2-agonists, such as tremor, tachycardia, and nervousness, are often pronounced, and some patients may not want to take the treatment because of this response.

CORTICOSTEROIDS

It is critical that corticosteroids be given to treat the inflammation that occurs during an acute exacerbation. Early treatment, which may include the use of intravenous corticosteroids, is effective in preventing an increase in the severity of symptoms and may avoid hospitalization and relapses. Because intravenous lines are uncomfortable and can be difficult to place in a child, studies have investigated the use of oral delivery of corticosteroids in the emergency setting and have found that oral administration is as good as the intravenous route. If the child cannot adequately be given oral corticosteroids, the intravenous route should be considered. Other adjunct interventions in severe exacerbations should be considered as well. These include intravenous magnesium sulfate or heliox.[2]

Case Study

A 5-year-old previously healthy boy with no medical history is being seen in the emergency department (ED) with wheezing, retractions, and respiratory distress, with an SPO_2 of 99% on room air. You initiate a bronchodilator according to protocol and begin a complete assessment. A chest radiograph reveals hyperinflated lung fields with no concern for pneumonia or cardiac disease.

What would you want to review before considering asthma as the primary reason for the ED visit?

See Evolve Resources for answers.

HOSPITALIZATION AND RESPIRATORY FAILURE

Regardless of the care given in the emergency department, some children will not respond adequately and will require hospitalization. These patients are often referred to as *refractory to conventional therapy.* Criteria for hospitalization vary; however, continuing deterioration or failure to improve with therapy is an indication for intensive monitoring and treatment. Yet the treatment within the inpatient unit is not much different than in the emergency department, with the exception of ipratropium bromide, because it is not recommended after admission. Box 27-8 lists criteria considered for hospitalization.

Figure 27-4 describes a care pathway one may take if there is a lack of improvement to traditional therapies described in the asthma guidelines. As therapies progress they often are associated with increased risk of side effects and mortality because of the severity of illness. When a patient is captured by the increasing therapy level, that is one of the first therapies that is weaned after a period of stability. Additionally, if intravenous bronchodilators are initiated, inhaled bronchodilators are weaned and stopped. Likewise, if inhaled anesthetics are initiated, intravenous bronchodilators are weaned. For more information about heliox and inhaled anesthetics, see Chapter 18.

Box 27-8 Criteria for Hospitalization

- Poor response to 4 hours of bronchodilator therapy
- Requires continuous bronchodilator therapy
- Previous visit to emergency department within 24 hours
- Hospitalization for asthma within the past year
- Previous hospitalization with admission to the intensive care unit
- History of mechanical ventilation for asthma
- Poor access to medical care
- Recent increase in need for oral corticosteroids

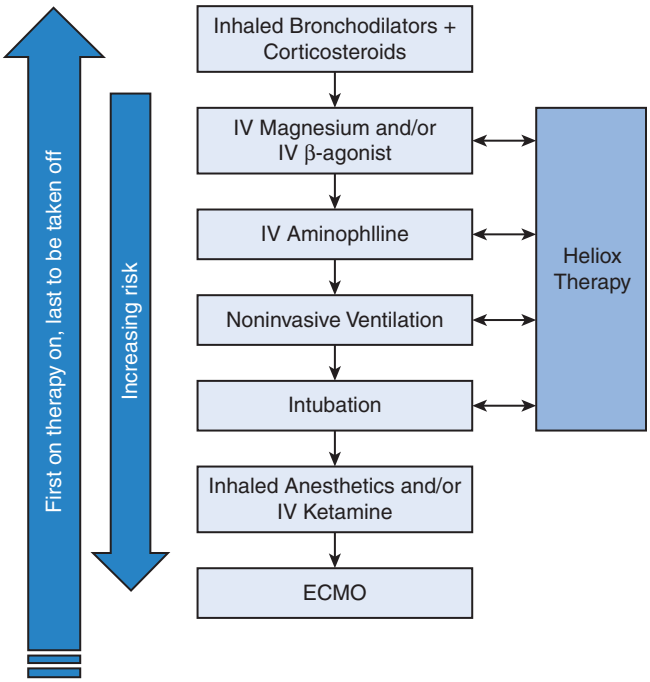


FIGURE 27-4 Potential care pathway for escalating therapies for patients not responding to initial therapies. *ECMO,* Extracorporeal membrane oxygenation.

INTUBATION

If all attempts to reverse bronchospasm and improve air flow are futile, careful consideration is given to intubation and mechanical ventilation. Diligent patient monitoring is essential, and immediate steps are taken once the patient demonstrates respiratory muscle fatigue or failure.

It is best to intubate on a semielective basis rather than in an emergent situation, and the clinician most experienced in managing pediatric airways should perform it. Intubation is attempted only under a controlled setting with continuous cardiorespiratory monitoring and resuscitation equipment and medication available.

Once intubated and stabilized, the patient is monitored in a pediatric intensive care unit, which may mean transporting the child to another medical facility.

MECHANICAL VENTILATION

After intubation, the child is mechanically ventilated with 6 to 8 mL/kg IBW with low to moderate positive end-expiratory pressure (PEEP) to assist with distal airway collapse and degree of auto-PEEP present. Larger tidal volumes may be required if prolonged expiratory times and low rates are used. The mode of ventilation and set respiratory rate are determined according to the patient's degree of sedation, peak inspiratory pressures generated, oxygenation, and acceptable levels of $Paco_2$. Initially the Fio_2 is 1.0, with the goal to decrease the level to 0.5 or less when able. Ventilation with permissive hypercapnia is allowed with an inspiratory-to-expiratory ratio allowing for adequate exhalation.

NOTE: When using noninvasive mechanical ventilation, a moderate to high level of PEEP (more than 8 cm H_2O) may be required to assist with distal airway collapse.

All patients receiving mechanical ventilation are at risk of complications, including auto-PEEP, air trapping, pneumothorax, hypotension, acute respiratory distress syndrome, and death. Children with asthma are especially prone to such problems because of the high degree of airway resistance and the need for high inspiratory pressures.

EXERCISE-INDUCED BRONCHOSPASM

Sometimes referred to as *exercise-induced asthma*, EIB begins during exercise and tends to reach its peak 5 to 10 minutes after the child has ceased activity. It can be particularly worse in cold weather and may take another 20 to 30 minutes for symptoms to spontaneously resolve. EIB is caused by a loss of heat or water from the airway during exercise. This is often caused by hyperventilation of cool or dry air.

The prevalence of EIB has been reported to vary from 40% to 90% in children with asthma, with greater prevalence in children with severe asthma. Absenteeism from school and poverty have been associated with findings of EIB. Early detection of EIB in school-aged children through screening could facilitate early treatment, enhance exercise-related activities, and possibly decrease the number of school absences. Notifying day care personnel, schoolteachers, and coaches that a child has EIB can alert them to monitor symptoms and may elicit a more effective response should symptoms occur.

The diagnosis of EIB is based on a history that is compatible with asthma symptoms that occur with or directly after exercise. An exercise challenge can be performed to confirm the diagnosis.

The management of these episodes is generally of a preventive nature. Recommended treatment is inhalation of a β2-agonist, cromolyn sodium, nedocromil, or salmeterol, given 5 to 60 minutes before exercise, preferably closer to the start of exercise if possible. Providing a 5- to 10-minute "warmup" period before any exercise is recommended as well. An increase or change in long-term control medications may be appropriate in some children with EIB. Outdoor activities may need to be adjusted if conditions are unfavorable. This is particularly important if the pollen, weed, or mold count is elevated. Extreme cold and windy weather are also circumstances that may call for more caution to ensure that asthma symptoms do not develop during the activities. Efforts to prevent EIB require open communication with the schoolteacher and coach to allow premedication by the student athlete under a physician's guidance.

ASTHMA AT SCHOOL

One-third of those with asthma in the United States are younger than 18 years of age. Dealing with asthma while at school can present problems for the child, the parents, and the school personnel. Asthma symptoms can interfere with many activities that the school-aged child desires to pursue. It is the leading cause of school absences, with an average of more than 10 days per year missed. A child with severe asthma may miss more than 30 days per year. An obvious conclusion drawn from these statistics is that missing school may result in poor academic achievement, inability to participate in school activities, and low self-esteem. The goal for a school-aged child with asthma is to keep symptoms under control and participate fully in any physical and extracurricular activities the school system may offer.

Various organizations provide resources to aid in the care of children with asthma in school. The educational interventions can address each particular school, because not all schools have the same needs or programs. A child-centered, school-based asthma education program has been associated with an increase in knowledge of asthma, improvement in skills for peak flow meter and inhaler use, and a reduction in the severity of asthma symptoms.

School personnel, including teachers, coaches, and nurses, need to be familiar with the early warning signs of an impending asthma attack and what to do if the symptoms are present. It is recommended that a copy of the child's asthma action plan be kept at the school and that the teacher and school nurse be familiar with the plan. Unfortunately, many school systems do not employ a nurse dedicated to each individual school. Therefore, there are occasions when the nurse is not available and other school personnel may need to provide care for the child. It is essential that the asthma action plan, peak flow meter, and rescue medications be readily accessible to school staff.

Parents can take a proactive role by determining how "asthma friendly" the school's environment is for their child. Some key questions to ask are listed in

Box 27-9. The school building can present a hostile environment for children with asthma. There are numerous potential triggers found in most schools, including dust mites, mold, cockroaches, chalk dust, birds, rodents, animal dander, and strong odors (e.g., paint, chemicals, perfumes, pesticides). It is essential that these irritants be minimized or eliminated so that the child with asthma can attend school without risking further complications.

ASTHMA CAMPS

In recent years there has been a growth in the number of asthma camps for children. These camps offer children with asthma the opportunity to spend time with other children who have the same disorder. This type of experience can be priceless. The camps are structured to assist children in recognizing symptoms and how to respond to them, with particular attention to the use of an asthma action plan. Identification of triggers and avoidance techniques are discussed as well. The proper use of medication delivery devices and peak flow meters is also reinforced.

Positive effects from attending camp include a reduction in the rate of postcamp hospitalizations, school absences, and emergency department visits. The camps are usually operated with a team approach that includes physicians, respiratory therapists, social workers, and nurses.

Box 27-9 Is Your School Asthma Friendly?

- Does the school have a no smoking policy for all personnel, including teachers and custodial staff?
- Does the school maintain clean indoor air quality? How is this ensured?
- Is there a school nurse available at the school at all times? If not, how often is she/he there? Is she/he trained in pediatric asthma care?
- Can children with asthma take prescribed medications at school? Can they carry their rescue medications on their person? Must the medications be kept in a locked location?
- Does the school have an emergency plan for treating a child with a severe asthma episode?
- Does the school staff know the early warning signs of an asthma episode? Do they know the possible side effects of asthma medications and how they may affect the student's performance at school?
- Are students encouraged to participate in school activities and sports, regardless of their asthma?
- Are less strenuous activities provided if a recent exacerbation precludes full participation?
- Do teachers and coaches understand that exercise, especially in cold air, can trigger asthma?
- Is the school staff provided with opportunities to learn about asthma and allergies?
- Is there a copy of the asthma action plan in each student's classroom?
- Do school personnel understand that asthma is not an emotional or psychological disease but strong emotions can trigger an acute episode?

Key Points

- Asthma is a chronic yet reversible disease if properly maintained and monitored.
- Proper education and ongoing reinforcement of that education are vitally important for the successful self-management of asthma.
- Prolonged expiratory phased ventilation in asthma may be required; however, to maintain adequate alveolar ventilation, a larger tidal volume will be required.
- Long-acting β-agonist (LABA) use may mask symptoms of uncontrolled airway inflammation and contribute to asthma-related death.
- The use of clinical assessment tools, such as an asthma score, can be helpful; however, some indications of health, such as breath sounds, can be misleading. For example, silent or quiet breath sounds can be an ominous sign or a sign of improvement depending on the remaining factors of your clinical assessment.

Assessment Questions

See Evolve Resources for answers.

1. The incidence of asthma has done what over the past 10 years?
   - **A.** Remained stable
   - **B.** Increased
   - **C.** Decreased
   - **D.** Decreased in incidence but increased in severity
2. When gathering information about a patient's medical history, it is essential to include:
   - **A.** Recurrent wheezing or chest tightness
   - **B.** Shortness of breath and cough
   - **C.** Nocturnal symptoms
   - **D.** All of the above
3. Dust mites are better controlled in what environment?
   - **A.** Less relative humidity
   - **B.** When bedding is washed in water hotter than 130° F
   - **C.** When pillows and mattress are enclosed in zippered allergen-impermeable covers
   - **D.** All of the above
4. When educating a patient or family member, it is always essential to remember to:
   - **A.** Not ask open-ended questions
   - **B.** Ask open-ended questions
   - **C.** Try not to maintain eye contact for long periods
   - **D.** Avoid questions that deal with a patient's expectations of his or her asthma management
5. The purpose of a spacer is to slow aerosol velocity, to minimize particle impaction in the oropharynx, and to:
   - **A.** Enhance deposition in the lower respiratory tract
   - **B.** Allow for larger particles
   - **C.** Decrease the size of the particles
   - **D.** Change aerosol particles to vapor, thus allowing better delivery of medication

6. Omalizumab is generally dosed for patients with IgE levels between:
   - **A.** 30 and 1500 IU/L
   - **B.** 30 and 700 IU/L
   - **C.** 500 and 1200 IU/L
   - **D.** 3000 and 5500 IU/L
7. What is the best way to manage cockroaches?
   - **A.** Carpet removal
   - **B.** Boric acid
   - **C.** Acetic acid
   - **D.** Bleach
8. Triggers of airflow obstruction include:
   - **A.** Aspirin and nonsteroidal antiinflammatory drugs, exercise, cold air, irritants, gastroesophageal reflux, respiratory infections, and psychological stress
   - **B.** Aspirin, exercise, cold air, gastroesophageal reflux, respiratory infections, and excessive use of LABAs
   - **C.** Respiratory infections, cold or warm air, psychological stress, aspirin, exercise, and antiinflammatory drugs
9. In adult asthma, the inflammatory findings, such as eosinophilic airway inflammation, hypergranulation of mast cells, increased IgE levels, and increased allergic response, are caused in part by an inappropriate activation of:
   - **A.** CD4+ T cells
   - **B.** IL-4
   - **C.** T cells
   - **D.** Th2 cells
10. What are the five components of asthma?
    - **A.** Inflammation, acute bronchoconstriction, airway edema, mucous plugging, airway hyperresponsiveness, and wheezing
    - **B.** Inflammation, acute bronchoconstriction, airway edema, mucous plugging, airway hyperresponsiveness, and airway remodeling
    - **C.** Inflammation, acute bronchoconstriction, airway edema, mucous plugging, airway hyperresponsiveness, and increased levels of nitric oxide
    - **D.** Inflammation, acute bronchoconstriction, airway edema, mucous plugging, airway hyperresponsiveness, and an allergic presentation

REFERENCES

1. Department of Health and Human Services. Healthy People 2010 Midcourse Review. US Government Printing Office; 2007:3-27.
2. National Asthma Education and Prevention Program. Guidelines for the Diagnosis and Management of Asthma (EPR-3). NIH pub. no. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program; 2007.
3. Centers for Disease Control and Prevention. National Asthma Control Program. Available at: http://www.cdc.gov/asthma/NACP.htm.
4. Centers for Disease Control and Prevention. The 15-Minute Asthma Visit. Medscape. Available at: http://www.medscape.com/viewarticle/745863. Accessed 8/01/2011.
5. Centers for Disease Control and Prevention. Asthma Control During Travel. Medscape. Available at: http://www.medscape.com/viewarticle/741288. Accessed 5/02/2011.
6. Hunt JF, Fang K, Malik R, et al. Endogenous airway acidification. Implications for asthma pathophysiology. *Am J Respir Crit Care Med*. 2000;161(3 Pt 1):694.
7. Ricciardolo FL, Gaston B, Hunt J. Acid stress in the pathology of asthma. *J Allergy Clin Immunol*. 2004;113(4):610.
8. Horvath G, Schmid N, Fragoso MA, et al. Epithelial organic cation transporters ensure pH-dependent drug absorption in the airway. *Am J Respir Cell Mol Biol*. 2007;36(1):53.
9. Platts-Mills TA. Allergen avoidance in the treatment of asthma and rhinitis. *N Engl J Med*. 2003;349:207.
10. Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med*. 2006;355:2226.
11. Dweik RA, Boggs PB, Erzurum SC, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med*. 2011;184(5):602-615.
12. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM, SMART Study Group. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest*. 2006;129:15.
13. Lanier B, Bridges T, Kulus M, Taylor AF, Berhane I, Vidaurre CF. Omalizumab for the treatment of excerbations in children with inadequately controlled allergic (IgE-mediated) asthma. *J Allergy Clin Immunol*. 2009;124(6):1210-1216.
14. 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.

28 Cystic Fibrosis

Brian K. Walsh

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. Describe how the diagnosis of cystic fibrosis is made.
2. Understand the pathophysiology of cystic fibrosis.
3. List the common pulmonary manifestations of cystic fibrosis.
4. List the common nonpulmonary manifestations of cystic fibrosis.
5. List the current treatments used to manage cystic fibrosis pulmonary disease.
6. Discuss the overall prognosis of patients with cystic fibrosis.

Key Terms

autosomal recessive
bronchiectasis
carrier
cystic fibrosis transmembrane conductance regulator
failure to thrive
genotype
heterozygote
homozygote
immunoreactive trypsinogen
meconium ileus
newborn screening
pancreatic insufficiency
phenotype
sweat chloride test

Cystic fibrosis (CF) is a genetic disorder with primary manifestations in the respiratory, digestive, and reproductive systems caused by dysfunction of the **cystic fibrosis transmembrane conductance regulator** (CFTR). It was first described in 1938 when autopsy studies recognized distinct fibrocystic changes of the glandular ducts in the pancreases of severely malnourished infants.[1]

The signs and symptoms of classic CF are related to the overproduction of thick, viscous secretions in multiple organ systems:

- Chronic obstruction, infection, and inflammation of the airways
- Exocrine **pancreatic insufficiency** with malabsorption and small bowel obstruction
- Infertility in males
- Elevated sweat chloride levels

There is considerable variability in the frequency and severity of clinical manifestations and complications, some of which are discussed in this chapter. Successful care of children with CF therefore requires a multidisciplinary team approach individualized to the needs of the patient.[2]

EPIDEMIOLOGY

CF has an annual incidence of 1 in 3200 to 3700 live births and a prevalence of approximately 30,000 affected individuals in the United States.[3,4] Disease frequency varies in other racial and ethnic groups: 1 in

9200 Hispanics; 1 in 10,900 Native Americans; 1 in 15,000 African Americans; and 1 in 31,000 Asian Americans.[5] It is estimated that 1 in 28 Caucasians and 1 in 60 African Americans in the United States are carriers.[5] In 2010 the median age at diagnosis was 5 months, down from 6 months in 2000.[6] Now, with routine newborn screening, it is anticipated that this will continue to decline to roughly 1 month.

GENETICS AND MOLECULAR BIOLOGY

CF is caused by a defect in the CFTR gene located on the long arm of chromosome 7. The gene, which is approximately 189,000 base pairs in length, was first cloned in 1989.[7] The mature CFTR protein is composed of 1480 amino acids and functions as a cyclic adenosine monophosphate–regulated chloride channel that mediates the flow of ions and water across the apical membrane of epithelial cells lining the airways, intestines, vas deferens, biliary tree, sweat ducts, and pancreatic ducts.[8] CFTR dysfunction alters sodium, chloride, and water transport, resulting in thickened, viscous secretions that plug the ducts of these organs.

CF is inherited in an **autosomal recessive** manner. An individual with CF is a **homozygote** possessing two abnormal CFTR alleles. Each parent of a child with CF is an obligate **carrier** (or **heterozygote**), possessing one normal CFTR allele and one mutated allele. Each child of two carriers has a 1 in 4 chance of having CF, a 2 in 4 chance of being an asymptomatic carrier, and a 1 in 4 chance of having two normal alleles. Siblings of an individual with CF have about a 7 in 10 chance of being a carrier; there is a family history in only 17% of newly diagnosed patients.

DIAGNOSIS

The diagnosis of CF is based on the presence of one or more distinguishing clinical features with biochemical or genetic confirmation. Box 28-1 lists signs and symptoms that should prompt a clinician to consider an evaluation for CF. Even though the disease occurs most often among individuals of Western European descent, it should be considered in the differential diagnosis of a patient of any racial background who presents with these features. Box 28-2 summarizes the diagnostic criteria for CF.

SWEAT CHLORIDE TESTING

The gold standard for the diagnosis of CF is the **sweat chloride test.** Normal secretion and resorption of chloride in the sweat glands are dependent on adequate CFTR function. A sweat chloride concentration 60 mmol/L or greater confirms the diagnosis. A concentration between 40 and 59 mmol/L in infants older than 6 months is considered intermediate and the test should be repeated along with CFTR mutation analysis. Normal individuals can occasionally have elevated sweat chloride concentrations not related to CFTR dysfunction.

Sweat chloride testing should be performed according to nationally published guidelines at accredited centers. The sweat is obtained by stimulating the skin on the forearm with pilocarpine iontophoresis (Figure 28-1).

Box 28-1 Signs and Symptoms That Should Prompt Evaluation for Cystic Fibrosis

RESPIRATORY
- Recurrent wheezing
- Chronic cough
- Frequent thick sputum production
- Severe, prolonged, or recurrent sinopulmonary infections
  - Sinusitis
  - Bronchitis
  - Bronchopneumonia
- Respiratory infections with pathogens associated with cystic fibrosis
  - *Staphylococcus aureus*
  - *Pseudomonas aeruginosa*
  - *Haemophilus influenzae*
  - *Burkholderia cepacia* complex
- Persistently abnormal chest radiograph
  - Hyperinflation
  - Persistent atelectasis
  - Bronchiectasis
- Nasal polyps
- Clubbing of the nail beds

GASTROINTESTINAL
- Failure to thrive
- Frequent greasy, foul-smelling stools
- Rectal prolapse
- Meconium ileus
- Distal intestinal obstruction syndrome
- Pancreatic insufficiency
- Recurrent pancreatitis

HEPATOBILIARY
- Hepatomegaly
- Portal hypertension
- Focal biliary cirrhosis
- Prolonged neonatal jaundice
- Cholestasis
- Cholelithiasis

REPRODUCTIVE
- Obstructive azoospermia
- Congenital bilateral absence of the vas deferens

NUTRITIONAL DEFICITS
- Fat-soluble vitamin deficiency (vitamins A, D, E, K)
- Hypoproteinemia, with or without edema
- Hypochloremic metabolic alkalosis

Box 28-2 Diagnostic Criteria for Cystic Fibrosis

At least one item from each of the following categories must be present:

HISTORY OR CONDITION

Clinical signs or symptoms consistent with cystic fibrosis in at least one organ system
or
Sibling with confirmed cystic fibrosis
or
Positive newborn screening result for cystic fibrosis

LABORATORY TESTING

Sweat chloride level ≥60 mmol/L
or
Presence of two disease-causing CFTR mutations
or
Abnormal nasal potential difference

CFTR, Cystic fibrosis transmembrane conductance regulator.

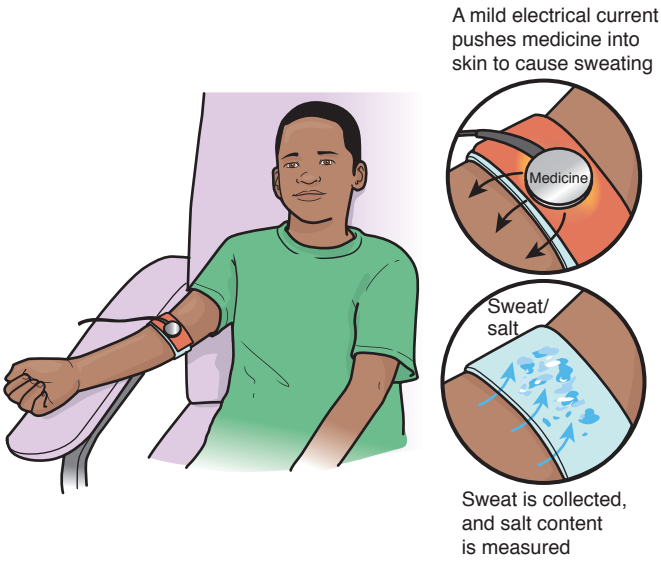


FIGURE 28-1 Sweat test being performed. Electrodes are positioned on the forearm to stimulate the skin to produce sweat.

Technical errors can result in false-negative and false-positive results. In addition to inadequate sweat collection, malnutrition, edema, and hypoalbuminemia can also yield false-negative results. Therefore patients with clinical features suggestive of CF but normal or borderline sweat test results should have the test repeated. Conditions that can produce false-positive results include malnutrition, eczema, adrenal insufficiency, pseudohypoaldosteronism, and hypothyroidism.

CFTR MUTATION ANALYSIS

A diagnosis of CF can be confirmed with the identification of two disease-causing CFTR mutations. The most common mutation is deletion of a phenylalanine residue at position 508 (annotated as F508del or ΔF508), which represents 30% to 80% of all mutations, depending on the ethnic group.[10] Mutations are categorized into five functional classes based on the type of defect in the formation of the CFTR protein.[11] Generally, class I through III mutations cause more severe disease compared with class IV or V mutations.[12] There are individuals with recognized CFTR mutations **(genotype)** who may not necessarily have the typical clinical manifestations **(phenotype)** of CF. The CF phenotype–genotype correlation is complex and poses many challenges when trying to develop a rational surveillance and care plan.[13]

NASAL TRANSEPITHELIAL POTENTIAL DIFFERENCE

Measuring the difference in voltage potentials across the nasal epithelium is another method used in the diagnosis of CF, particularly when sweat chloride and CFTR mutation analysis results are inconclusive.[14] However, the availability of this test remains limited, and it should only be performed at experienced centers.

NEWBORN SCREENING

As of January 2010, all 50 states and the District of Columbia included CF in standard **newborn screening.**[6] The most common method is measurement of **immunoreactive trypsinogen** (IRT) obtained from a dried heel-stick blood sample. Alternatively, many European countries and many states in the United States combine IRT detection with DNA analysis.[15] Evidence from observational studies suggest that children with CF identified through newborn screening have benefited from earlier diagnosis and initiation of therapy.[16] Indeed, early diagnosis has helped prevent severe malnutrition and improve long-term growth and has been associated with reduced therapy.

Not all identified CFTR mutations are associated with clinical disease. There are situations in which an infant identified as being at risk for CF with an abnormal newborn screening result does not have a diagnostic sweat chloride value of 60 mmol/L or higher or is found to have up to two CFTR mutations, one of which is not recognized as a disease-causing mutation. The term *CFTR-related metabolic syndrome (CRMS)* has recently been proposed as a step toward developing rational guidelines for this unique population of patients with an indeterminate diagnosis.[17] Studies suggest that the course of CRMS may be less severe compared with "classic" CF,[18] although long-term prospective data are still lacking.

PULMONARY DISEASE

Although CF is a multisystem disorder, pulmonary disease is the primary cause of morbidity and mortality.[19] As a result of CFTR dysfunction, there is abnormal sodium, chloride, and water transport across the respiratory epithelium. This in turn leads to the production of thick, viscous mucus, with a perpetual cycle of airway obstruction, chronic infection, and airway

inflammation.[20] As the disease progresses, there is development of **bronchiectasis,** or abnormal dilation and distortion of the airways. Bronchiectatic airways are more easily collapsible, further perpetuating the cycle of obstruction, infection, and inflammation.

MUCUS PRODUCTION AND AIRWAY OBSTRUCTION

The lungs of a newborn with CF are histologically normal at birth. However, airway dysfunction appears to begin as early as the first year of life, with the earliest pathologic change being thickened mucus and plugging of the submucosal gland ducts in the large airways. These changes appear to precede chronic infection and inflammation.

Goblet cells and submucosal glands are the predominant secretory structures of normal airways. There are increased goblet cells and hypertrophy of submucosal glands in the CF airways, which leads to an increase in secretions and sputum production. Airway secretions are relatively dehydrated and viscous. Thick and viscid mucus is such a common feature that at one time the disease was referred to as "mucoviscidosis."

Mucociliary clearance is variable in CF, with some patients having severe impairment and others having normal clearance. The reduction in clearance is believed to be caused by the increased volume of respiratory secretions and the abnormally thick mucus. Studies have shown the cilia from patients with CF to be normal, although chronic inflammation may result in a loss of ciliated cells.

BACTERIAL INFECTION

The presence of endobronchial pathogens changes with age. *Staphylococcus aureus* and *Haemophilus influenzae* typically appear early in life, with *S. aureus* reaching maximum prevalence at 6 to 17 years of age and *H. influenzae* peaking at 2 to 5 years of age. A distinctive feature of CF is increased susceptibility to chronic airway colonization and infection with *Pseudomonas aeruginosa.* Median age of acquisition is very early in life, around 1 year. More than 73% of adults with CF in the United States are chronically infected with *Pseudomonas*.[6] It is strongly associated with accelerated lung function decline and survival. Once there is colonization of the airways, *Pseudomonas* is often difficult to eradicate despite aggressive antibiotic therapy.

Infection with *Burkholderia cepacia* complex occurs in about 2.5% of patients with CF.[4] It was identified as an important pathogen in CF in the early 1980s. This organism demonstrates *in vitro* resistance to a number of antibiotics. Infection may result in acute necrotizing pneumonia and septic shock. Once colonization occurs, there is the possibility of catastrophic deterioration and a poorer prognosis for survival. It is often transmitted either directly or indirectly by person-to-person transmission, with risk factors including hospitalization and having a colonized sibling. The emergence of *B. cepacia* complex has profoundly affected infection control policies and has caused a change in activities and visitation among children with CF.[21] The most common isolates in CF are *B. multivorans* (genomovar II) and *B. cenocepacia* (genomovar III), the latter of which is associated with more rapid clinical deterioration. The prevalence of methicillin-resistant *S. aureus* (MRSA) has also increased over the last decade[22] and has been associated with poorer outcomes compared with patients who have never been culture positive for MRSA.[23]

Patients with CF who do not respond to antimicrobial agents may have colonization of other organisms. These include *Stenotrophomonas maltophilia, Achromobacter xylosoxidans,* nontuberculous mycobacteria (particularly *Mycobacterium avium* complex and *M. abscessus* complex), and *Aspergillus* species.

AIRWAY INFLAMMATION

Inflammation of the airways is a major component of CF and may occur early in the disease process. Recent studies of bronchoalveolar lavage fluid from infants suggest that airway inflammation is present in those as young as 4 weeks old, likely occurring before infection. An abundance of neutrophils and the enzyme neutrophil elastase may be responsible for the airway destruction and inflammatory response found in the lungs of patients with CF.

CLINICAL MANIFESTATIONS

Nearly half of all patients with CF are diagnosed as a result of pulmonary symptoms. The diagnosis of CF should be considered in every patient who presents with chronic or recurrent lower respiratory tract disorders, including bronchitis, bronchiectasis, pneumonia, and refractory asthma. Children with CF have frequent pulmonary exacerbations, with the most consistent feature being a chronic cough. The cough may be dry and hacking or paroxysmal, with the patient gagging, choking, or even vomiting during coughing episodes. Sputum often becomes mucopurulent and difficult to expectorate. Other symptoms include tachypnea, retractions, dyspnea, and use of accessory muscles. Occasionally, patients will present with hemoptysis and fever. Wheezing, crackles, rhonchi, and decreased air exchange are common findings during auscultation of the chest.

The chest radiograph in more advanced disease may show hyperinflation with a flattened diaphragm secondary to air trapping (Figure 28-2). Mucus plugging and patchy atelectasis can also be seen. Diffuse fibrosis, bronchial wall thickening, and bronchiectasis are found predominantly in the upper lobes. Over time, however, all of the lung fields become involved. Pneumothorax occurs most often in older patients with more advanced disease and is a result of ruptured subpleural blebs. The recurrence rate is high at 50% to 90%.[24] The progressive lung disease and chronic hypoxemia lead to an increase in pulmonary vascular resistance, pulmonary hypertension, and cor pulmonale. As cor pulmonale progresses,

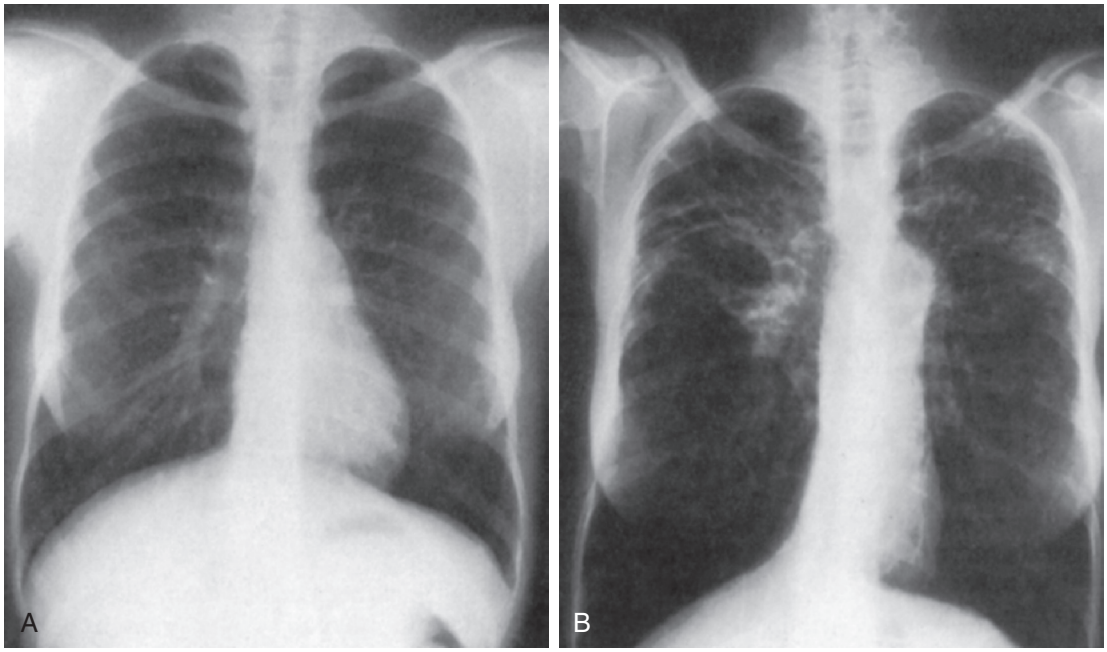


FIGURE 28-2 Cystic fibrosis. Chest radiographs from a patient at age 14 years **(A)** and 22 years **(B)** illustrating the changes of advancing disease.

the electrocardiogram shows thickening in the wall and enlargement of the right ventricle.

Pulmonary function testing initially demonstrates air flow obstruction. As the disease progresses, both a restrictive and an obstructive pattern can be seen, along with a decrease in air flow. About 50% of patients with CF have a positive methacholine challenge test, which indicates airway hyperreactivity. Digital clubbing and pulmonary hypertrophic osteoarthropathy are universal findings in CF patients with advanced pulmonary disease. Acute pulmonary exacerbations of CF vary in severity and are usually defined by subjective symptoms. Although there is no clear definition of a CF exacerbation,[25] most are associated with the characteristics found in Box 28-3.

Box 28-3 Signs and Symptoms of a Pulmonary Exacerbation in Cystic Fibrosis

- Increased cough
- Increased sputum production
- Change in sputum appearance
- Hemoptysis
- Dyspnea
- Tachypnea
- Chest pain
- Change in findings of chest physical examination
- Decrease in oxyhemoglobin saturation
- Change in chest radiograph
- Deterioration in pulmonary function
- Fever
- Weight loss
- Decreased appetite
- Increased fatigue
- Decreased exercise tolerance

TREATMENT OF PULMONARY DISEASE

Treatment of the pulmonary manifestations of CF focuses on routine therapy aimed at physically removing thickened mucus from the airways and pharmacologic control of infection with aggressive use of antibiotics.[26] Each of the various components of respiratory care for a child with CF is described in detail.

AEROSOL THERAPY

Aerosol therapy is an important aspect of CF respiratory care in the hospital and in the home. A number of medications designed to address specific aspects of CF pulmonary disease are used and are described in this section. Put together, a commonly used sequence is as follows: bronchodilator, hypertonic saline, recombinant human DNAse, airway clearance therapy, maintenance medication (inhaled corticosteroid or antibiotic). A more detailed discussion of aerosol therapy can be found in Chapter 11.

Bronchodilators

Airway hyperreactivity is common in most patients with CF. Inhalation of a bronchodilator followed by an airway clearance technique is the most common treatment regimen used routinely between exacerbations. Medications used most often include short-acting β2-agonists, such as albuterol, and anticholinergic agents, such as ipratropium bromide. The medication is delivered with either a metered-dose inhaler or a nebulizer. Although bronchodilators are routinely used, their responsiveness has been shown to be variable in patients with CF. Occasionally a patient worsens after bronchodilator therapy. In these patients,

treatment with ipratropium bromide has resulted in significant improvement in pulmonary function, especially in adult patients. Some patients respond better to combination therapy using albuterol and/or ipratropium bromide. Finally, it is important to evaluate for allergic bronchopulmonary aspergillosis (ABPA) in situations of marked wheezing and deteriorating lung function despite seemingly appropriate medical management.

Mucolytic Agents

The sputum of patients with CF not only is produced in greater abundance but also has abnormal viscosity. This is believed to be caused by increased glycoprotein sulfation and the high concentrations of DNA released from dead neutrophils.

Recombinant human DNAse (rhDNAse) has been developed to reduce the viscosity of purulent CF sputum. The synthetically produced rhDNase breaks up thickened mucus by disrupting the long, sticky DNA molecules, thereby eliciting significant improvement in the lung function of patients with mild pulmonary disease after receiving aerosolized rhDNase.

Nebulized 7% hypertonic saline is used to facilitate airway clearance by rehydrating the airway surface layer. Because hypertonic saline causes bronchospasm in some patients, it is generally recommended to premedicate with a β2-agonist. In general, it has been found to be an inexpensive, safe, effective additional therapy in CF patients with stable lung function. Its use has been associated with a modest improvement in lung function and reduced frequency of pulmonary exacerbations.[27] A systematic review concluded that incorporation of hypertonic saline is beneficial in the routine care of children with CF who are older than 6 years of age.[28]

AIRWAY CLEARANCE THERAPY

As discussed earlier, the pathophysiology of CF lung disease involves the production of thick, viscous airway secretions resulting in a perpetual cycle of small airway obstruction, inflammation, and infection. Thus, airway clearance therapies are a fundamental aspect of routine and acute respiratory care. A more detailed discussion of the various techniques and devices can be found in Chapter 12. There are limited data to establish the superiority of any airway clearance therapy modality over others.[29] Thus selection of a particular airway clearance technique or device will largely depend on a combination of factors, including patient age, disease severity, tolerance, perceived benefit, feasibility, and personal preference. It is very common for an airway clearance therapy regimen to evolve as the child matures.

ANTIBIOTICS

Aerosolized antibiotics such as tobramycin are often used as chronic suppressive therapy to treat patients infected with *P. aeruginosa* in order to prolong the time between pulmonary exacerbations and slow the progression of lung function decline. A unit dose of 300 mg/5 mL is considered standard. It is given twice a day for 28-day cycles every other month. Additional inhaled antibiotics with antipseudomonal activity include aztreonam and colistin. However, the main focus in the treatment of pulmonary symptoms continues to be secretion removal and antibiotic therapy. Because the airway infection cannot be eradicated, the goal of antibiotic therapy in the treatment of CF is suppression of the infecting organism to a level at which clinical symptoms are minimal.

Antibiotic Selection

Antibiotic therapy is usually given for 2 weeks during pulmonary exacerbations. Antibiotics can be administered orally, by nebulization, or intravenously. The choice of antibiotic is based on results of the individual patient's sputum or throat culture and the *in vitro* sensitivity profile of the specific organism. Agents known to be particularly effective against *S. aureus* and *Pseudomonas* species are usually chosen. For patients infected with *P. aeruginosa,* combination therapy with a β-lactam and an aminoglycoside is typically administered. Ciprofloxacin is a common choice of oral antibiotic. Therapy can be extended to cover *S. aureus* if it is also present in the sputum. Because of abnormal pharmacokinetics of most antibiotics in patients with CF, a higher than normal dose is usually required to achieve therapeutic levels.

Hospitalization

Advances in providing stable long-term vascular access have allowed intravenous administration of antibiotics at home, with the patient continuing school activities. Criteria for proceeding with hospitalization and intravenous therapy include severe illness, but also moderate illness that is unresponsive to home therapy, or even mild illness complicated by growth failure. If a patient does not respond to outpatient management, hospitalization is recommended, with a 10- to 21-day course of intensive antibiotic therapy. Hospitalization for a pulmonary exacerbation also includes aggressive treatment to remove secretions. Despite timely and aggressive medical therapy, one registry study observed that upwards of 25% of patients fail to recover baseline lung function after an exacerbation.[30]

ANTIINFLAMMATORY AGENTS

Because inflammation of the airways is a significant aspect of CF pathophysiology, antiinflammatory agents are an important part of the treatment regimen.

Macrolide Antibiotics

Macrolides are a relatively recent addition to the list of available antiinflammatory agents. The specific mechanisms by which they improve CF pulmonary disease is not fully understood, but they are believed to be related, in part, to their immunomodulatory effects.[31]

Azithromycin is given (in doses of 250 mg or 500 mg for those weighing less than or greater than 40 kg, respectively) three times per week. There are limited data on potential long-term side effects with prolonged therapy, though recent reports have suggested a possible increase in risk for nontuberculous mycobacterial infection.[32]

Corticosteroids

Systemic corticosteroids have been shown in clinical trials to improve lung function; however, side effects are serious and include growth suppression and increased susceptibility to osteoporosis and cataracts. They may, however, play a limited role in the management of acute pulmonary exacerbations. Studies have reported using inhaled corticosteroids in CF with improvement in lung function and respiratory symptoms, but the studies had small sample sizes, and they are currently not recommended for routine use unless there is evidence of an asthma component warranting chronic therapy.

Ibuprofen

Ibuprofen has been demonstrated to slow the progression of lung disease over a 2-year period. However, specific dosing and close pharmacokinetic monitoring are required when using this medication.[33]

LUNG TRANSPLANTATION

Lung transplantation is an option for CF patients with severe and end-stage lung disease.[34] There has been no evidence of redevelopment of CF in transplanted lungs, but new problems related to lung rejection and opportunistic infection in patients receiving immunosuppressive agents can occur. Although more than 200 patients with CF underwent first-time lung transplantation in 2010,[6] the rate of decline of forced expiratory volume in 1 second (FEV_1) as well as worsening of clinical status are key factors in determining the timing of referral for lung transplantation. In addition, the median regional waiting period for donor lungs for patients with CF may assist in the timing of referral. Chapter 21 provides a thorough discussion of lung transplantation.

SMALL-MOLECULE CFTR MODULATORS

With the approval of ivacaftor by the US Food and Drug Administration in January 2012 came a radical shift in the approach to CF care and management. All the treatment modalities discussed thus far in this chapter have focused on the downstream effects of CFTR dysfunction. Ivacaftor and other small-molecule CFTR modulators currently in development represent a class of medications specifically designed to reverse the underlying cause of CF-related disease. Ivacaftor is an oral CFTR "potentiator," increasing chloride transport function among individuals with at least one copy of the G551D (class III) mutation.[35] Another class of CFTR modulators is the CFTR "correctors," which are designed to facilitate intracellular trafficking of the CFTR protein to the cell surface.[36] The long-term benefits and potential side effects of small-molecule CFTR modulators remain to be seen. Nevertheless, this represents a significant step toward the development of personalized, allele-specific therapy.

NONPULMONARY MANIFESTATIONS

Although pulmonary compromise is the main factor that limits longevity in patients with CF, there are a number of other organ systems affected by the disease. Certain conditions can prompt consideration of the diagnosis of CF. Common conditions include **meconium ileus** (obstruction of the small bowel with meconium in neonates), prolonged neonatal jaundice, rectal prolapse, and **failure to thrive** (global growth failure).

UPPER AIRWAY DISORDERS

Nearly all patients with CF have sinusitis, most often involving the maxillary and ethmoid sinuses. It is often difficult to control despite oral and intravenous antibiotic therapy. The abnormally thick mucus that is characteristic of CF occludes the sinus passages and prevents drainage. These patients also have a high incidence of nasal polyps, which occur most often in older children and adolescents. More than half of patients who require surgical removal of polyps experience a recurrence. CF should be suspected in children who present with chronic sinusitis and nasal polyposis.

GASTROINTESTINAL DISORDERS

Pancreatic Insufficiency

More than 90% of patients with CF have pancreatic insufficiency. CFTR dysfunction results in insufficient secretion of pancreatic fluid, which causes plugging and obstruction of the pancreatic ducts. Siblings with CF often share similar degrees of pancreatic insufficiency. Symptoms are controlled with supplementation of pancreatic enzymes. Therapy is individualized to weight and caloric intake, and supplements must be taken at each meal. Formula-fed and breastfed infants require supplementation with each feeding, and older children also require supplementation with snacks.

Failure of the pancreas to produce sufficient enzymes results in malabsorption of fat and protein. The presence of steatorrhea, which is excessive loss of fat in the stool, is often the first indication of CF. These children frequently produce bulky, foul-smelling, oily stools and may experience rectal prolapse. Complaints of constipation or stomach cramps, especially after eating, can lead to a decrease in appetite and oral intake. Infants often present with failure to thrive, failing to gain weight despite a voracious appetite and failing to meet developmental milestones. Other clinical consequences include hypoproteinemia with or without edema and deficiency of vitamins A, D, E, and K.

The incidence of diabetes mellitus is much greater in children with CF than in the general pediatric population.[37] As fibrosis of the pancreas progresses, endocrine function becomes affected, and CF-related diabetes (CFRD) can develop. At 10 years of age, there is an increasing incidence of CFRD, and annual screening with an oral glucose tolerance test is recommended. Weight loss is usually the first symptom. Initiation of insulin therapy has been associated with increased body mass and improved lung function.

Meconium Ileus and Distal Intestinal Obstruction Syndrome

Failure to secrete water into the gut is another manifestation of CFTR dysfunction, and abnormal intestinal electrolyte and water transport can lead to a number of disorders. The earliest clinical manifestation of CF may be meconium ileus. Occurring at birth, nearly every full-term infant who has meconium ileus is considered to have CF until proven otherwise. Presentation includes abdominal distention, vomiting, and abdominal radiographs showing distended loops of bowel with gas bubbles trapped among meconium, giving a ground-glass appearance. With an incidence higher in older patients, distal intestinal obstruction syndrome occurs when the thick, sticky stool of a patient with CF adheres to the bowel wall and obstructs the small intestine and colon. Only rarely is this seen in a patient with pancreatic sufficiency.

Rectal Prolapse

Episodes of rectal prolapse are related to malnutrition, abnormal stooling patterns (e.g., diarrhea, constipation), and increased abdominal pressure with frequent coughing. Onset rarely occurs after 5 years of age. The association with CF is so great that a sweat test should be considered in any child presenting with rectal prolapse.

Gastroesophageal Reflux Disease

Patients with CF often experience heartburn and gastric reflux, especially those with advanced pulmonary disease. This may be the result of frequent coughing and increased abdominal pressure. Treatment includes dietary restrictions and often long-term acid-suppression therapy with proton pump inhibitors or histamine-2 blockers.

HEPATOBILIARY DISORDERS

The hepatobiliary manifestations of CF occur less often than the gastrointestinal disorders. Serious complications are uncommon before adolescence. Cirrhosis and portal hypertension are the most common hepatic disorders that occur in patients with CF, although only 2% to 4% of patients develop any apparent liver disease.[38] Prolonged neonatal jaundice may also occur in neonates and should raise suspicion for CF.

Gallbladder abnormalities are common in patients with CF. Microgallbladder is the most common biliary tract disorder. It is believed that mucus obstruction of the cystic duct results in atrophy of the gallbladder. Most patients are asymptomatic. The incidence of abnormalities increases with age, with gallstones occurring quite commonly in patients with pancreatic insufficiency. Cholecystectomy is considered in patients who are symptomatic with recurrent abdominal pain.

PROGNOSIS

Earlier diagnosis through the recent establishment of nationwide newborn screening and advances in CF care has resulted in continually improving outcomes, including survival. In 2010 the median predicted age of survival was 38 years, substantially increased from 27 years in 1986.[39] This is a long stride from the life expectancy of less than 1 year when CF was described by Anderson in the late 1930s.[1] Although patients with CF continue to survive longer, some children still succumb to the disease before reaching adulthood despite advances in diagnostic techniques and treatment. Various factors influence a patient's prognosis, including the progression of pulmonary disease, the involvement of other organ systems, nutritional status, and the home environment. Investigations to better understand and even modify these factors will make a difference in the lives of many children. The respiratory therapist is an essential member of the CF multidisciplinary team delivering direct care to every patient. In addition, the therapist assesses, teaches, and periodically reviews the most effective airway clearance technique for each patient.

Key Points

- CF is a clinical diagnosis corroborated by laboratory testing (biochemical and/or genetic).
- CFTR dysfunction results in thick and viscous secretions in the airways and other organ systems.
- Most CF care and management focuses on the downstream effects of CFTR dysfunction (airway clearance, antiinflammatory agents, antibiotics, nutrition), though there may soon be an increase in the use of medications that reverse the underlying cause of CF-related disease.
- Although lung disease is the primary cause of morbidity and mortality, there are a number of nonpulmonary manifestations of CF.
- With advancements in many aspects of CF care, overall prognosis continues to improve.

Assessment Questions

See Evolve Resources for the answers.

1. Which of the following is true regarding the diagnosis of cystic fibrosis (CF)?
   - **A.** The sweat chloride concentration is 60 mmol/L or greater.
   - **B.** CFTR mutation analyses may be helpful when considering a diagnosis of CF.
   - **C.** Nasal transepithelial potential difference measurements may assist in the diagnosis of CF.
   - **D.** There may or may not be a history of CF in a sibling.
   - **E.** All of the above
2. The increased production of thick, viscous airway secretions in a patient with CF is caused by all of the following except:
   - **A.** Abnormal cilia
   - **B.** Increased goblet cells
   - **C.** Hypertrophied submucosal glands
   - **D.** A and C
3. CF can present with which of the following signs and symptoms?
   - **A.** Chronic airway obstruction
   - **B.** Pancreatic insufficiency and malnutrition
   - **C.** Male infertility
   - **D.** Clubbing of the nail beds
   - **E.** All of the above
4. Bacterial pathogens commonly encountered in an individual with CF include all of the following except:
   - **A.** *Staphylococcus aureus*
   - **B.** *Pseudomonas aeruginosa*
   - **C.** *Burkholderia cepacia* complex
   - **D.** *Salmonella* species
   - **E.** *Haemophilus influenzae*
5. Which of the following factors influences selection of a particular airway clearance therapy method?
   - **A.** Patient age
   - **B.** Disease severity
   - **C.** Perceived benefit
   - **D.** Personal preference
   - **E.** All of the above
6. Which of the following medications are used in the management of CF pulmonary disease?
   - **A.** Albuterol
   - **B.** Ipratropium bromide
   - **C.** Nebulized antibiotics such as tobramycin
   - **D.** Nebulized 7% hypertonic saline
   - **E.** All of the above
7. The chest radiograph of a patient with CF can have all of the following except:
   - **A.** Hyperinflation with flattened diaphragm
   - **B.** Diffuse fibrosis and bronchiectasis
   - **C.** Blebs and pneumothoraces
   - **D.** Patchy atelectasis
   - **E.** All of these radiographic findings may be seen
8. Which of the following is true regarding small-molecule CFTR modulators?
   - **A.** Ivacaftor, an oral CFTR potentiator, is indicated for all patients with CF.
   - **B.** Unlike other treatments to date, they represent a new class of medications that are designed to reverse the underlying cause of CF-related disease.
   - **C.** Data on the long-term benefits and potential side effects are not yet available.
   - **D.** B and C
9. In 2010 the median predicted age of survival among patients with CF was _____ years.
   - **A.** 10
   - **B.** 15
   - **C.** 25
   - **D.** 38
10. The most common upper airway problems experienced by children with CF include:
    - **A.** Nasal polyps
    - **B.** Sinusitis
    - **C.** Croup
    - **D.** Subglottic stenosis
    - **E.** A and B

REFERENCES

1. Anderson DH. Cystic fibrosis of the pancreas and its relation to celiac disease: a clinical and pathological study. *Am J Dis Child*. 1938;56:344.
2. Cohen-Cymberknoh M, Shoseyov D, Kerem E. Managing cystic fibrosis: strategies that increase life expectancy and improve quality of life. *Am J Respir Crit Care Med*. 2011;183:1463.
3. Rosenstein BJ, Cutting GR. The diagnosis of cystic fibrosis: a consensus statement. Cystic Fibrosis Foundation Consensus Panel. *J Pediatr*. 1998;132:589.
4. National Newborn Screening and Genetics Resource Center. *National Newborn Screening Report—2000*. Austin, TX: NNSGRC; 2003.
5. Hamosh A, FitzSimmons SC, Macek Jr M, Knowles MR, Rosenstein BJ, Cutting GR. Comparison of the clinical manifestations of cystic fibrosis in black and white patients. *J Pediatr*. 1998;132:255.
6. Patient Registry Annual Data Report 2010. Bethesda, MD: Cystic Fibrosis Foundation; 2011.
7. Riordan JR, Rommens JM, Kerem B, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. *Science*. 1989;245:1066.
8. Guggino WB, Banks-Schlegel SP. Macromolecular interactions and ion transport in cystic fibrosis. *Am J Respir Crit Care Med*. 2004;170:815.
9. Mishra A, Greaves R, Smith K, et al. Diagnosis of cystic fibrosis by sweat testing: age-specific reference intervals. *J Pediatr*. 2008;153:758.
10. Moskowitz SM, Chmiel JF, Sternen DL, et al. Clinical practice and genetic counseling for cystic fibrosis and CFTR-related disorders. *Genet Med*. 2008;10:851.

11. Kerem E. Pharmacological induction of CFTR function in patients with cystic fibrosis: mutation-specific therapy. *Pediatr Pulmonol*. 2005;40:183.
12. McKone EF, Emerson SS, Edwards KL, Aitken ML. Effect of genotype on phenotype and mortality in cystic fibrosis: a retrospective cohort study. *Lancet*. 2003;361:1671.
13. Bombieri C, Claustres M, De Boeck K, et al. Recommendations for the classification of diseases as CFTR-related disorders. *J Cyst Fibros*. 2011;10:S86.
14. Sermet-Gaudelus I, Girodon E, Sands D, et al. Clinical phenotype and genotype of children with borderline sweat test and abnormal nasal epithelial chloride transport. *Am J Respir Crit Care Med*. 2010;182:929.
15. 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:S4.
16. Balfour-Lynn IM. Newborn screening for cystic fibrosis: evidence for benefit. *Arch Dis Child*. 2008;93:7.
17. 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:S106.
18. Ren CL, Desai H, Platt M, Dixon M. Clinical outcomes in infants with cystic fibrosis transmembrane conductance regulator (CFTR) related metabolic syndrome. *Pediatr Pulmonol*. 2011;46:1079.
19. Rosenfeld M, Emerson J, McNamara S, et al. Risk factors for age at initial Pseudomonas acquisition in the cystic fibrosis EPIC observational cohort. *J Cyst Fibros*. 2012;11:446.
20. Ratjen FA. Cystic fibrosis: pathogenesis and future treatment strategies. *Respir Care*. 2009;54:595.
21. Mahenthiralingam E, Baldwin A, Dowson CG. Burkholderia cepacia complex bacteria: opportunistic pathogens with important natural biology. *J Appl Microbiol*. 2008;104:1539.
22. Goss CH, Muhlebach MS. Review: Staphylococcus aureus and MRSA in cystic fibrosis. *J Cyst Fibrosis*. 2011;10:298.
23. Dasenbrook EC, Checkley W, Merlo CA, Konstan MW, Lechtzin N, Boyle MP. Association between respiratory tract methicillin-resistant Staphylococcus aureus and survival in cystic fibrosis. *JAMA*. 2010;303:2386.
24. Flume PA. Pneumothorax in cystic fibrosis. *Curr Opin Pulm Med*. 2011;17:220.
25. Goss CH, Burns JL. Exacerbations in cystic fibrosis. 1: epidemiology and pathogenesis. *Thorax*. 2007;62:360.
26. Cystic Fibrosis Foundation, Borowitz D, Robinson KA, et al. Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. *J Pediatr*. 2009; 155:S73.
27. Donaldson SH, Bennett WD, Zeman KL, Knowles MR, Tarran R, Boucher RC. Mucus clearance and lung function in cystic fibrosis with hypertonic saline. *N Engl J Med*. 2006; 354:241.
28. Wark P, McDonald VM. Nebulised hypertonic saline for cystic fibrosis. *Cochrane Database Syst Rev*. 2009;(2);CD0011506.
29. Flume PA, Robinson KA, O'Sullivan BP, et al. Cystic fibrosis pulmonary guidelines: airway clearance therapies. *Respir Care*. 2009;54:522.
30. Sanders DB, Bittner RC, Rosenfeld M, Hoffman LR, Redding GJ, Goss CH. Failure to recover to baseline pulmonary function after cystic fibrosis pulmonary exacerbation. *Am J Resp Crit Care Med*. 2010;182:627.
31. Wagner T, Burns JL. Anti-inflammatory properties of macrolides. *Pediatr Infect Dis J*. 2007;26:75.
32. Renna M, Schaffner C, Brown K, et al. Azithromycin blocks autophagy and may predispose cystic fibrosis patients to mycobacterial infection. *J Clin Invest*. 2011;121:3554.
33. Konstan MW, Schluchter MD, Xue W, Davis PB. Clinical use of ibuprofen is associated with slower FEV1 decline in children with cystic fibrosis. *Am J Respir Crit Care Med*. 2007; 176:1084.
34. Braun AT, Merlo CA. Cystic fibrosis lung transplantation. *Curr Opin Pulm Med*. 2011;17:467.
35. Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med*. 2011;365:1663.
36. Van Goor F, Hadida S, Grootenhuis PD, et al. Correction of the F508del-CFTR protein processing defect in vitro by the investigational drug VX-809. *Proc Natl Acad Sci U S A*. 2011;108:18843.
37. Moran A, Brunzell C, Cohen RC, et al. Clinical care guidelines for cystic fibrosis–related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. *Diabetes Care*. 2010;33:2697.
38. Colombo C. Liver disease in cystic fibrosis. *Curr Opin Pulm Med*. 2007;13:529.
39. CFF Patient Registry. *2012 Annual Data Report to the Center Directors*. Bethesda, MD: Cystic Fibrosis Foundation; 2013.

29 Acute Respiratory Distress Syndrome

Jordan S. Rettig*

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. Define the criteria to diagnose acute respiratory distress syndrome.
2. Describe the pathologic stages of acute respiratory distress syndrome.
3. Describe the pathophysiology of acute respiratory distress syndrome.
4. Describe the role of brain–lung crosstalk.
5. Explain the clinical approach to the management of a patient with acute respiratory distress syndrome.
6. Apply appropriate ventilator strategies in conventional mechanical ventilation of patients with acute respiratory distress syndrome.
7. Outline adjunct therapies in the management of acute respiratory distress syndrome.
8. Understand the role of high-frequency ventilation and extracorporeal membrane oxygenation in the management of acute respiratory distress syndrome.

Key Terms

acute lung injury
acute respiratory distress syndrome
hypoxemia
inflammatory mediators
brain-lung crosstalk
lower inflection point
low tidal volume ventilation
open lung strategy
oxygenation index
permissive hypercapnia

Acute respiratory distress syndrome (ARDS) is an **acute lung injury** characterized by pulmonary edema and alveolar collapse secondary to the disruption of the alveolar–capillary membrane and surfactant dysfunction. Subsequently **hypoxemia** and widespread infiltrates on chest radiograph can occur. This sequence of events may be triggered by both pulmonary and nonpulmonary insults. Pulmonary edema in the absence of heart failure was described nearly a century ago. These conditions were originally characterized by the inciting injury rather than the resulting clinical manifestation and included such names as *shock lung*, *noncardiogenic pulmonary edema*, and *traumatic wet lung*.[1] In 1967, Ashbaugh and colleagues[2] recognized ARDS in 12 patients as a constellation of pathophysiologic findings, highlighting ARDS as a final common pathway initiated by a variety of insults.

DEFINITION

ARDS is a diffuse, hypoxemic acute lung injury. Radiographically, there are bilateral areas of consolidation with air bronchograms that reflect alveolar filling and atelectasis (Figure 29-1). Clinically, the patient demonstrates moderate to severe respiratory failure, hypoxemia, and decreased pulmonary compliance. The

*The author would like to acknowledge the contributions of the former authors, Jan Hau Lee and Ira M. Cheifetz.

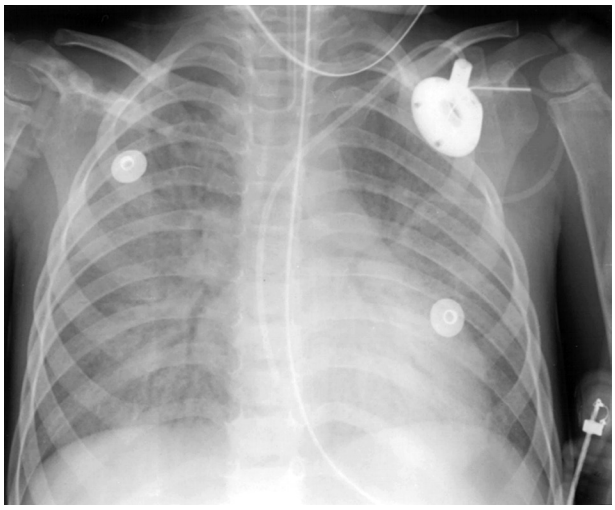


FIGURE 29-1 Chest radiograph of a patient with acute respiratory distress syndrome (ARDS). Note the infiltrates in all five lobes, the air bronchograms that appear as a result of areas of consolidation, and the loss of lung volume.

American-European Consensus Conference on ARDS (AECC) was assembled in 1994 to codify the definition of ARDS and clinical criteria for diagnosis (Table 29-1).[3] The AECC definition has facilitate many landmark trials in ARDS. However, there are important limitations to this definition. The time frame of "acute onset" was not specifically defined, there was often moderate interobserver variability in defining bilateral infiltrates on chest radiographs, and some patients with ARDS have elevated pulmonary artery wedge pressure because of increased pleural pressure or aggressive fluid resuscitation.

To address these limitations, a consensus panel was held in Berlin in 2011 to revise the definition for ARDS (see Table 29-1).[4,5] In contrast to the AECC definition, the Berlin definition specifies the time frame for the development of ARDS, better defines the nature of infiltrates on radiologic investigation, and incorporates both positive end-expiratory pressure (PEEP) and the Pao_2/Fio_2 ratio to define the severity of hypoxemia.

In 2015 the Pediatric Acute Lung Injury Consensus Conference (PALICC) Group recommended a definition for Pediatric ARDS (PARDS). Among other changes, the **oxygenation index** (OI) is used to determine level of severity for patients receiving invasive mechanical ventilation, with mild being OI of less than 8, moderate being 8 or more but below 16, and severe being OI of 16 or more. The term *acute lung injury* from the Berlin definition is no longer used[6] (Table 29-1).

The oxygenation index (OI)[7-10]:

$$OI = (\overline{Paw} \times Fio_2) / Pao_2 \times 100$$

where $\overline{Paw}$ is the mean airway pressure, Fio_2 is the fraction of inspired oxygen, and Pao_2 is the arterial oxygen tension. The OI equation accounts not only for the ratio of administered Fio_2 to arterial oxygenation but also the mean airway pressure during mechanical ventilation support. OI has been correlated with outcome, can be objectively used to define entry or response criteria for clinical studies, and can describe

Table 29-1 Definition of Pediatric ARDS

Age	Exclude patients with perinatal-related lung disease			
Timing	Within 7 days of known clinical insult			
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload			
Chest imaging	Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease			
Oxygenation	Noninvasive mechanical ventilation		Invasive mechanical ventilation	
	PARDS (no severity stratification)	Mild	Moderate	Severe
	Full face mask bilevel ventilation or CPAP ≥5 cm H_2O[2] PF ratio ≤ 300 SF ratio ≤ 264[1]	4 ≤ OI < 8 5 ≤ OSI < 7.5[1]	8 ≤ OI ≤ 16 7.5 ≤ OSI ≤ 12.3[1]	OI ≥ 16 OSI ≥ 12.3[1]
Special Populations				
Cyanotic heart disease	Standard criteria above for age, timing, origin of edema, and chest imaging with an acute deterioration in oxygenation not explained by underlying cardiac disease.[3]			
Chronic lung disease	Standard criteria above for age, timing, and origin of edema with chest imaging consistent with new infiltrate and acute deterioration in oxygenation from baseline that meet oxygenation criteria above.[3]			
Left ventricular dysfunction	Standard criteria for age, timing, and origin of edema with chest imaging changes consistent with new infiltrate and acute deterioration in oxygenation that meet criteria above not explained by left ventricular dysfunction.			

OI, Oxygenation index; *OSI*, oxygen saturation index; *PARDS*, pediatric acute respiratory distress syndrome.

criteria for more highly invasive therapies such as extracorporeal membrane oxygenation (ECMO).[7-10]

ETIOLOGY

ARDS can be caused by numerous insults that both directly and indirectly affect the lung via the generation of **inflammatory mediators.** Direct pulmonary insults include pneumonia, aspiration, chest trauma, and smoke inhalation. Indirect lung injury may be the result of generalized systemic conditions, such as sepsis, closed head injury, multiple trauma, transfusion reactions, and hemorrhagic shock. Although numerous insults may generate an inflammatory response, innate genetic differences regulate the immune responses of the lungs and are important in pathogenesis and determining mortality from ARDS.[11,12]

PREVALENCE

The diversity of underlying causes makes it difficult to determine the true prevalence of ARDS. Several studies agree that of all adult intensive care unit (ICU) admissions, approximately 7% of patients meet the AECC ARDS diagnosis criteria.[3,9,13,14] A European study (ALIVE) involving 78 ICUs from nine countries in which all patients (n = 5457) were admitted to one of the participating units for at least 4 hours during a 2-month study period reported that 7.4% had, or developed, ALI/ARDS.[15]

The prevalence of PARDS appears to be lower than for adults.[16,17] A recent study conducted in Europe involving 21 pediatric ICUs (PICUs) showed a much lower incidence rate of 3.9 per 100,000 person-years in children 15 years old or younger.[18] The low incidence of ARDS in children is also reflected by the fact that ARDS accounted for a small proportion (1.4% to 2.7%) of all PICU admissions.[19,20]

There are important limitations when trying to quantify ARDS in pediatric patients based on the Berlin and AECC definitions. The PALICC group highlights the following important limitations: (1) definitions requiring direct measurement of Pao_2 may underestimate ARDS prevalence in children where arterial access may be less likely; (2) the P/F ratio may be altered by ventilator manipulation and PEEP management; and (3) differences in risk factors, etiologies, pathophysiology, and outcomes between adults and children were not considered in either the AECC or Berlin definitions. Therefore it is unclear whether there is an accurate understanding of the true incidence of ARDS in pediatric patients.[21] What remains clear is that ARDS or PARDS is a low-frequency event in the PICU, but the patients are some of the most challenging to manage.

CLINICAL COURSE

The main function of the respiratory system is to provide adequate oxygenation and carbon dioxide elimination. The term *respiratory distress* indicates that the patient is using compensatory mechanisms to preserve adequate gas exchange. Respiratory failure is a late clinical finding resulting from the failure of these compensatory mechanisms. In the setting of respiratory failure, the lungs are unable to preserve adequate gas exchange. Subsequently, tissue oxygen delivery can be impaired, resulting in anaerobic metabolism and lactic acid formation. Additionally, hypercapnia and worsening acidosis are the result of inadequate ventilation. In patients with ARDS, impairment of oxygenation is typically an early finding, whereas impairment of ventilation occurs much later in the disease process.[22]

Respiratory disease, especially in infants and young children, can rapidly progress from respiratory distress to the acute onset of respiratory failure and significant impairment in gas exchange. Although respiratory failure is classically described by arterial blood gas values (Pao_2 less than 60 mm Hg and/or $Paco_2$ greater than 50 mm Hg), clinically it is best recognized at the bedside as a syndrome of the progression of the physical signs and symptoms of respiratory distress. Infants and young children are particularly prone to developing respiratory distress and failure because of the following:

- Smaller caliber of airways resulting in a greater resistance to air flow
- Increased chest wall compliance, which can cause paradoxical breathing and restrict lung capacitance as a result of chest wall retractions, as may occur with forceful inspiratory effort
- Greater propensity for rapid fatigue of the respiratory muscles and the diaphragm

However, the progression of respiratory failure to ARDS is more likely to occur in adult patients, as indicated by the prevalence data described earlier.[16,17]

STAGES OF ACUTE RESPIRATORY DISTRESS SYNDROME

The clinical course of ARDS is characterized by distinct clinical, radiographic, and pathologic manifestations.[23] The first stage consists of direct or indirect acute injury to the lung tissue. Clinically patients may display mild tachypnea and dyspnea and tend to have normal radiographic findings. The second stage, or latent period, lasts a variable period after the onset of acute injury. During this time the patient may appear clinically stable but begins to develop early signs of pulmonary injury or insufficiency manifested by hyperventilation with hypocarbia and respiratory alkalosis. The chest radiograph may remain clear or may begin to demonstrate a fine reticular pattern related to the development of pulmonary interstitial fluid.[24,25]

The third stage, acute respiratory failure, is heralded by the rapid onset of respiratory failure with hypoxemia refractory to supplemental oxygen. Diffuse pulmonary edema and worsening compliance cause significant atelectasis and intrapulmonary

shunting. Clinically patients develop rapid, shallow tachypnea with increased work of breathing. The physical signs of respiratory failure vary with age and include subcostal and supraclavicular retractions, grunting (i.e., an attempt to generate an increased intrinsic PEEP), nasal flaring, and head bobbing. Lung examination usually reveals diffuse crackles on auscultation. Radiographically there are bilateral areas of consolidation with air bronchograms that reflect alveolar filling and atelectasis (see Figure 29-1).[24,25] A significant percentage of these patients will require endotracheal intubation and mechanical ventilation. However, noninvasive ventilation may be an alternative for a subgroup of patients with mild ARDS.[26,27]

MORTALITY

Most studies indicate that mortality associated with ARDS is related to nonrespiratory causes (i.e., patients die *with*, rather than *of*, ARDS).[14,28,29] In a cohort study of 416 adult patients with ARDS over a span of 8 years, Stapleton et al. reported that sepsis syndrome with multiple organ failure (MOF) is the most common cause of mortality (30%-50%), whereas respiratory failure only accounted for a small percentage (13%-9%) of deaths.[30] The severity of hypoxemia in ARDS is a risk factor for mortality. This is evident from increasing mortality rates in the three different groups under the Berlin definition (mortality rate of 27% [mild] vs. 32% [moderate] vs. 45% [severe]).[4] However, given the fact that most patients with ARDS die from causes other than directly from respiratory failure, other factors including other underlying diseases affect the mortality.[12] In adults, these factors include age, severity of disease, and predisposing conditions for ARDS.[31]

Recent published systematic reviews suggest that mortality from ARDS is declining[32,33]; however, the reason behind this overall improvement in outcome is not clear. Except for low tidal volume ventilation, no single intervention for adult ARDS has been clearly shown to decrease mortality.[34] This highlights the pressing need for development of effective management strategies for ARDS.

Mortality rates for PARDS are generally accepted as lower compared with adult ARDS. A large report of 328 PICU admissions for ARDS indicated a mortality rate of 22%.[35] This prospective evaluation additionally demonstrated that, as in adults, pneumonia, sepsis, and aspiration are the most common causes of ALI and ARDS in children. More recent data, albeit involving a smaller number of children with ARDS, showed a fairly similar mortality rate of 18%.[17] It is important to note that to date there have been no studies examining long-term mortality in PARDS.

MORBIDITY

Although mortality is an important outcome, the numbers of children dying from ARDS remains relatively low. One of the greatest challenges is to mitigate morbidity in survivors. The Berlin definition group and LUNG SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure) both showed an increase in duration of mechanical ventilation in survivors across increasing severity classes of ARDS.[36] The PARDS data is not as clear at this point, though it does indicate a similar trend.[37] Other outcomes of interest include a need for ECMO, hospital length of stay, and physical and neurocognitive function after discharge. At this time there is no recent or convincing data regarding these outcomes.[38]

PATHOLOGY AND ROLE OF IMMUNOMODULATORS

PATHOLOGY AND PATHOPHYSIOLOGY

The clinical stages of ARDS coincide with three pathologic stages, namely the exudative stage, the proliferative stage, and the fibrotic stage. The exudative stage is marked by the development of diffuse injury to the alveolar–capillary membrane. Influx of inflammatory cells and mediators destroy type I pneumocytes, resulting in sloughing of these cells and subsequent formation of a protein-rich hyaline membrane on the denuded basement membrane. Furthermore, activation of the endothelium and leukocytes results in barrier dysfunction and the formation of microthrombi within the vasculature, which contributes to the propagation of acute lung injury and alterations in pulmonary vascular tone. Disruption of both the epithelial and endothelial surfaces of the alveolar–capillary membrane significantly increases permeability and results in flooding of the alveoli with proteinaceous fluid.

The loss of the alveolar–capillary integrity and the subsequent development of pulmonary edema in both the interstitial and alveolar spaces are caused by both altered capillary permeability and oncotic gradients early in the disease process and by increases in pulmonary vascular resistance in later stages of ARDS. Pulmonary compliance is significantly worsened by the presence of edema and can result in widespread atelectasis. Pulmonary compliance is further affected by the inactivation of surfactant that results from the presence of plasma protein, such as fibrin, and inflammatory mediators, such as proteinases, in the alveolar space.[39,40] The development of microthrombi within the pulmonary vasculature together with the release of numerous vasoactive mediators from inflammatory cells and the activated endothelium contributes to the development of pulmonary hypertension and further contributes to the ventilation–perfusion abnormalities characteristic of ARDS. The degree of epithelial injury and the subsequent ability to clear edema fluid, as well as the reversibility of pulmonary hypertension are important predictors of outcome in ARDS.[41,42]

The proliferative stage occurs 1 to 3 weeks after the initiation of injury and is characterized by an attempt to repair the disrupted epithelium. This involves the

proliferation of type II pneumocytes to replace type I cells on the denuded basement membrane and to begin to replace surfactant. Although the turnover of type II cells is typically low, it accelerates after acute lung injury, and these cells may differentiate abnormally.[43,44] Epithelial repair requires not only the close coordination of numerous growth factors but also an intact basement membrane to provide a platform for cell adhesion and migration.[45] Inflammatory cells continue to be recruited to phagocytose hyaline membrane and debris, which provides a framework for the elaboration of fibrous tissue.[46] Alternatively, fibroblasts proliferate to convert hemorrhagic exudates into cellular granulation tissue.

The ability of the lung to recover depends on the presence of functional epithelium to clear the alveolar fluid and the body's ability to attenuate the inflammatory process. If lung injury and inflammation persist, the patient may develop severe physiologic abnormalities and may progress to the fibrotic stage of ARDS. This injury can be seen as early as 5 to 7 days after the onset of disease, although this is more definitive after several weeks. Histologically, the alveolar space becomes filled with mesenchymal cells, and lung tissue is replaced by collagenous tissue.[47] In addition, there is increased evidence of angiogenesis (new growth of blood vessels from preexisting ones). Vascular changes occur throughout the later stages of ARDS with obliteration of small precapillary vessels and an increase in the medial thickness of intraacinar pulmonary arteries. Overall, these changes markedly decrease the available surface area for gas exchange and result in intractable respiratory failure or chronic lung disease, potentially requiring prolonged ventilator support. Treatment strategies seek to avoid this final, intractable stage of ARDS.

INFLAMMATORY MEDIATORS

Numerous mediators of inflammation are implicated in the pathogenesis of ARDS.[48,49] It is unclear, however, whether some of these mediators directly cause ARDS or are a secondary product of the inflammation resulting from lung injury. Direct lung injury from aspiration or smoke inhalation, for example, may result in inflammation and the release of inflammatory cytokines that augment microvascular permeability. Regardless of whether inflammatory mediators are primarily or secondarily involved in the pathogenesis of ARDS, they are clearly complex contributors to its development. The effects of mediators and inflammatory cells involved in ARDS, as well as those of their regulatory molecules, are tightly interwoven and ultimately result in a balance between proinflammatory and antiinflammatory and proedematous and antiedematous factors.[50] Although inflammatory mediators could themselves disrupt the capillary–alveolar membrane, they may also create effects that keep the inflammatory response in check. This may account for the lack of success of pharmacologic inhibitors to decrease the mortality associated with ARDS. Research efforts continue to investigate potential ways to more effectively modulate the inflammatory response during ARDS.[48,50,51] Given the relatively low mortality associated with PARDS, ongoing research also focuses on finding novel biomarkers to predict both morbidity and mortality.[52,53]

BRAIN–LUNG CROSSTALK

An emerging area of research is focused on the relationship between brain and lung injury: **brain–lung crosstalk.** Acutely brain-injured patients are at risk for aspiration pneumonitis, ARDS, transfusion-associated lung injury, and neurogenic pulmonary edema (NPE). NPE has traditionally been thought to be driven by two primary mechanisms. It has been demonstrated that there is a hydrostatic component to NPE.[54] Both pulmonary and systemic vasoconstriction may occur with intracranial hypertension. Pulmonary vasoconstriction increases the pulmonary capillary hydrostatic pressure, and systemic vasoconstriction increases venous return, resulting in pulmonary edema.[55-58] The second mechanism is pulmonary capillary permeability. α-Adrenergic agonists released in response to brain injury may directly increase permeability or cause the release of secondary mediators.[59] Brain injury has also been directly associated with increased intracranial production of other proinflammatory mediators and subsequent release of these mediators into the systemic circulation, resulting in lung injury.[60,61] Patients with significant neurologic injury will likely develop pulmonary complications and may develop ARDS.

Traditional concepts of lung protective ventilation may prove difficult in acutely brain injured patients because of the need for neurologically protective measures, such as mitigating intracranial pressure by maintaining normal levels of carbon dioxide.[62] Altering ventilator strategies to provide neurologic protection may put the patient at greater risk of ventilator-induced lung injury (VILI). As always, it is important to balance lung protection with the need to support other organ systems.

PULMONARY MECHANICS

ARDS alters pulmonary mechanics in several ways. The loss of surfactant function coupled with the development of edema around and within the alveoli leads to alveolar collapse. The result is decreased lung compliance, lung volume, and functional residual capacity. This is associated with a large intrapulmonary shunt fraction that contributes to the significant hypoxemia associated with ARDS.

During ARDS, marked hysteresis of the pressure–volume loop occurs, such that significantly higher transpulmonary pressures are necessary to achieve a given lung volume on inspiration than on expiration. The point on the pressure–volume loop where the

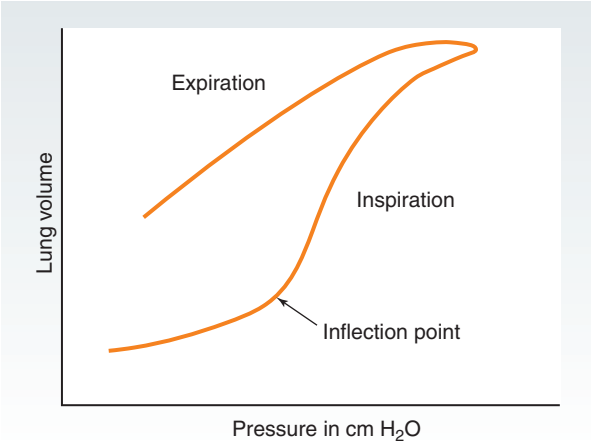


FIGURE 29-2 Representation of the pressure-volume (compliance) loop in acute respiratory distress syndrome (ARDS). Below the inflection point is the pressure at which the alveoli begin to collapse, leading to loss of lung volume, or functional residual capacity.

shape changes from concave to exponential is known as the **lower inflection point.** It reflects the pressure point at which alveoli begin to open and is located above functional residual capacity (Figure 29-2). This suggests that many gas exchange units will collapse at normal transpulmonary pressures in acutely injured lungs and may need significant PEEP to maintain patency during expiration. The clinical application of recruitment maneuvers followed by maintenance with an appropriate level of PEEP to prevent alveolar collapse is known as the **open lung strategy.**[63,64]

Finally, lung injury and areas of involvement in ARDS are heterogeneous and not uniform through all lung units. Some areas of the lung, typically in the dependent regions, are grossly affected. Other regions of the lung, typically in the nondependent regions, may be relatively unaffected.[65] This creates varying areas of compliance within the lung itself. Dependent regions are generally fluid filled, atelectatic, and noncompliant. Nondependent areas are relatively normal and thus at risk for overdistention (i.e., volutrauma) and barotrauma during mechanical ventilation.

TREATMENT AND VENTILATORY SUPPORT

Management of a patient with respiratory distress or failure includes an assessment of airway, breathing, and circulation and prompt cardiopulmonary resuscitation. Identification and targeted therapy for the underlying cause and elimination of any potential source for exacerbation of the disease is a critical first step in treatment.

The goal in the treatment of ARDS is to treat the underlying disease, achieve adequate tissue oxygenation, and avoid morbidity. All ARDS patients require supplemental oxygen, and most require mechanical ventilation. Ensuring adequate cardiac output and hemoglobin levels further helps tissue oxygenation. Overhydration may augment pulmonary edema, so fluids should be carefully titrated and monitored to normalize volume and maintain cardiac output. Antibiotics are used to treat pneumonia and sepsis. Adequate nutrition should be provided to optimize caloric intake. Careful choices should be made about a sedative regimen.

Every patient with ARDS is hypoxemic by definition. Prolonged administration of high concentrations of oxygen can damage the lungs because of the formation of highly reactive oxygen free radicals. Human and animal studies suggest that a prolonged Fio_2 greater than 0.60 should be avoided to prevent oxygen-induced pulmonary damage.[66-68] However, the exact Fio_2 cutoff for oxygen toxicity in ARDS patients remains unknown and may be less than 0.60.

POSITIVE END-EXPIRATORY PRESSURE

The mainstay in treating ARDS is the administration of PEEP. No gas exchange will occur in atelectatic or fluid-filled alveoli. PEEP helps maintain alveolar patency and restore functional residual capacity. PEEP also maintains transthoracic pressure above the point at which additional alveoli will collapse during expiration. PEEP is typically increased to a level that allows adequate oxygenation as defined by an arterial oxygen saturation (Sao_2) of 85% or greater at an acceptable Fio_2 of 0.60 or less. It should be noted that the minimal acceptable arterial oxygen saturation remains very controversial.[69] A PEEP level of 10 to 15 cm H_2O, or even higher, may be required to achieve adequate oxygenation. However, as PEEP levels exceed 12 to 15 cm H_2O, the increase in intrathoracic pressure may adversely affect cardiac output, primarily by decreasing systemic venous return.[70] As PEEP is increased, the patient should be monitored for a decrease in cardiac output with a decrease in peripheral perfusion.[71] In most cases, a decrease in cardiac output can be compensated for by intravascular volume loading or carefully chosen inotropic support (being mindful not to increase left ventricular afterload).[72]

The ARDS Network investigated the optimal PEEP-Fio_2 strategy for adults with ARDS.[73] The results of this prospective randomized multicenter study indicate that in adult ARDS patients who are ventilated with 6 mL/kg tidal volumes and an end-inspiratory plateau pressure of less than 30 cm H_2O, a "moderately high" or "very high" PEEP strategy produced similar survival rates. It must be noted that this study investigated two relatively aggressive PEEP strategies. Subsequent studies performed outside the United States also showed similar results. In a study involving 30 ICUs and 983 adult patients with ARDS, there was no difference in hospital mortality despite the reduction in the need for rescue therapies in the "high" PEEP group.[49] A recent systematic review on the effect of PEEP in ARDS showed that the subgroup of ARDS patients who may stand to benefit most from a "high" PEEP strategy are those with the worst degree of hypoxemia.[74]

The implication of current clinical studies in this area is that once appropriate PEEP is applied to maintain the

lungs at an ideal lung volume, a further increase in PEEP in an attempt to reduce the Fio_2 does not lead to an improved outcome.

LOW TIDAL VOLUME VENTILATION

Ventilation is achieved through a combination of respiratory rate, tidal volume, and inspiratory time. Historically, ventilator tidal volumes between 10 and 15 mL/kg were used for patients with ARDS. Because the remaining compliant lung volume in a patient with ARDS is significantly reduced, these tidal volumes often required inflation pressures that resulted in pulmonary overdistention and progressive secondary lung injury.[75-77]

The ARDS Network reported in the *New England Journal of Medicine* in 2000 that in adult patients with acute lung injury and ARDS, low tidal volume mechanical ventilation (6 mL/kg) decreased mortality by 22% and increased the number of ventilator-free days as compared with a more traditional tidal volume (12 mL/kg).[34] The mortality rate was 31.0% in the low tidal volume group and 39.8% ($p = 0.007$) in the higher tidal volume group. Additionally, the plateau pressure (Pplat) was significantly decreased in the low tidal volume group compared with the control group.

Although still unproven, the results of this landmark study are likely applicable to infants and children with ARDS. Until a similar large-scale prospective randomized trial is accomplished in pediatrics, it seems reasonable to use the low tidal volume guideline. A metaanalysis of **low tidal volume ventilation** in patients without acute lung injury showed that this lung-protective strategy results in less lung injury and mortality.[78] This collective evidence suggests that low tidal volumes should be used in patients with more normal lung function. However, this metaanalysis only included adult patients. It remains uncertain whether larger tidal volumes can be safely applied in children with normal lung function.

Before the ARDS Network's low tidal volume study, several studies offered conflicting results on this topic. Amato et al. concluded that a lung-protective ventilation strategy was associated with a significant decrease in mortality at 28 days but was not associated with a higher rate of survival to hospital discharge.[79] A major limitation in the application of the results of this study is the high mortality rate in the control group (71%). In contrast, the next article in the same issue of the *New England Journal of Medicine* was a report by Stewart et al. that concluded that a low tidal volume strategy does not reduce mortality for adult patients with ARDS.[80]

The apparently conflicting results from the low tidal volume studies by Amato, Stewart, and the ARDS Network become more consistent when considering the plateau pressures used. In the ARDS Network study, the protocol was designed to maintain plateau pressure less than 50 cm H_2O in the control group and less than 30 cm H_2O in the low tidal volume group.[34] The results indicate that in the low tidal volume group Pplat remained 26 cm H_2O or less throughout the first week of ventilation, whereas in the control group Pplat ranged from 33 ± 9 to 37 ± 9 cm H_2O over the first week. In the Amato study, Pplat remained less than 32 cm H_2O for the protective ventilation group; in the control group Pplat ranged from 34.4 ± 1.9 to 37.8 ± 1.2 cm H_2O over the first 7 days of ventilation.[79] Of interest, the study by Stewart et al. revealed no improvement with mortality with low tidal volume ventilation; however, in both groups Pplat was maintained at less than 29 cm H_2O throughout the study.[80] This finding is similar to the study by Brochard et al., which also failed to demonstrate improved survival with low tidal volume ventilation.[81] For both groups, Pplat was maintained at less than 32 cm H_2O throughout the first week of ventilation.

Thus the data support the conclusion that for adult patients with ARDS, Pplat should be limited to less than approximately 32 cm H_2O to improve outcome. The applicability of this conclusion to PARDS patients requires investigation. It is very possible that the "critical" limit on Pplat for infants and children will be less than 32 cm H_2O and vary with patient age and size.

It must be stressed that although the ARDS Network study indicates that a 6 mL/kg tidal volume led to improved mortality compared with a 12 mL/kg tidal volume, the tidal volume associated with the least mortality may lie somewhere between 6 and 12 mL/kg, or possibly even less than 6 mL/kg. Last, it should be stressed that most previous ARDS trials were based on a "magic bullet" strategy in which a single intervention is studied. Mortality from ARDS has improved over the past decade without ever truly finding the "magic bullet." Most likely, the improvements in the care of ARDS patients have been multifactorial. Although difficult, future clinical studies should investigate a combination of therapies to further decrease mortality from ARDS.

Multiple modes of mechanical ventilation are currently used in clinical practice to provide respiratory support for patients with ARDS. To date, no data exist to determine the ventilatory mode that provides the greatest benefit and the least risk to an individual patient. Prospective randomized multicenter studies of mechanical ventilation and ARDS in pediatrics are limited. For most clinical questions, data are extrapolated from studies in the adult population.

When "toxic" conventional ventilatory support is required to achieve the desired gas exchange goals, clinicians often transition to high-frequency oscillatory ventilation (HFOV). Only one randomized controlled study of HFOV in the pediatric population has been performed, which showed improved oxygenation and reduced need for supplementation oxygen at 30 days with HFOV.[82] However, it must be noted that the control group was not ventilated with a low tidal volume approach. Despite the paucity of data showing the superiority of HFOV in pediatric ARDS, the use of this alternative mode of ventilation remains common in PICUs worldwide.[83] Readers are referred to Chapter 17

for a more comprehensive discussion of HFOV. Briefly, the OSCAR study group reported that the use of HFOV in adults with ARDS had no significant effect on 30-day mortality.[84] Simultaneously, the OSCILLATE study group reported that early application of HFOV in adults increases mortality.[85] It is unclear how relevant adult studies looking at nonrescue application of HFOV are to pediatric practice, in which HFOV remains commonly used as a rescue modality.[86]

Current medical evidence does not show that a particular mode of conventional mechanical ventilation (pressure controlled or volume controlled) or alternative modes of ventilation (e.g., airway pressure release ventilation, HFOV) results in a significant difference in mortality in patients with ARDS. Except for low tidal volume strategy, no particular conventional or unconventional mode of ventilation has been demonstrated to improve clinical outcomes in ARDS.

GAS EXCHANGE GOALS

Improved oxygenation is not correlated with improved outcome. This was best demonstrated in the ARDS Network low tidal volume study, in which the control (12 mL/kg) group demonstrated improved oxygenation for the first 72 hours of ventilation.[34] If this study had been designed as an acute gas exchange study, the conclusion would have been false, and mortality for ARDS could have increased. This lack of association between oxygenation and survival has been demonstrated in multiple other studies.[87-89] Timmons et al. demonstrated no correlation between oxygenation or ventilation in survivors or nonsurvivors of pediatric ARDS.[90] Dobyns et al. showed that in acute hypoxic respiratory failure in children, although oxygenation improved with inhaled nitric oxide, there was no difference in mortality.[87] Improved oxygenation without a significant improvement in survival was also demonstrated in a follow-up study of inhaled nitric oxide in combination with high-frequency oscillatory ventilation.[88]

The concept of accepting lower arterial oxygenation saturation is termed **permissive hypoxemia.**[72,91] Although the acceptable arterial oxygen saturation target remains controversial, ventilatory strategies should aim to provide adequate tissue and organ oxygenation while minimizing oxygen toxicity and ventilator-induced lung injury. It should be noted that long-term neurologic effects of permissive hypoxemia have not been studied. Clinicians must weigh the potential benefits and risks of this approach for each individual clinical situation.

PERMISSIVE HYPERCAPNIA

A logical consequence of low tidal volume ventilation is hypercapnia. Limiting the peak inspiratory pressure by reducing the tidal volume may decrease minute ventilation and result in hypercapnia. The exact degree of respiratory acidosis that can be safely tolerated remains controversial. However, most undesirable effects are reversible and minor with respiratory acidosis when pH is greater than approximately 7.20.[92] Laboratory studies have suggested that respiratory acidosis may in fact be lung-protective.[93]

Of note, a Cochrane review of the large multicenter low tidal volume studies of adult ARDS was unable to reach a firm conclusion on the implications of **permissive hypercapnia.**[94] It should be stressed that these low tidal volume studies were not designed to answer the specific question of hypercapnia. However, the medical literature does support the beneficial role of permissive hypercapnia in ARDS. Limited evidence suggests that low-volume, pressure-limited ventilation with permissive hypercapnia may improve outcome in patients with ARDS.[95,96] In a 10-year study, Milberg et al. reported a positive association between permissive hypercapnia and outcomes.[97] Recent data from a laboratory model of ischemia-reperfusion acute lung injury indicate that hypercapnic acidosis is protective and that buffering of the hypercapnic acidosis attenuates its protective effects.[93] In allowing permissive hypercapnia, the rate at which carbon dioxide rises may be more important than the actual value itself. A rapid regression to normocapnia may be more deleterious to the cardiac system than hypercapnia itself.

It should be noted that permissive hypercapnia is generally not recommended for patients with intracranial pathology in which increased cerebral blood flow related to hypercapnia may be detrimental or those with significant pulmonary hypertension in which the elevated carbon dioxide level may further increase pulmonary vascular resistance.

ADJUNCT THERAPIES

Some patients are unable to achieve acceptable therapeutic goals while avoiding oxygen toxicity or an intolerably high peak inspiratory pressure with conventional ventilator strategies. Two of the more commonly used therapeutic modalities for treating patients with ARDS are HFOV and ECMO.[85,98-101] HFOV was described briefly in the prior section on Treatment and Ventilatory Support. ECMO is discussed briefly in this section. The reader is referred to Chapters 17 and 19 (and the Evolve website) for a more comprehensive discussion of these important topics.

ECMO is used in patients with severe ARDS who are unable to achieve acceptable therapeutic goals despite maximal therapies at intolerably high ventilator settings and/or inotropic support. In patients with severe ARDS and preserved cardiac function, venovenous ECMO can be used to minimize oxygen toxicity and minimize VILI while achieving acceptable oxygenation and carbon dioxide clearance. Keeping in mind that ECMO is usually implemented in critically ill children with an extremely high mortality rate, the survival data from the Extracorporeal Life Support Organization registry for children with ARDS is fairly good at approximately 65% overall.[101] Experience with

the 2009-2010 H1N1 influenza A pandemic suggests that ECMO may be an important management strategy in future viral epidemics and pandemics, with survival rates reported in excessive of 70%.[102,103]

One of the biggest questions surrounding the use of ECMO support is how to maximize lung recovery. ELSO guidelines include PCV with low inflation 26 pressures (10 cm H_2O), higher PEEP (15 cm H_2O), low respiratory rate (5 beats/minute), and Fio_2 of 0.5 27 or less, but there is a significant variability in practice.[104] In a 2014 survey of ELSO centers, the majority (77%) reported "lung rest" to be the primary goal of mechanical ventilation during ECMO, and 81% of participants reported using tidal volumes of 6 mL/kg or less, including 34% who used "ultraprotective" tidal volumes of 4 mL/kg.[105] To survive ECMO with good functional outcome, maintaining lung protective ventilation during venovenous ECMO is essential. The current literature does not provide much guidance on this question. However, it stands to reason that the basic principles of lung-protective ventilation should still be applied.

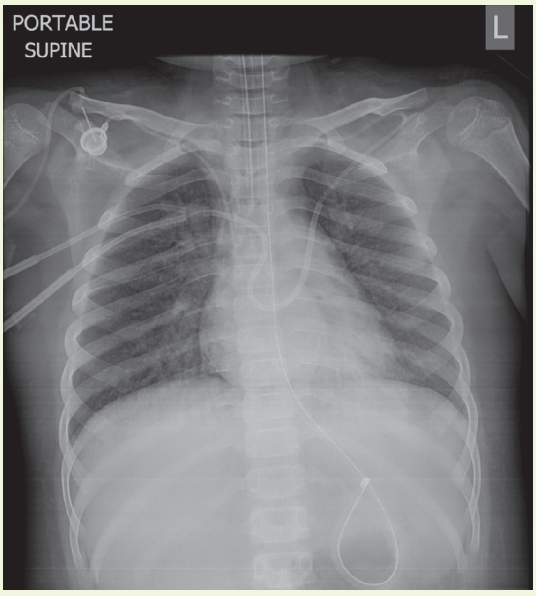
Other potential adjunct therapies include trials of corticosteroids, prone positioning, inhaled nitric oxide, and surfactant replacement. Metaanalyses of corticosteroid use within the first 2 weeks in adults with established ARDS demonstrated that steroids may reduce mortality and total days of mechanical ventilation.[106,107] Although controversial, there does not seem to be a role for steroids in the prevention of progression of ARDS.[106] Unfortunately, there are no studies of corticosteroids for treatment of ARDS in children.

Prone positioning improves oxygenation in pediatric and adult patients with ARDS through various mechanisms, such as improvements in ventilation–perfusion matching and chest wall mechanics.[108] However, proning is associated with a risk of endotracheal tube obstruction and accidental catheter or tube dislodgment. A metaanalysis has shown that proning improves survival in those with severe ARDS.[109] Unfortunately the only study to date on proning in children with acute lung injury was closed because of futility.[89] This prospective randomized multicenter study by Curley et al. revealed no change in mortality with prone positioning.[89] The PROSpect protocol is currently being planned and is anticipated to compare both HFOV and CMV as well as prone and supine position for each group.

Studies of inhaled nitric oxide for pediatric ALI/ARDS have demonstrated improved oxygenation acutely, but this improvement in gas exchange has not translated into improved survival.[87,88] Willson et al. reported that exogenous surfactant (calfactant) acutely improved oxygenation and significantly decreased mortality in infants and children with acute lung injury; however, this study revealed no significant decrease in duration of mechanical ventilation, length of PICU admission, or length of hospital stay.[110] Furthermore, the control group had a higher percentage of higher risk immune-incompetent patients. There is evidence indicating that it may be useful in cardiac patients with pulmonary hypertension.[111,112]

Case Study

A 15-year-old boy with a significant medical history of acute lymphoblastic leukemia in remission presented with fever, cough, and shortness of breath. On presentation, he was noted to have bilateral crackles on auscultation and a pulse oximeter reading of 85% on room air. Supplemental oxygen was provided, and he was admitted to the general ward for further management. The patient's oxygen requirement continued to increase with increasing work of breathing. Chest radiograph showed worsening bilateral infiltrates. He was transferred to the PICU and was intubated in view of the rapid progression of illness. Respiratory virus isolation was notable for H1N1 influenza. The patient was supported on conventional mechanical ventilation for 3 days before transitioning to high-frequency ventilation. Before his transition to high-frequency ventilation, his arterial blood gas on conventional mechanical ventilation, with peak inspiratory pressure of 28, PEEP 13, mean airway pressure of 19, and Fio_2 of 90%, was pH 7.33, Pao_2 46 mm Hg, $Paco_2$ 57 mm Hg, Hco_3 30.0, base excess (BE) 6. Unfortunately his condition worsened, with refractory hypoxemia (high-frequency ventilation with mean airway pressure of 35, amplitude of 60, frequency of 8 Hz, and Fio_2 100%, with an arterial blood gas of pH 7.31, Pao_2 57 mm Hg, $Paco_2$ 75 mm Hg, Hco_3 32.0, BE 10.6), and he was cannulated for venovenous ECMO with a dual-lumen cannula in the right internal jugular vein. After 3 weeks on ECMO, he was decannulated, weaned, and then extubated. After 8 weeks, he was discharged home without the need for ongoing respiratory support.



1. Does this case satisfy the criteria for PARDS? What features of PARDS are present, and what additional information, if any, is required?
2. What conventional mechanical ventilation strategies should be considered in this type of patient?
3. What other adjunct therapies, if any, could have been considered in the management of this case?

See Evolve Resources for answers.

SUMMARY

Acute lung injury and acute respiratory distress syndrome represent a continuum of clinical disease of varying pulmonary (direct) and nonpulmonary (indirect) etiologies. Although much has been learned about the pathophysiology of acute lung injury over the past 2 decades, the only treatment strategy that has been proven to improve clinical outcome is low tidal volume ventilation. However, the optimal tidal volume remains unclear, because it may not be 6 mL/kg. Furthermore, it should be noted that in the years before publication of the low tidal volume ventilation data, overall survival rates for adult and pediatric patients with acute lung injury had been gradually increasing. Future clinical investigations are likely to study combined therapeutic strategies.

Key Points

- The definition for PARDS excludes those with perinatal-related lung disease, specifies that timing is within 7 days of initial insult, does not require that infiltrates on chest imaging are bilateral, and uses the OI and oxygen saturation index for patients on NIV to determine level of severity.
- Classically, ARDS is divided into three pathologic stages: exudative, proliferative, and fibrotic. Neutrophils are central to the pathogenesis of ARDS. Regardless of the inciting event, ARDS begins with inflammatory injury to the alveolar epithelium and endothelium, which results in accumulation of protein-rich edema in the alveoli. Recovery from ARDS depends on the resolution of inflammation, removal of the edema, and reparative processes of the epithelium.
- Mechanical ventilation forms the cornerstone of ARDS management. Mechanical ventilation strategies must aim to minimize ventilator-induced lung injury. Such strategies include low tidal volume ventilation, optimization of PEEP and mean airway pressure, and possibly (based on the clinical scenario) permissive hypoxemia and permissive hypercapnia. High-frequency ventilation, as described elsewhere in this textbook, is often used in pediatric acute lung injury based on tremendous clinical experience; however, this modality has never been studied in comparison with low tidal volume ventilation in pediatrics.
- Beyond mechanical ventilation, other adjunct therapies may be considered in severe cases of acute lung injury or ARDS. Although clinically used, data are lacking to definitively support prone positioning, exogenous surfactant administration, or inhaled nitric oxide for the management of severe hypoxemia. ECMO, as described elsewhere in the textbook, can be lifesaving when refractory hypoxemia develops.
- Meticulous attention to treatment of precipitating factors, sedation, fluid management, and nutrition is important in the overall management of a child with acute lung injury.

Assessment Questions

See Evolve Resources for the answers.

1. A patient undergoing mechanical ventilation has a mean airway pressure of 18 cm H_2O, and the blood gas shows a Pa_{O_2} of 90 mm Hg at an Fi_{O_2} of 0.80. What is this patient's oxygenation index (OI)?
   A. 20
   B. 16
   C. 140
   D. 90
2. For the patient in the previous question, what is the severity of his pediatric acute respiratory distress syndrome (PARDS) according to the 2015 Pediatric Acute Lung Injury Consensus Conference Group recommendations ?
   A. ALI
   B. Mild
   C. Moderate
   D. Severe
3. Which of the following are pathologic stages of acute respiratory distress syndrome (ARDS)?
   I. Exudative
   II. Proliferative
   III. Fibrotic
   IV. Edematous
   A. I, II, III
   B. II, IV
   C. II, III, IV
   D. III, IV
4. A 68-year-old man with a history of chronic alcoholic use was admitted to the unit for aspiration pneumonia. His clinical course was complicated by ARDS. Which of the following treatment strategies for acute lung injury in adult patients was demonstrated to improve mortality in a prospective randomized clinical trial?
   A. Prone positioning
   B. Inhaled nitric oxide
   C. Low positive end-expiratory pressure
   D. Low tidal volume ventilation
5. A 6-year-old child with a history of acute lymphoblastic leukemia was admitted to the intensive care unit for *Klebsiella pneumoniae* septic shock. He developed PARDS on the third day of septic shock. The overall goals in the treatment of PARDS for this child include:
   I. Treating the underlying disease
   II. Achieving adequate tissue oxygenation
   III. Minimizing ventilator-induced lung injury
   IV. Ensuring normocarbia
   A. I, II
   B. II, III
   C. II, IV
   D. I, II, III
6. The criteria used to define PARDS include:
   I. Hypoxemia
   II. Bilateral pulmonary infiltrates
   III. Timing within 7 days of known clinical insult
   IV. Perinatal lung disease
   A. I, II, III, IV
   B. I, III
   C. I, IV
   D. I, II, III

7. Which of the following are useful therapies in pediatric patients with acute lung injury?
   - **I.** Permissive hypercapnia
   - **II.** Permissive hypoxemia
   - **III.** Administration of activated protein C for sepsis
   - **IV.** Low tidal volume ventilation
   - **A.** I, II
   - **B.** I, IV
   - **C.** I, II, III
   - **D.** I, II, IV
8. Which of the following characteristics of infants and young children (as compared with older children and adults) causes this population to be particularly prone to respiratory failure?
   - **I.** Small-caliber airways
   - **II.** Increased chest wall compliance
   - **III.** Greater propensity for rapid fatigue of respiratory muscles
   - **IV.** Reduced cardiac function in children compared with adults
   - **A.** III, IV
   - **B.** I, II
   - **C.** I, II, III
   - **D.** I, II, III, IV
9. The most common nonpulmonary risk factor in patients with ARDS is:
   - **A.** Multiple trauma
   - **B.** Cardiac failure
   - **C.** Sepsis
   - **D.** Acute pancreatitis
10. Of the choices listed, which is generally the latest clinical finding in pediatric patients with PARDS?
    - **A.** Hypoxemia
    - **B.** Decreased pulmonary compliance
    - **C.** Increased work of breathing
    - **D.** Hypercapnia

REFERENCES

1. Bernard GR. Acute respiratory distress syndrome: a historical perspective. *Am J Respir Crit Care Med*. 2005;172:798.
2. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet*. 1967;2:319.
3. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med*. 1994;149:818.
4. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin definition. *JAMA*. 2012; 307:2526.
5. Ferguson ND, Fan E, Camporota L, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. *Intensive Care Med*. 2012;38:1573-1582.
6. Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med*. 2015;16(5):428-439.
7. Rivera RA, Butt W, Shann F. Predictors of mortality in children with respiratory failure: possible indications for ECMO. *Anaesth Intensive Care*. 1990;18:385.
8. Durand M, Snyder JR, Gangitano E, et al. Oxygenation index in patients with meconium aspiration: conventional and extracorporeal membrane oxygenation therapy. *Crit Care Med*. 1990;18:373.
9. Monchi M, Bellenfant F, Cariou A, et al. Early predictive factors of survival in the acute respiratory distress syndrome. A multivariate analysis. *Am J Respir Crit Care Med*. 1998;158:1076.
10. Mehta S, Granton J, MacDonald RJ, et al. High-frequency oscillatory ventilation in adults: the Toronto experience. *Chest*. 2004;126:518.
11. Matsuda A, Kishi T, Jacob A, Aziz M, Wang P. Association between insertion/deletion polymorphism in angiotensin-converting enzyme gene and acute lung injury/acute respiratory distress syndrome: a meta-analysis. *BMC Med Genet*. 2012;13:76.
12. Kangelaris KN, Sapru A, Calfee CS, et al. The association between a Darc gene polymorphism and clinical outcomes in African American patients with acute lung injury. *Chest*. 2012;141:1160.
13. Roupie E, Lepage E, Wysocki M, et al. Prevalence, etiologies and outcome of the acute respiratory distress syndrome among hypoxemic ventilated patients. SRLF Collaborative Group on Mechanical Ventilation. Société de Réanimation de Langue Française. *Intensive Care Med*. 1999;25:920.
14. Bersten AD, Edibam C, Hunt T, Moran J. Incidence and mortality of acute lung injury and the acute respiratory distress syndrome in three Australian States. *Am J Respir Crit Care Med*. 2002;165:443.
15. Brun-Buisson C, Minelli C, Bertolini G, et al. Epidemiology and outcome of acute lung injury in European intensive care units. Results from the ALIVE study. *Intensive Care Med*. 2004;30:51.
16. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. *N Engl J Med*. 2005;353:1685.
17. Zimmerman JJ, Akhtar SR, Caldwell E, Rubenfeld GD. Incidence and outcomes of pediatric acute lung injury. *Pediatrics*. 2009;124:87.
18. López-Fernández Y, Azagra AM, de la Oliva P, et al. Pediatric acute lung injury epidemiology and natural history study: incidence and outcome of the acute respiratory distress syndrome in children. *Crit Care Med*. 2012;40:3238.
19. Yu WL, Lu ZJ, Wang Y, et al. The epidemiology of acute respiratory distress syndrome in pediatric intensive care units in China. *Intensive Care Med*. 2009;35:136.
20. Hu X, Qian S, Xu F, et al. Incidence, management and mortality of acute hypoxemic respiratory failure and acute respiratory distress syndrome from a prospective study of Chinese paediatric intensive care network. *Acta Paediatr*. 2010;99:715.
21. Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med*. 2015;16(5):428-439.
22. Gattinoni L, Bombino M, Pelosi P, et al. Lung structure and function in different stages of severe adult respiratory distress syndrome. *JAMA*. 1994;271:1772.
23. Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med*. 2000;342:1334.
24. Aberle DR, Brown K. Radiologic considerations in the adult respiratory distress syndrome. *Clin Chest Med*. 1990; 11:737.

25. Effmann EL, Merten DF, Kirks DR, Pratt PC, Spock A. Adult respiratory distress syndrome in children. *Radiology*. 1985; 157:69.
26. Antonelli M, Conti G, Esquinas A, et al. A multiple-center survey on the use in clinical practice of noninvasive ventilation as a first-line intervention for acute respiratory distress syndrome. *Crit Care Med*. 2007;35:18.
27. Piastra M, De Luca D, Marzano L, et al. The number of failing organs predicts non-invasive ventilation failure in children with ALI/ARDS. *Intensive Care Med*. 2011;37:1510.
28. Ferring M, Vincent JL. Is outcome from ARDS related to the severity of respiratory failure? *Eur Respir J*. 1997;10:1297.
29. Estenssoro E, Dubin A, Laffaire E, et al. Incidence, clinical course, and outcome in 217 patients with acute respiratory distress syndrome. *Crit Care Med*. 2002;30:2450.
30. Stapleton RD, Wang BM, Hudson LD, Rubenfeld GD, Caldwell ES, Steinberg KP. Causes and timing of death in patients with ARDS. *Chest*. 2005;128:525.
31. Walkey AJ, Summer R, Ho V, Alkana P. Acute respiratory distress syndrome: epidemiology and management approaches. *Clin Epidemiol*. 2012;4:159.
32. Phua J, Badia JR, Adhikari NK, et al. Has mortality from acute respiratory distress syndrome decreased over time?: a systematic review. *Am J Respir Crit Care Med*. 2009;179:220.
33. Zambon M, Vincent JL. Mortality rates for patients with acute lung injury/ARDS have decreased over time. *Chest*. 2008;133:1120.
34. Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342:1301.
35. Flori HR, Glidden DV, Rutherford GW, Matthay MA. Pediatric acute lung injury: prospective evaluation of risk factors associated with mortality. *Am J Respir Crit Care Med*. 2005; 171:995.
36. Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA*. 2016;315(8):788-800.
37. Yehya N, Servaes S, Thomas NJ. Characterizing degree of lung injury in pediatric acute respiratory distress syndrome. *Crit Care Med*. 2015;43(5):937-946.
38. Yehya N, Thomas NJ. Relevant outcomes in pediatric acute respiratory distress syndrome studies. *Fron Pediatr*. 2016;4:51.
39. Seeger W, Günther A, Walmrath HD, Grimminger F, Lasch HG. Alveolar surfactant and adult respiratory distress syndrome. Pathogenetic role and therapeutic prospects. *Clin Investig*. 1993;71:177.
40. Lewis JF, Veldhuizen R, Possmayer F, et al. Altered alveolar surfactant is an early marker of acute lung injury in septic adult sheep. *Am J Respir Crit Care Med*. 1994;150:123.
41. Matthay MA, Wiener-Kronish JP. Intact epithelial barrier function is critical for the resolution of alveolar edema in humans. *Am Rev Respir Dis*. 1990;142:1250.
42. Ware LB, Matthay MA. Alveolar fluid clearance is impaired in the majority of patients with acute lung injury and the acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2001;163:1376.
43. Tanswell AK, Byrne PJ, Han RN, Edelson JD, Han VK. Limited division of low-density adult rat type II pneumocytes in serum-free culture. *Am J Physiol*. 1991;260:L395.
44. Berthiaume Y, Lesur O, Dagenais A. Treatment of adult respiratory distress syndrome: plea for rescue therapy of the alveolar epithelium. *Thorax*. 1999;54:150.
45. Piantadosi CA, Schwartz DA. The acute respiratory distress syndrome. *Ann Intern Med*. 2004;141:460.
46. Bitterman PB. Pathogenesis of fibrosis in acute lung injury. *Am J Med*. 1992;92:39S.
47. Kuhn C, Boldt J, King Jr TE, Crouch E, Vartio T, McDonald JA. An immunohistochemical study of architectural remodeling and connective tissue synthesis in pulmonary fibrosis. *Am Rev Respir Dis*. 1989;140:1693.
48. Ranieri VM, Suter PM, Tortorella C, et al. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. *JAMA*. 1999;282:54-61.
49. Matthay MA, Zemans RL. The acute respiratory distress syndrome: pathogenesis and treatment. *Annu Rev Pathol*. 2011;6:147-163.
50. Matthay MA, Zimmerman GA. Acute lung injury and the acute respiratory distress syndrome: four decades of inquiry into pathogenesis and rational management. *Am J Respir Cell Mol Biol*. 2005;33:319-327.
51. Rinaldo JE, Christman JW. Mechanisms and mediators of the adult respiratory distress syndrome. *Clin Chest Med*. 1990;11:621.
52. Dolinay T, Kim YS, Howrylak J, et al. Inflammasome-regulated cytokines are critical mediators of acute lung injury. *Am J Respir Crit Care Med*. 2012;185:1225.
53. Orwoll BE, Sapru A. Biomarkers in pediatric ARDS. future directions. *Front Pediatr*. 2016;4:55.
54. Smith WS, Matthay MA. Evidence for a hydrostatic mechanism in human neurogenic pulmonary edema. *Chest*. 1997; 111(5):1326.
55. Maron MB, Dawson CA. Pulmonary venoconstriction caused by elevated cerebrospinal fluid pressure in the dog. *J Appl Physiol Respir Environ Exerc Physiol*. 1980;47:1025.
56. Hoff JT, Nishimura M, Garcia-Uria J, Miranda S. Experimental neurogenic pulmonary edema. Part 1: The role of systemic hypertension. *J Neurosurg*. 1981;54:627.
57. Sedý J, Zicha J, Nedvídková J, Kunes J. The role of sympathetic nervous system in the development of neurogenic pulmonary edema in spinal cord-injured rats. *J Appl Physiol*. 1985;112:1.
58. Šedý J, Kuneš J, Zicha J. Pathogenetic mechanisms of neurogenic pulmonary edema. *J Neurotrauma*. 2015;32(15):1135-1145.
59. Colice GL, Matthay MA, Bass E, Matthay RA. Neurogenic pulmonary edema. *Am Rev Respir Dis*. 1984;130:941.
60. Mascia L. Acute lung injury in patients with severe brain injury: a double hit model. *Neurocrit Care*. 2009;11:417.
61. Hutchinson PJ, O'Connell MT, Rothwell NJ, et al. Inflammation in human brain injury: intracerebral concentrations of IL-1alpha, IL-1beta and their endogenous inhibitor IL-1ra. *J Neurotrauma*. 2007;24:1545.
62. Rettig JS, Duncan ED, Tasker RC. Mechanical ventilation during acute brain-injury in children. *Pediatr Respir Rev*. 2016;20:17-23.
63. Papadakos PJ, Lachmann B. The open lung concept of mechanical ventilation: the role of recruitment and stabilization. *Crit Care Clin*. 2007;23:241, ix-x.
64. Meade MO, Cook DJ, Guyatt GH, et al. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA*. 2008;299:637.
65. Gattinoni L, Caironi P, Pelosi P, Goodman LR. What has computed tomography taught us about the acute respiratory distress syndrome? *Am J Respir Crit Care Med*. 2001; 164:1701.
66. Thiel M, Chouker A, Ohta A, et al. Oxygenation inhibits the physiological tissue-protecting mechanism and thereby exacerbates acute inflammatory lung injury. *PLoS Biol*. 2005; 3:e174.
67. Li LF, Liao SK, Ko YS, Lee CH, Quinn DA. Hyperoxia increases ventilator-induced lung injury via mitogen-activated protein kinases: a prospective, controlled animal experiment. *Crit Care*. 2007;11:R25.

68. Altemeier WA, Sinclair SE. Hyperoxia in the intensive care unit: why more is not always better. *Curr Opin Crit Care*. 2007;13:73.
69. Abdelsalam M, Cheifetz IM. Goal-directed therapy for severely hypoxic patients with acute respiratory distress syndrome: permissive hypoxemia. *Respir Care*. 2010;55:1483.
70. Mitaka C, Nagura T, Sakanishi N, Tsunoda Y, Amaha K. Two-dimensional echocardiographic evaluation of inferior vena cava, right ventricle, and left ventricle during positive-pressure ventilation with varying levels of positive end-expiratory pressure. *Crit Care Med*. 1989;17:205.
71. Cheifetz IM, Craig DM, Quick G, et al. Increasing tidal volumes and pulmonary overdistention adversely affect pulmonary vascular mechanics and cardiac output in a pediatric swine model. *Crit Care Med*. 1998;26:710.
72. Pollack MM, Fields AI, Holbrook RP. Cardiopulmonary parameters during high PEEP in children. *Crit Care Med*. 1980; 8:372.
73. Brower RG, Lanken PN, MacIntyre N, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med*. 2004; 351:327.
74. Briel M, Meade M, Mercat A, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA*. 2010;303:865.
75. Dreyfuss D, Basset G, Soler P, Saumon G. Intermittent positive-pressure hyperventilation with high inflation pressures produces pulmonary microvascular injury in rats. *Am Rev Respir Dis*. 1985;132:880.
76. Kolobow T, Moretti MP, Fumagalli R, et al. Severe impairment in lung function induced by high peak airway pressure during mechanical ventilation. An experimental study. *Am Rev Respir Dis*. 1987;135:312.
77. de Prost N, Ricard JD, Saumon G, Dreyfuss D. Ventilator-induced lung injury: historical perspectives and clinical implications. *Ann Intensive Care*. 2011;1:28.
78. Serpa Neto A, Cardoso SO, Manetta JA, et al. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: a meta-analysis. *JAMA*. 2012;308:1651.
79. Amato MB, Barbas CS, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med*. 1998;338:347.
80. Stewart TE, Meade MO, Cook DJ, et al. Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. Pressure- and Volume-Limited Ventilation Strategy Group. *N Engl J Med*. 1998;338:355.
81. Brochard L, Roudot-Thoraval F, Roupie E, et al. Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on Tidal Volume reduction in ARDS. *Am J Respir Crit Care Med*. 1998;158:1831.
82. Arnold JH, Hanson JH, Toro-Figuero LO, Gutiérrez J, Berens RJ, Anglin DL. Prospective, randomized comparison of high-frequency oscillatory ventilation and conventional mechanical ventilation in pediatric respiratory failure. *Crit Care Med*. 1994;22:1530.
83. Randolph AG, Meert KL, O'Neil ME, et al. The feasibility of conducting clinical trials in infants and children with acute respiratory failure. *Am J Respir Crit Care Med*. 2003;167:1334.
84. Young, D, Lamb SE, Shah S, et al. High-frequency oscillation for acute respiratory distress syndrome. *N Engl J Med*. 2013;368:806-813.
85. Ferguson ND, Cook DJ, Guyatt GH, et al. High-Frequency Oscillation in Early Acute Respiratory Distress Syndrome. *N Engl J Med*. 2013;368:795-805.
86. Rettig JS, Smallwood CD, Walsh BK, et al. High-frequency oscillatory ventilation in pediatric acute lung injury: a multicenter international experience. *Crit Care Med*. 2015; 43(12):2660-2667.
87. Dobyns EL, Cornfield DN, Anas NG, et al. Multicenter randomized controlled trial of the effects of inhaled nitric oxide therapy on gas exchange in children with acute hypoxemic respiratory failure. *J Pediatr*. 1999;134:406.
88. Dobyns EL, Anas NG, Fortenberry JD, et al. Interactive effects of high-frequency oscillatory ventilation and inhaled nitric oxide in acute hypoxemic respiratory failure in pediatrics. *Crit Care Med*. 2002;30:425.
89. Curley MA, Hibberd PL, Fineman LD, et al. Effect of prone positioning on clinical outcomes in children with acute lung injury: a randomized controlled trial. *JAMA*. 2005; 294:229.
90. Timmons OD, Havens PL, Fackler JC. Predicting death in pediatric patients with acute respiratory failure. Pediatric Critical Care Study Group. Extracorporeal Life Support Organization. *Chest*. 1995;108:789.
91. Randolph AG. Management of acute lung injury and acute respiratory distress syndrome in children. *Crit Care Med*. 2009;37:2448.
92. Feihl F, Perret C. Permissive hypercapnia. How permissive should we be? *Am J Respir Crit Care Med*. 1994;150:1722.
93. Laffey JG, Engelberts D, Kavanagh BP. Buffering hypercapnic acidosis worsens acute lung injury. *Am J Respir Crit Care Med*. 2000;161:141.
94. Petrucci N, Iacovelli W. Ventilation with lower tidal volumes versus traditional tidal volumes in adults for acute lung injury and acute respiratory distress syndrome. *Cochrane Database Syst Rev*. 2004;CD003844.
95. Hickling KG, Henderson SJ, Jackson R. Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. *Intensive Care Med*. 1990;16:372.
96. Hickling KG, Walsh J, Henderson S, Jackson R. Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. *Crit Care Med*. 1994; 22:1568.
97. Milberg JA, Davis DR, Steinberg KP, Hudson LD. Improved survival of patients with acute respiratory distress syndrome (ARDS): 1983-1993. *JAMA*. 1995;273:306.
98. Green TP, Timmons OD, Fackler JC, Moler FW, Thompson AE, Sweeney MF. The impact of extracorporeal membrane oxygenation on survival in pediatric patients with acute respiratory failure. Pediatric Critical Care Study Group. *Crit Care Med*. 1996;24:323.
99. Arnold JH, Anas NG, Luckett P, et al. High-frequency oscillatory ventilation in pediatric respiratory failure: a multicenter experience. *Crit Care Med*. 2000;28:3913.
100. Brogan TV, Thiagarajan RR, Rycus PT, Bartlett RH, Bratton SL. Extracorporeal membrane oxygenation in adults with severe respiratory failure: a multi-center database. *Intensive Care Med*. 2009;35:2105.
101. Domico MB, Ridout DA, Bronicki R, et al. The impact of mechanical ventilation time before initiation of extracorporeal life support on survival in pediatric respiratory failure: a review of the Extracorporeal Life Support Registry. *Pediatr Crit Care Med*. 2012;13:16.
102. Norfolk SG, Hollingsworth CL, Wolfe CR, et al. Rescue therapy in adult and pediatric patients with pH1N1 influenza infection: a tertiary center intensive care unit experience from April to October 2009. *Crit Care Med*. 2010;38:2103.
103. Turner DA, Rehder KJ, Peterson-Carmichael SL, et al. Extracorporeal membrane oxygenation for severe refractory respiratory failure secondary to 2009 H1N1 influenza A. *Respir Care*. 2011;56:941.

104. Extracorporeal Life Support Organization (ESLO) Guidelines for Adult Respiratory Failure v1.3. 2013. Available at: http://www.elso.org/Portals/0/IGD/Archive/Management of Mechanical Ventilation During Extracorporeal Membrane Oxygenation.
105. Marhong, JD, Telesnicki T, Munshi L, Del Sorbo L, Detsky M, Fan E. Mechanical ventilation during extracorporeal membrane oxygenation. An international survey. *Ann Am Thorac Soc*. 2014;11(6):956-961.
106. Peter JV, John P, Graham PL, Moran JL, George IA, Bersten A. Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: meta-analysis. *BMJ*. 2008;336:1006.
107. Tang BM, Craig JC, Eslick GD, Seppelt I, McLean AS. Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: a systematic review and meta-analysis. *Crit Care Med*. 2009;37:1594.
108. Gattinoni L, Tognoni G, Pesenti A, et al. Effect of prone positioning on the survival of patients with acute respiratory failure. *N Engl J Med*. 2001;345:568.
109. Sud S, Friedrich JO, Taccone P, et al. Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis. *Intensive Care Med*. 2010;36:585.
110. Willson DF, Thomas NJ, Markovitz BP, et al. Effect of exogenous surfactant (calfactant) in pediatric acute lung injury: a randomized controlled trial. *JAMA*. 2005;293:470.
111. Kawakami H, Ichinose F. Inhaled nitric oxide in pediatric cardiac surgery. *Int Anesthesiol Clin*. 2004;42(4):93-100.
112. Ichinose F, Roberts Jr JD, Zapol WM. Inhaled nitric oxide: a selective pulmonary vasodilator: current uses and therapeutic potential. *Circulation*. 2004;109(25):3106-3111.

30 Shock

Jordan S. Rettig, Olivia L. Hoffman

Outline

Learning Objectives

After reading this chapter, the reader will be able to:

1. Define *shock* and the key elements of shock pathophysiology.
2. Understand the concept of oxygen delivery and consider it in the context of select pediatric clinical cases.
3. Recognize the clinical presentation of select shock states—anaphylaxis and sepsis—and describe basic principles of management and treatment.
4. Identify the necessary elements of diagnosing and treating pediatric patients with meningitis.

Key Terms

anaphylaxis
meningitis
oxygen delivery
sepsis
shock

SHOCK

Shock represents a disruption of the natural homeostasis that exists within the body to ensure adequate oxygen delivery to all tissues. In this abnormal metabolic state, the body is unable to maintain a sufficient supply of oxygen despite often increased demand, resulting in a complex cascade of compensatory mechanisms designed to restore this balance. When untreated, shock may lead to organ failure and death, particularly when the recognition of its onset is delayed. *Cardiac output* is the term typically used to encompass the delivery of blood and thus oxygen to organs and tissues in the body. Thus, in shock, cardiac output is impaired; the nature of this impairment is based on the specific shock state.

DEFINITION AND CLASSIFICATION

Formally defined, shock represents an acute abnormal physiologic state characterized by inadequate delivery of oxygen and other nutrients to meet metabolic demand. In some shock states, there may be impaired oxygen utilization despite appropriate delivery. At a cellular level, these derangements result in less efficient energy metabolism, with diversion to secondary metabolic pathways (e.g., anaerobic) to maintain cellular function. When shock is unchecked, cellular function is severely compromised, with resultant cell death and a refractory shock state. If shock is reversed and tissue oxygenation is restored, organs and organ systems can function better. Although there are common features that characterize shock states, it is of value to discuss the nomenclature of various shock states (Table 30-1).

Typically, shock can be classified into four general states: hypovolemic, cardiogenic, obstructive, and distributive. The first, hypovolemic shock, is most common worldwide among infants and children, most often resulting from severe dehydration. When there is a loss of intravascular volume, cardiac output is impaired as stroke volume decreases. In hypovolemic shock, rapid restoration of the vascular volume is paramount. For hemorrhagic shock, a subtype of hypovolemic shock, acute blood loss causes shock and thus treatment requires replacement of the lost blood volume. Other potential causes of hypovolemic shock include osmolar diuresis such as from diabetic ketoacidosis or infectious enteritis. Healthy children often have intact compensatory mechanisms, which allow them to tolerate acute losses of 10% to 15% of their circulatory blood volume. Early signs of compensated hypovolemic shock include tachycardia, decreased pulse pressure, and peripheral vasoconstriction, with often a normal systemic arterial blood pressure. With timely and aggressive volume resuscitation, this shock state can readily be reversed.

Table 30-1 Pathophysiologic and Clinical Shock Classification

Hypovolemic	Low-volume shock state with intravascular volume loss as cause; examples include severe dehydration and hemorrhage leading to hemorrhagic shock
Cardiogenic	Primary heart pump failure with resultant low cardiac output; examples include myocarditis and cardiomyopathy
Obstructive	Physiologic or physical impairment to heart pump function resulting in low cardiac output state; examples include cardiac tamponade and pulmonary embolism
Distributive	Low systemic vascular resistance and high cardiac output state resulting in maldistribution of blood flow; examples include septic shock, anaphylaxis, adrenal crisis, and neurogenic shock

Cardiogenic shock, as its name implies, describes primary failure of the heart pump. In children, cardiogenic shock may be observed after cardiac surgery or from primary disease processes such as myocarditis or cardiomyopathy; however, the list of etiologies is long, making diagnosis and treatment of the underlying cause a challenge. In each of these instances, cardiovascular function is impaired, and often vasoactive or mechanical support such as extracorporeal membrane oxygenation (ECMO) may be required to prevent cardiac and systemic ischemia. As described in detail later in this chapter, the goal of these therapies is to optimize cardiac output by optimizing the preload, afterload, and contractile function of the heart.

A third classification of shock is obstructive, which characterizes a shock state in which a physical obstruction to blood flow impairs cardiac output and ultimately oxygen delivery. Examples include cardiac tamponade, tension pneumothorax, and pulmonary embolism. In this type of shock, intravascular volume and myocardial function are normal, but there is a functional obstruction to intrathoracic blood flow impeding the heart's ability to pump blood and thus oxygen to the body.

The final and perhaps most broad category of shock is distributive, which includes such shock states as sepsis, anaphylaxis, adrenal crisis, and neurogenic shock. Each of these shock states is characterized by a maldistribution of blood flow to tissues with a resultant low systemic vascular resistance state. Whether mitigated by cytokines released by infectious organisms, histamine release secondary to allergen exposure, or loss of sympathetic tone from decreased adrenergic or neuronal control, each of these shock states results in insufficient oxygen delivery or utilization to meet the body's metabolic demands. Given the significance of septic and anaphylactic shock to morbidity among pediatric patients, this chapter discusses these shock states more extensively.

Sepsis

Sepsis, or sepsis syndromes are differentiated by the role of infection in their pathophysiology; however, the potential for culture-negative sepsis does exist. As illustrated in Box 30-1, there is a broad but specific spectrum of sepsis syndromes in pediatric patients. The latest definitions of sepsis and septic shock, as outlined by Sepsis-3, published in 2016, define sepsis as "life-threatening organ dysfunction caused by a dysregulated host response to infection" and septic shock as "a subset of sepsis in which underlying circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone."[1,2] Septic shock, which is a common cause for admission to the pediatric intensive care unit, is often a complication of hypovolemia, and has distributive and sometimes cardiogenic shock features. Early septic shock can often be managed with volume resuscitation, antimicrobials, and supportive therapy; however, once progressed, it may require vasoactive support as detailed later. Late or refractory septic shock may not respond to fluids and catecholamines and may rapidly progress to multiorgan dysfunction, failure, and death. The key to the management of septic shock is early identification and early, appropriate antimicrobial treatment.

Box 30-1 Definition of Sepsis and Sepsis Syndrome in Pediatric Patients

Bacteremia: Culture-confirmed presence of live bacteria in blood

Infection: Lab confirmation of infection (e.g., polymerase chain reaction, stain or culture) or clinical syndrome with high probability of infection (e.g., community-acquired pneumonia)

SIRS: Meets at least 2 of 4 criteria, one of which must be abnormal temperature or WBC count
1. Core temperature abnormality
2. Tachycardia or bradycardia
3. Tachypnea
4. WBC count elevated or depressed

Sepsis: SIRS criteria with infection

Sepsis syndrome: Sepsis plus at least one of the following: acute mental changes, decreased PaO_2, increased plasma lactate, or decreased urine output

Septic shock: Sepsis syndrome plus hypotension that responds to fluid therapy and/or drug therapy

Refractory septic shock: Sepsis syndrome plus hypotension for more than 1 hour that is not responsive to fluid and/or drug therapy and necessitates use of vasopressors

Multiple organ system failure: Any combination of disseminated intravascular coagulation, acute respiratory distress syndrome, renal failure, and hepatobiliary dysfunction

SIRS, Systemic inflammatory response syndrome; *WBC,* white blood cell.
From Goldstein B, Giroir B, Randolph A: International Consensus Conference on pediatric sepsis: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med* 6(1):2, 2005.

Gram-positive and gram-negative bacteria, as well as viruses, may cause septic shock, with the clinical patterns of shock often distinguishable by organism. Classically described as "cold shock," gram-negative organisms often result in severe vasoconstriction, with epinephrine typically the vasoactive agent of choice. Gram-positive sepsis more often manifests as "warm" or vasodilatory shock, with norepinephrine used to increase systemic vascular resistance and thus cardiac output. In this "warm" or "hyperdynamic" shock state, the cardiac output is increased, reflecting high-output failure, and the concurrent decrease in systemic vascular resistance results in impaired oxygen delivery and utilization.

When septic shock is refractory to fluid or catecholamines, consideration must also be given to adrenal insufficiency as a component of the shock state, particularly in patients who are at risk for impairment in their hypothalamic-pituitary-adrenal axis or who have had a history of steroid exposure. In such patients, the clinical status may not improve unless the patient receives "stress-dose" steroids with hydrocortisone.[2]

Select patients with refractory shock who fail conventional therapy may be considered for salvage therapy with ECMO. For these individuals, ECMO can provide circulatory support until the causative organism is sufficiently treated to allow for potential and gradual organ system recovery. The risk of morbidity and mortality with ECMO for septic shock patients remains high; thus its use is limited. Patients may require central cannulation to venoarterial ECMO to sustain adequate circulation. The current algorithm for management of sepsis is best detailed in the *Surviving Sepsis Campaign: Revised 2011 Guidelines* (Figure 30-1).[3]

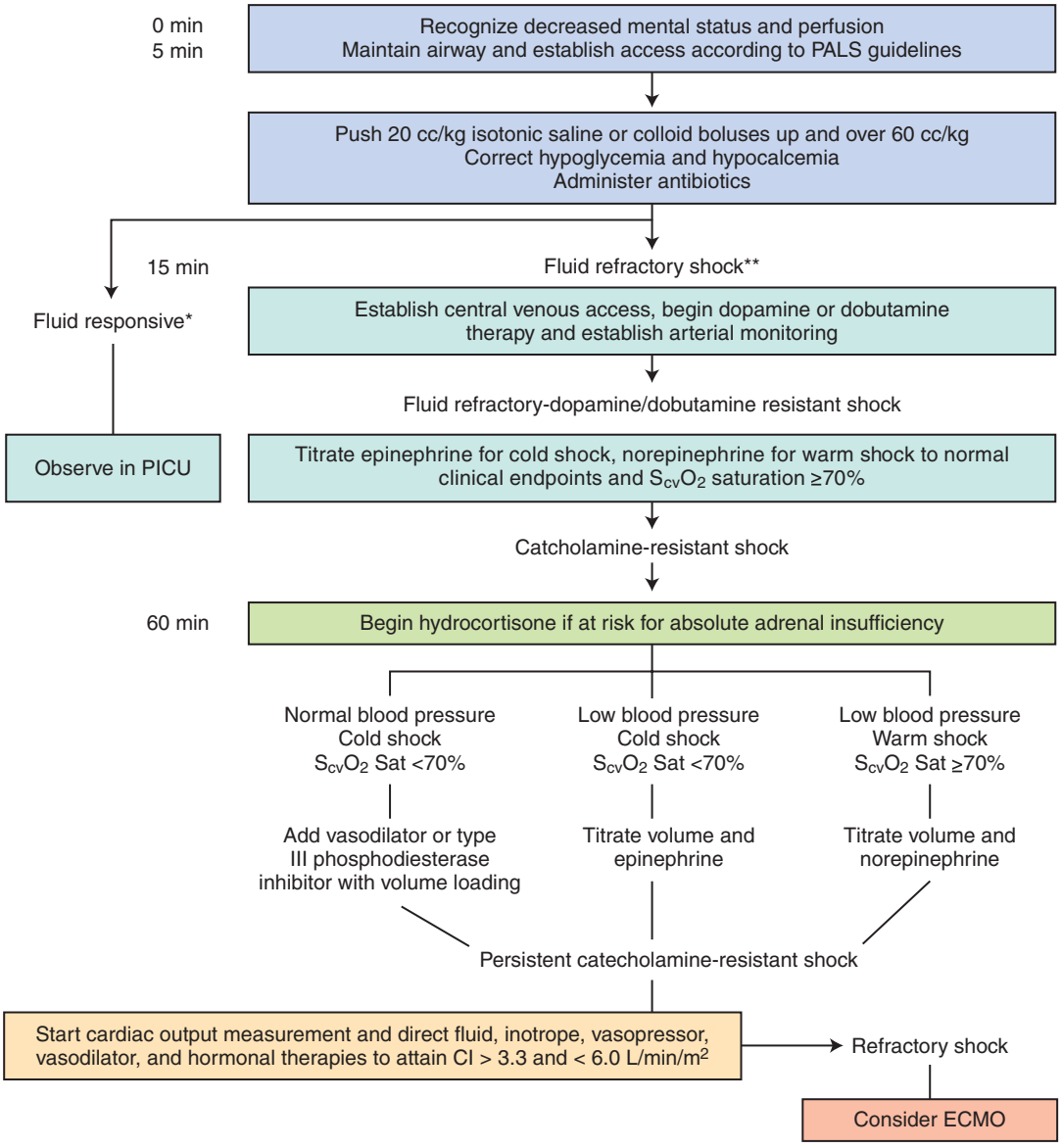


FIGURE 30-1 Algorithm for pediatric shock treatment. *CI,* Cardiac index; *ECMO,* extracorporeal membrane oxygenation; *PALS,* Pediatric Advanced Life Support; *PICU,* pediatric intensive care unit. (From Dellinger RP, Levy MM, Carlet JM, et al.: Surviving Sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 36(1):296-327, 2008.)

Anaphylaxis

A second type of distributive shock that results from peripheral vasodilation is anaphylactic shock. **Anaphylaxis** occurs when a foreign antigen interacts with the body and elicits a systemic, immediate hypersensitivity reaction caused by immunoglobulin E–mediated release of mediators from tissue mast cells and circulating basophils.[4] A variety of substances can elicit these reactions.[5,6] There are times, however, when a cause of anaphylaxis may not be found despite an exhaustive search.[7,8]

After the introduction of an antigen into the body, either by an enteral or parenteral route, reaction with the IgE antibody on tissue mast cells or circulating basophils occurs. This evokes the release of a number of chemical mediators responsible for the clinical and hemodynamic symptom complex elicited. Histamine is one of the most prominent mediators and is believed to be responsible for the increase in airway resistance and the fall in partial pressure of oxygen as a result of its contractile action on the smooth muscle of the lung.[7] There is vasodilation and increased vascular permeability that produce a rapid loss of intravascular volume, which then stimulates the release of catecholamines. Initially, systemic vascular resistance is reduced and cardiac output is increased; however, with prolonged shock these reverse and the decrease in preload and afterload leads to myocardial depression.

The presentation of a child with anaphylaxis varies depending on the severity of symptoms. Some children may present with only a skin eruption or edema, whereas other patients may present with respiratory compromise or cardiovascular collapse and shock characteristic of an overt anaphylactic episode.[6,7] The presentation with an urticarial rash or respiratory symptoms is much more common than a cardiovascular source of symptoms.[5,8] However, shock and cardiovascular collapse can occur without a preceding cutaneous manifestation.[7] Other presenting symptoms may include gastrointestinal complaints or neurologic symptoms such as dizziness, headache, or syncope. Symptoms may begin within minutes of antigen presentation or may be delayed for several hours. If symptoms begin immediately on exposure, the reaction tends to be more severe and can be rapidly fatal. An episode may be biphasic, in which symptoms abate for several hours and then return. Attacks may also persist for several days and have multiple recurrences with asymptomatic periods in between.

The rapid recognition of anaphylaxis and prompt initiation of therapy is essential. The treatment of anaphylactic shock can be divided into two major phases. First, as with any shock state, attention is directed to the ABCs—airway, breathing, circulation. Airway compromise may be present and takes priority. Once the airway is secure, oxygenation and ventilation are assessed. There is often bronchospasm with concomitant wheezing. Providing oxygen will help ensure adequate oxygenation, and the wheezing often abates with the administration of epinephrine for circulatory support. Epinephrine is the mainstay of therapy. Circulatory dysfunction and shock are the next most pressing issues. For circulatory collapse, large volume infusions, as in other types of shock, help to restore the circulating blood volume. Hypotension can be severe and resistant to therapy. Circulatory support with repeated doses of epinephrine and a continuous epinephrine infusion help support the patient until the directed therapy can begin.[4,5]

Once the vital functions have been addressed, attention should turn to combating the antigen exposure. If the antigen and route are known—for instance, if a blood transfusion is being administered—limitation the antigen exposure becomes the next priority. Antihistamines should be given to counter the effect of the inciting mediator. A combination of H1 (diphenhydramine) and H2 (ranitidine) inhibitors is superior to an H1 antagonist alone for resolution of symptoms.[7] Corticosteroids may have a role in anaphylaxis by improving the inflammatory response and may help alleviate late-phase reactions. Aerosolized β-adrenergic agents may be useful if the bronchospasm is unresponsive to epinephrine.[7]

PATHOPHYSIOLOGY

The key pathophysiologic derangement that occurs in shock is the impairment of oxygen delivery and utilization. Without adequate cardiac output, oxygen cannot be effectively delivered to body tissues, and the systemic effects of this substrate-depleted state result in the clinical manifestations of shock.

Cardiac Output

In physiologic terms, the cardiac output is the amount of blood pumped from the heart to the organs and tissues of the body. It can be expressed mathematically as liters of blood pumped per minute.[9] Children are different from each other in terms of their size, so all hemodynamic measurements must be corrected for these size differences. When the cardiac output is corrected for size, the cardiac index (cardiac output divided by body surface area) is derived.[10] In children, normal values for the cardiac index are in the range of 3.3 to 6.0 L/minute/m^2.[2,11] A cardiac index of less than 2.0 L/minute/m^2 has been associated with an increase in mortality.[2]

The cardiac output is determined by the heart rate and the stroke volume.[2,12,13] The heart rate is simply how fast the heart beats per minute and the stroke volume is the amount of blood pumped out of the heart with each mechanical beat. Three components contribute to the stroke volume: preload, ionotropy, and afterload.[12,14]

Components of Stroke Volume

Preload is measured as the central venous pressure, is a representation of the amount of volume present in the

heart and great vessels at rest, and is dependent on adequate venous return. Preload varies as the intravascular volume increases and decreases. The Frank-Starling principle states that the initial stretch on the myocardial muscle fibers, and the resultant contractile ability, increases up to a threshold limit determined by the individual's myocardial compliance.[14] At this point, the contractile ability cannot increase further (Figure 30-2).

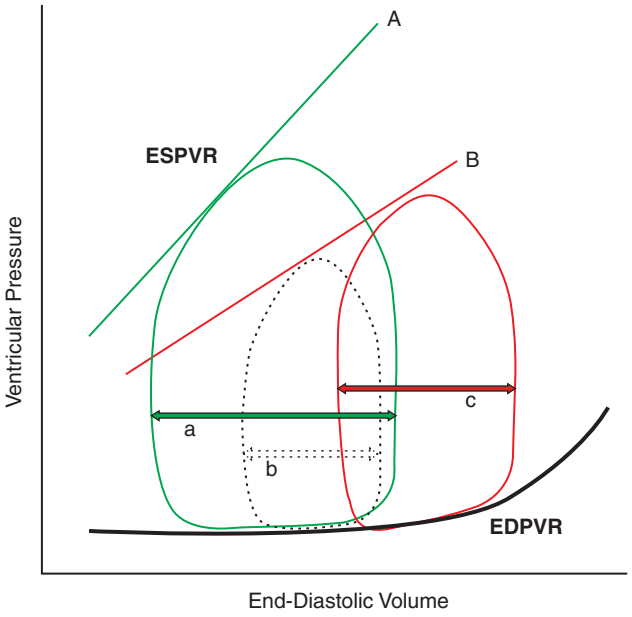


FIGURE 30-2 Pressure-volume loops in the normal and failing ventricle. Decreased inotropy (systolic failure) shifts the pressure-volume loop along its end-systolic pressure volume relationship *(ESPVR)* from line A to line B, resulting in a decreased stroke volume (ray *a* to ray *b*). During compensation, the ventricle partially restores stroke volume (ray *c*) by increasing its end-diastolic volume (EDV), which necessitates operating at a higher filling pressure. Note the shape of the end-diastolic pressure volume relationship *(EDPVR).* (Adapted from Rogers Pediatric Intensive Care. From Costello JM, Mazwi ML, McBride ME, et al.: Critical care for paediatric patients with heart failure. *Cardiol Young* 25 Suppl 2:74-86, 2015.)

Inotropy is the term that characterizes the contractile state of the heart muscle. Inotropic problems may occur despite an adequate preload if the contractile state is compromised. Further, problems with contractility increase the susceptibility of the myocardium to increases in afterload.[1] When discussing therapeutic interventions, it is important to differentiate inotropes from vasopressors, as they will have very different implications for cardiac output.

Afterload is a measure of the resistance or force against which the heart must pump. Resistance to the flow of blood in a vessel is proportional to the length of the vessel and the viscosity of the blood and inversely proportional to the radius of the vessel to the fourth power.[10] The vessel's cross-sectional area determines the vascular resistance and is highly dependent on the arterial elastance. Generally speaking, as afterload increases, stroke volume decreases. Infants and children have a limited ability to increase stroke volume and instead will attempt to compensate for a reduction in cardiac output by increasing their heart rate.[8] Therefore tachycardia is one of the first signs of compromised perfusion and oxygen delivery in children. Hypotension is an unreliable and late finding of shock in children, occurring when the compensatory mechanisms have already failed.[15,16]

Shock should be thought of as a problem of supply and demand and can be classified by the adequacy of the cardiac output or its components: heart rate, preload, inotropy, or afterload.[17] This schema also provides for therapeutic interventions targeted to the area of the circulatory system experiencing a problem (Figure 30-3). Many of these physiologic parameters can be measured clinically in a child with shock, thereby allowing continuous monitoring and assessment of the response to therapeutic interventions.[10,13,15]

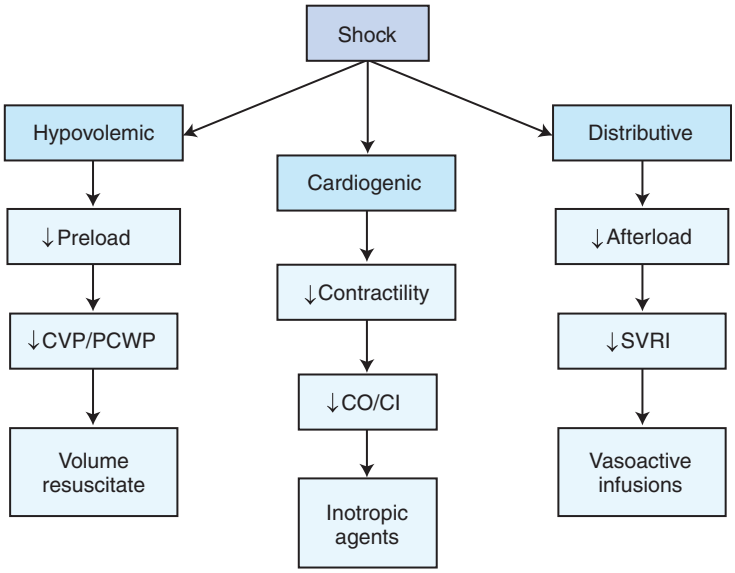


FIGURE 30-3 Diagrammatic representation of shock, its classification, clinical measures of altered stroke volume, and treatment strategies. *CI,* Cardiac index; *CO,* cardiac output; *CVP,* central venous pressure; *PCWP,* pulmonary capillary wedge pressure; *SVRI,* systemic vascular resistance index.

Box 30-2 Formulas for Oxygen Content, Delivery, and Consumption

OXYGEN CONTENT

Ca_{O_2} (mL/dL) = Amount of O_2 dissolved in blood + Amount bound to hemoglobin

Amount of O_2 dissolved (mL of O_2/mL of blood) = 0.003 × Pa_{O_2} (mm Hg)

Amount bound = 1.34 × Hemoglobin (g/dL) × % Oxygen saturation

OXYGEN DELIVERY

D_{O_2} = O_2 Content × Cardiac output

OXYGEN CONSUMPTION

V_{O_2} (mL/minute) = (Arterial − Venous) O_2 content × Cardiac output (mL/minute)

0.003, A constant that represents milliliters of oxygen dissolved in 100 mL of blood; *1.34*, a constant that represents the amount of oxygen that can be bound per gram of hemoglobin

Nutrients and Oxygen in Blood

The cardiac output is responsible for transferring blood and nutrients from the heart to the tissues and organs and back again. The nutrients are carried in the blood by two physical methods.[16] First, some nutrients and oxygen are dissolved in the blood, accounting for a relatively small amount of oxygen transport. Second, nutrients and oxygen can be bound to red blood cells or macromolecules and "carried" by the cardiac output to the site of utilization. Oxygen delivery depends significantly on hemoglobin concentration.[15] The amount of oxygen bound to hemoglobin is described by the oxyhemoglobin dissociation curve and is affected by physical properties such as temperature and acidosis.[18] The contribution of each of these components is symbolized in a mathematical formula that represents the arterial oxygen content (Box 30-2).[18-20] The case study features an example that demonstrates how the mathematical formulas shown in Box 30-2 may be used to quantify oxygen transport. Once the oxygen content is calculated, it can be considered within the framework of the cardiac output.

Oxygen Delivery

The concept of oxygen delivery is fundamental to the understanding of shock and is illustrated by the following clinical highlight.

Delivery of Blood to the Tissues

The cardiac output delivers oxygenated blood to the tissues on a global or systemic level.[14,18,21] Delivery of oxygenated blood, however, is only one part of this complex physiologic process. **Oxygen delivery** depends on oxygen-carrying capacity (% hemoglobin), oxygen provided (oxygen bound to hemoglobin plus dissolved

Clinical Highlight

A 5-year-old girl is in septic shock in the pediatric intensive care unit as a result of an overwhelming infection. She has a hemoglobin level of 10 g/dL, a cardiac output of 4.0 L/minute, and arterial blood gas findings of pH 7.35; P_{CO_2}, 36 mm Hg; Pa_{O_2}, 85 mm Hg; HCO_3^2, 20 mEq/L; and a corresponding oxygen saturation of 95%. A mixed venous blood sample demonstrates pH, 7.32; P_{CO_2}, 34 mm Hg; Pa_{O_2}, 37 mm Hg; and an oxygen saturation of 62%.

Calculate the oxygen content, delivery, and consumption as follows:

ARTERIAL OXYGEN CONTENT

Ca_{O_2} = Amount dissolved in blood + Amount bound to hemoglobin (arterial side)

Amount dissolved = 0.003 × Pa_{O_2}

Amount dissolved = 0.003 × 85 mm Hg
= 0.255 or 0.255 mL of O_2 in 100 mL of blood

Amount bound = 1.34 × Hemoglobin × % O_2 saturation

Amount bound = 1.34 × 10 × 0.95 = 12.73 mL of oxygen per 100 mL of blood

CaO_2 = 0.255 + 12.73
= 12.99 mL of O_2 per 100 mL of blood

MIXED VENOUS OXYGEN CONTENT

$C\bar{v}o_2$ = Amount dissolved + Amount bound to hemoglobin (venous side) = 0.003 × $P\bar{v}o_2$

Amount dissolved = 0.003 × $P\bar{v}o_2$

Amount dissolved = 0.003 × 37 mm Hg
= 0.115 or 0.115 mL of O_2 in 100 mL of blood

Amount bound = 1.34 × Hemoglobin × % O_2 saturation

Amount bound = 1.34 × 10 × 0.62
= 8.31 mL of O_2 per 100 mL of blood

$C\bar{v}o_2$ = 0.115 + 8.31 = 8.425 mL of O_2 per 100 mL of blood

OXYGEN DELIVERY

D_{O_2} = O_2 content × Cardiac output

D_{O_2} = 12.99 mL of O_2 per 100 mL of blood × 4000 mL/minute

Arterial D_{O_2} = 519.6 mL/minute

OXYGEN CONSUMPTION

$\dot{V}o_2$ (mL/minute) = (Arterial − Venous) O_2 content × Cardiac output (mL/minute)

$\dot{V}o_2$ (mL/minute) = (12.99 − 8.425) mL of O_2 per 100 mL of blood × 4000 mL/minute = 182.6

oxygen), and cardiac output.[2] Once oxygenated and nutrient-rich blood reaches the target organ, the organ must be able to utilize the substrates it receives.[21] There must be uptake of oxygen in the tissues and cells of the organ along with the exchange of organ byproducts that are then transported back to the lungs. A major component of these byproducts is carbon dioxide, which has a higher solubility in the blood than oxygen.[18]

Oxygen consumption is a measure of the amount of oxygen, or substrate, utilized by the organs of the body.[17] Comparing the amount of oxygen being supplied to the organs from the arterial circuit and the amount of oxygen remaining in the venous circuit after removal by the organs provides an estimate of how much is being consumed.[18,22,23] As cardiac output decreases and metabolic demands remain the same, the tissues will extract more oxygen to maintain the same consumption, but the oxygen returning to the heart in the venous circulation will be less.[2] In children, oxygen consumption depends more on oxygen delivery than oxygen extraction.[15] Oxygen consumption greater than 200 mL/minute/m^2 has been associated with improved survival.[2,15] The amount of nutrient consumed by the organs relative to delivery is referred to as the *oxygen extraction*.[21] Oxygen extraction is independent of supply for patients with shock. As shock worsens, organ tissue perfusion decreases, and the organ extracts fewer nutrients from the blood. This measure of the severity of shock has been associated with survival.[10] Regardless of the cause of the shock, alterations in cellular metabolism, mitochondrial dysfunction, abnormal carbohydrate metabolism, and the failure of many energy-dependent enzyme reactions lead to difficulty with utilization of substrate at the cellular level and eventually cell death.[12] These changes in cellular oxygen utilization alter the consumption of oxygen in each of the organs, leading to organ dysfunction. Organ system dysfunction resulting from shock, if left untreated, ultimately leads to failure of multiple organ systems. The term *multiorgan dysfunction syndrome* (MODS) has been applied to this disseminated pathologic response.[12]

Metabolic Response

The body's response to poor tissue perfusion results in a number of metabolic reactions. Many of the manifestations of shock represent the body's compensatory mechanisms, which attempt to maintain effective tissue perfusion and correct the abnormalities of shock. These responses attempt to maintain mean circulatory pressure, maximize cardiac output, redistribute perfusion to the most vital organs, and optimize the unloading of oxygen to the tissues.[12] The compensatory mechanisms are designed to autoregulate in the setting of hemodynamic or metabolic dysfunction.

The central nervous system releases adrenocorticotropic hormone in the setting of stress, which stimulates the adrenal glands to release cortisol. Adequate adrenocortical function is essential to survive critical illness, and most critically ill patients will exhibit elevated cortisol levels.[2,24] Many patients, however, exhibit a state of "relative" adrenal insufficiency because of an inadequate production of cortisol.[24] The sympathetic nervous system is regulated by arterial and cardiopulmonary baroreceptors and releases epinephrine and norepinephrine, which increase cardiac output by increasing heart rate and stroke volume. Cortisol assists the actions of these two catecholamines. Intrinsic vasoactive substances are released in response to increased metabolic activity and oxygen tension. The angiotensin/aldosterone–antidiuretic hormone/vasopressin system is activated to preserve intravascular volume.[2] Other vasodilators released locally and systemically include nitric oxide, prostacyclin, and kinins; vasoconstrictors include endothelin, renin, and oxygen free radicals. These substances affect the vascular tone and systemic vascular resistance, and therefore blood pressure.

The inflammatory response is a physiologic homeostatic mechanism designed to respond to injury or infection. Inflammatory mediator release usually provides beneficial effects; however, in shock, the inflammatory response becomes unregulated.[12] The production of immune mediators is triggered by ischemic or hypoxic insults and produces further tissue injury. Systemic inflammatory response syndrome (SIRS) is the term used to describe the nonspecific inflammatory process that accompanies these insults.[16] The immune response leads to changes in T and B lymphocyte responses, activation of the complement cascade, activation of coagulation factors, and cytokine release (tumor necrosis factor [TNF] and interleukin [IL]-6). These mediators exert their influence on the vasculature to produce inadequate perfusion or direct cellular injury.[12] All of these contribute to organ dysfunction and the eventual signs and symptoms the body may experience in shock.

MANAGEMENT AND TREATMENT

General Considerations

The overall goals of treatment for shock are to maintain adequate tissue perfusion, avoid end-organ damage, and treat the underlying primary process. Therapeutic strategies should enhance delivery of oxygen and nutrients to tissues, reduce oxygen demand, and correct metabolic abnormalities. Continuous monitoring of the patient's response to interventions is critical and may lead to redirection of therapies. Early aggressive therapy for shock, focused on maintaining blood pressure and oxygen delivery, improves outcomes in critically ill children.[1]

Assessment and Evaluation

The approach to the child in shock begins with an evaluation of vital functions as expounded by the ABCs of resuscitation.[25] Maintenance of the airway and attention to oxygenation and ventilation are the initial priorities no matter the type of shock. The circulatory system is evaluated by the presence of a pulse. The presence and quality of the pulse reflect systemic vascular tone as well as cardiac output. If a pulse is absent, cardiopulmonary resuscitation (CPR) needs to be performed and cardiotonic medications consistent with advanced life support need to be administered.[25] Vascular access should be rapidly obtained, and if there is difficulty with peripheral venous access, an intraosseous or central venous route should be used.[15]

Once the ABCs are established, attention should be directed to measuring vital signs and performing a secondary survey. Normal values for pulse, respiratory rate, and blood pressure are age dependent. The knowledge of these age-related differences is essential to medical care for any child.[16,29]

Next, a brief and directed patient history and physical examination should be obtained, focused on determining a potential cause of the shock. It is key to obtain essential information regarding the patient's medical history, especially any history of congenital heart disease, immunodeficiency, trauma, toxic ingestions or exposures, medications, and allergies.

Healthcare providers should evaluate the patient's systemic perfusion, which reflects the effectiveness of cardiac output. Capillary refill—the process of blanching the skin for several seconds and timing the return of blood flow to the blanched skin—is a quick, useful, and noninvasive assessment that provides important information regarding perfusion in the acute setting.[25] The normal capillary refill time should be less than 2 seconds, which correlates with a cardiac index (CI) of more than 2.0 L/minute/m^2.[25] Prolongation of capillary refill is considered a sign of inadequate tissue perfusion and ongoing or impending shock. Providers often next evaluate perfusion to the skin, the brain, and the kidney, because they are easy clinical assessments to perform and correlate better with hemodynamic measurements than capillary refill.[27]

Evaluation of skin color and temperature is easily performed by look and touch during a clinical examination. Children in shock may have pale, cyanotic, or mottled skin because of poor perfusion. Traditionally, practitioners have described two phases of septic shock.[2,15] In early septic shock, the skin appears well perfused, warm, and pink, which occurs from peripheral vasodilation and increased cardiac output. Later in the course of shock, cardiac output begins to fall, so the skin is likely to be cool, cyanotic, or mottled, which represents a decrease in the amount of substrate reaching the skin. Further assessment of the skin of a child with shock may reveal petechiae, poor skin turgor, or other rashes indicative of coagulopathy, hypovolemia, or an infectious etiology.

Examining the child's mental status, particularly the level of awareness, orientation, and response to commands, can assess perfusion to the child's brain. It is important to ensure that medications that might obscure the examination, such as opioids or benzodiazepines, have not been given. Children in shock may show signs of agitation or restlessness. Alternatively, they may also have a mental status that is stuporous or comatose. Using the Glasgow Coma Scale (GCS) may be a useful tool to gauge the child's mental status as well.

Monitoring the child's urine production assesses perfusion of the intraabdominal organs. If the child is making adequate urine (at least 1 mL/kg/hour), then the cardiac output to the kidneys, which produces renal blood flow and drives glomerular filtration, is considered adequate. Both the kidney and the brain have vasomotor autoregulation mechanisms that maintain blood flow and perfusion in shock until a critical threshold is reached and perfusion pressure falls below the ability of the organ to maintain adequate blood flow.[2,15] At this point, the shock is classified as decompensated shock. In decompensated shock, the blood pressure falls, compromising perfusion of end organs.

Laboratory values can often provide useful clues to the proper diagnosis and management of shock. Evaluation of the acid–base status including routine electrolytes and a blood gas (preferably arterial) with the calculation of the anion gap are important first steps.[28] As shock progresses, a metabolic acidosis and an elevated lactate level may occur. Lactate is a measure of anaerobic metabolism and is often elevated in shock but can also be elevated in many conditions in the absence of shock.[2]

Anemia, thrombocytopenia, and elevation of prothrombin time and partial thromboplastin time (PT/PTT) may identify a coagulopathy or disseminated intravascular coagulation (DIC). An elevated or reduced white blood cell count, leukocytosis or leukopenia, respectively, may indicate the presence of infection or an immunodeficiency. Elevated liver enzymes or serum creatinine may suggest hypoperfusion to the liver and kidneys, respectively, and the potential for subsequent dysfunction in these organs. An electrocardiogram and chest radiograph are often obtained in the initial evaluation for the cause of shock.

Monitoring

A child in shock requires ongoing assessment, intervention, and reassessment. Attention to the effects of an intervention on vital signs and end-organ perfusion must be continually observed. Children with

fluid-responsive shock can often be monitored with standard noninvasive methods, such as an automatic blood pressure cuff; however, if the child fails to respond to intravenous fluid boluses (e.g., more than 60 mL/kg), additional strategies for monitoring and maintaining age-appropriate vital signs may need to be incorporated. Furthermore, if a treatment does not have its intended effect on restoring homeostasis, the therapeutic approach and underlying cause need to be reconsidered.

A number of technologies are available in the pediatric intensive care unit (PICU) for the assessment and monitoring of a child in shock. These techniques augment the information derived from the vital signs and physical examination. The arterial catheter, CVP monitor, and pulmonary artery (PA) catheter are three of the more common strategies used to detect physiologic changes and supplement the clinical assessment of a child in shock. Echocardiography can also be an important noninvasive technique that provides valuable information regarding cardiac structure and function as contributors to the shock state.[13]

The placement of a catheter in a peripheral or central artery can be performed for the monitoring of blood pressure on a continuous basis in the PICU. Arterial catheterization can provide beat-to-beat monitoring of blood pressure.[12] The shape and characteristics of the waveform provide additional information regarding the characteristics of the cardiac output, including volume, afterload, and contractility. An arterial catheter also allows the medical team to regularly obtain blood samples for arterial blood gases.

The placement of a catheter in the central venous system, often in the internal jugular, subclavian, or femoral vein, allows for an assessment of the volume status of a child with shock. The catheter, when attached to a continuous column of fluid and a pressure transducer, measures the downstream intravascular pressure, or CVP, in the right atrium. This intravascular pressure represents preload, one of the contributors to stroke volume, which contributes to cardiac output. Because the left side of the heart receives its blood from the right side of the heart, the measurement of these right-sided heart pressures is accepted as an alternative for the dynamics on the left side of the heart in a patient whose myocardial and pulmonary compliance is normal. If biventricular function is equal and pulmonary artery resistance is low, CVP measurements closely reflect pulmonary artery wedge pressure.[29] This information helps the provider to diagnose and treat a patient in shock. If the CVP is high in the setting of normal myocardial compliance, then the intravascular volume is adequate and may not be accounting for the reduction in cardiac output. The CVP may be elevated if blood is unable to be ejected because of a failing myocardium. If the CVP is low, additional intravenous fluid needs to be given to improve the intravascular volume deficit being observed. A central venous catheter also provides easy access for blood sampling and measuring mixed venous oxygenation and provides access for rapid fluid resuscitation and provision of inotropic medications, if necessary.

The use of a PA catheter in children has been debated, but in children with fluid-refractory and dopamine-resistant shock, the PA catheter may provide additional information to make a more appropriate assessment of the hemodynamic status of the patient.[15,30] The use of PA catheters in children is supported by the American College of Critical Care Medicine for circumstances in which irreversible shock, manifesting as poor perfusion, acidosis, and hypotension, persists despite the use of therapies directed at the arterial blood pressure, CVP, and oxygen saturation indices.[13] In addition to the measurements obtained directly from the PA catheter, a number of derived values provide information regarding the homeostatic function of the child, including systemic vascular resistance as a measure of afterload and oxygen consumption and oxygen extraction.[31]

System-Based Treatment Approach

Respiratory. Airway and breathing should be rigorously monitored and maintained for patients in shock. Endotracheal intubation with mechanical ventilation may reduce the work of breathing and optimize oxygen demand. During intubation, induction agents, cardiotonic medications, and respiratory support modes must be chosen carefully, so as not to worsen an already compromised cardiovascular status.

Vascular volume. The rapid restoration of an adequate circulating blood volume is essential for a patient in shock regardless of the cause.[29-33] Crystalloid solutions, such as normal saline or lactated Ringer's solution, are the fluids of choice for initial resuscitation, because they maintain intravascular volume.[2,12,15,32,33] The use of colloids, such as albumin or starch, to maintain intravascular volume has not been demonstrated to have a beneficial effect on survival.[2,12,15] If there is evidence of anemia or suspected loss of blood, repletion of the intravascular volume with packed red blood cells should be performed.[2,15,16]

The initial administration of 20 mL/kg of fluid is recommended.[2,15,25,33] Reassessment of the patient's condition based on vital signs and end-organ perfusion helps determine the need for additional fluid.[13] The administration of intravenous fluid should decrease the heart rate and increase the MAP and CVP. Carcillo and colleagues demonstrated that when the initial amount of volume resuscitation administered within the first hour was cumulatively greater than 40 mL/kg, survival rates were improved[27]; therefore both the

amount of fluid and the rapidity of administration have outcome benefits. Rapid volume resuscitation restores intravascular volume and reduces the inflammatory response and coagulopathy that often accompany shock.[2] Large fluid deficits typically exist, and initial volume resuscitation usually requires 40 to 60 mL/kg but can be as much as 200 mL/kg in some cases of septic shock.[2,15,34] Continued fluid losses and persistent hypovolemia as a result of capillary leak can persist despite fluid resuscitation. Ongoing fluid replacement after the initial volume resuscitation is necessary to maintain adequate tissue perfusion, and large volumes may be required, because vascular permeability results in peripheral and third space losses.[34] When total administered volumes of 60 mL/kg are reached, intravascular monitoring and initiation of vasoactive support should be considered.

The development of rales, a gallop rhythm, hepatomegaly, and increased work of breathing may all indicate worsening cardiovascular function leading to pulmonary edema, because of the relationships according to the Frank-Starling principle.[35] Additional aliquots of fluid may be contraindicated at this point.[30,36] In these instances, careful invasive monitoring with PA catheters can provide valuable information and help guide further management.

Myocardial function. Once the intravascular volume is optimized, manipulation of other components of cardiac output should be attempted. Abnormalities in heart rate resulting in poor perfusion and shock should be addressed quickly. An unstable tachycardia, manifested with hypotension or signs of shock, should be treated with electrical therapy in the form of synchronized cardioversion or defibrillation immediately as per the Pediatric Advanced Life Support (PALS) algorithms.[25] Cardioversion synchronizes the delivery of the shock with the QRS complex to prevent deterioration to a more lethal arrhythmia, such as ventricular fibrillation, and should be used in patients who have a palpable pulse. Defibrillation delivers a shock regardless of the timing of the cardiac cycle and is indicated in pulseless rhythms that have resulted in cardiovascular collapse.[25]

Inotropic dysfunction can result from an abnormality in any of the structures of the heart or the abnormal contractility of the cardiac myocytes. Initially, adequate preload through the judicious use of fluid resuscitation to maintain stroke volume should be ensured. After preload has been restored, additional fluid may worsen the ability of the myocardium to maintain cardiac output, especially in cardiogenic shock; therefore support of the myocardium should then take place with inotropic agents that act by a number of different mechanisms and can be titrated to the appropriate clinical response, including the achievement of appropriate MAP, CVP, and cardiac index to ensure adequate perfusion.[15,36] Inotropic agents are used to increase contractility and cardiac output. Dobutamine is a primarily β1-adrenergic agonist with chronotropic and inotropic actions, as well as afterload reduction. Dopamine, the most commonly used inotrope, has varying α and β effects, depending on the dose. For example, it increases renal blood flow at low doses, while having vasoconstrictive properties at high doses as a result of release of norepinephrine. Epinephrine is a naturally circulating neurohormone, with mixed α and β effects depending on the dose, that increases contractility during stress and shock.[2] At low dose it provides inotropy, but at higher doses it increases peripheral vascular tone and acts as a vasopressor. Patients with heart failure and increased systemic vascular resistance may be harmed by these higher doses unless epinephrine is combined with an inodilator or vasodilator.[2] Norepinephrine is another common inotropic agent, also with mixed α and β effects, and is often effective for dopamine-resistant shock. It is a strong vasoconstrictor even at low doses but has better inotropic effects when combined with an inodilator. Norepinephrine is the first-line vasopressor for septic shock. Vasopressin is a potent vasoconstrictor with V1 and V2 effects leading to increased arterial blood pressure. It is often used as an second or third line vasoactive agent in refractory or catecholamine-resistant shock. In some clinical scenarios, it can replace epinephrine or norepinephrine. Since vasopressin has neurohormonal effects as well, it is important to be mindful that the dosing for use in refractory hypotension is different from that in diabetes insipidus.

Inodilators work through a different mechanism, enhancing inotropy while simultaneously vasodilating and reducing afterload, making it easier for the heart to eject blood.[2,35] Phosphodiesterase inhibitors such as milrinone mediate inotropy and vasodilation by preventing hydrolysis of cyclic adenosine monophosphate cAMP and therefore potentiate the effects of β receptor stimulation in cardiac and vascular tissue.[15] Alone, these improve contractility and diastolic relaxation and also cause vasodilation of pulmonary and systemic arterial vasculature. When combined with inotropes, vasodilators, and vasopressors, the interaction provides even better contractility and relaxation.[2]

If the problem with inadequate cardiac function is related to elevations in afterload, vasodilators should be administered.[36] Vasodilators reduce pulmonary vascular resistance or systemic vascular resistance, thereby improving cardiac output by reducing afterload.[2] Nitroprusside is a systemic and pulmonary vasodilator. Nitroglycerin has dose-dependent effects on coronary artery vasodilation, pulmonary vasodilation, and systemic vasodilation that increase with increasing doses. Prostaglandins can also be used as vasodilators, especially in ductal-dependent congenital heart disease. The use of vasodilators should be titrated to reducing afterload without causing tachycardia or diastolic hypotension. In many circumstances, inotropic agents in

combination with vasodilators may be useful.[2,15,25] Conversely, vasopressors such as norepinephrine and epinephrine increase vascular tone, peripheral vascular resistance, and afterload and have inotropic effects. This helps maintain perfusion to vital organs such as the brain, kidneys, and gastrointestinal tract.

Hematologic. In hemorrhagic shock or anemic shock, intravascular volume should be replaced with packed red blood cells. Although there are variable data regarding the ideal hemoglobin for pediatric patients in septic shock, it is known that mortality rates increase when hemoglobin levels are less than 6 mg/dL. Provision of blood improves circulating blood volume and increases delivery of oxygen and substrate to the tissues.

Coagulation abnormalities occur in all forms of shock. Activation of the coagulation cascade can lead to DIC, which results in thrombocytopenia, decreased fibrinogen, elevated fibrin split products, and microangiopathic hemolytic anemia.[12] In prolonged states of shock, thrombosis and hypofibrinolysis can occur. The rapid reversal of shock often prevents DIC and bleeding.[2] When resuscitation is inadequate, the replacement of clotting factors may be beneficial. Vitamin K, fresh frozen plasma, cryoprecipitate, and platelet transfusions should correct most coagulopathies. Activated factor VII has been effective in reversing refractory hemorrhagic shock in many situations. Patients with hemophilia or von Willebrand disease may need specific replacement therapy to control bleeding.

Endocrine. Maintaining metabolic and hormonal homeostasis is important in children with shock. Adrenal insufficiency is common in the intensive care setting and presents with low cardiac output and high systemic vascular resistance or with high cardiac output and low systemic vascular resistance.[1] Adrenal insufficiency should be considered in any child who is unresponsive to catecholamines, and there is a possibility that adrenal dysfunction actually contributes to the development of catecholamine-resistant shock.[24] This insufficiency has been associated with worsening of multiple organ failure and higher mortality.[24,37] Steroid replacement should be considered when a measured cortisol level is less than 18 mg/dL. Hydrocortisone has glucocorticoid and mineralocorticoid effects and should be given at either a "stress" dose of 2 mg/kg/day or a "shock" dose of 50 mg/kg/day during acute shock.[2,34]

Electrolyte abnormalities are common in the ICU, and following their values is an important part of the evaluation and management of the shock patient. As patients are resuscitated with fluid, sodium values may become abnormal and need correction or they may be abnormal as a part of the presenting signs of dehydration and hypovolemic shock. If kidney dysfunction is present, hyperkalemia may become an issue that contributes to cardiac dysfunction and/or arrhythmias. Hypocalcemia is a common, reversible contributor to cardiac dysfunction and should be treated to maintain normal ionized calcium levels. Increased intracellular calcium increases contractility, whereas decreased calcium leads to relaxation in cardiac and vascular smooth muscle cells.[2] Correction of electrolyte abnormalities is crucial for maintaining stability.

Hyperglycemia occurs as a result of glycogenolysis and gluconeogenesis mediated by increases in adrenocorticotropic hormone, glucocorticoids, glucagons, and catecholamines and decreases in insulin.[12] Hyperglycemia contributes to reduced immune system function and promotes microbial and fungal growth. Although there is now more evidence to suggest that tight glucose control may not be as beneficial as once thought, extremes in either direction are not desirable.[37]

Immunologic. Treatment with broad-spectrum antibiotics with activity against gram-positive and gram-negative organisms should be started as soon as septic shock is considered. The choice of antibiotics should be based on the suspected focus of infection,[39] and the first doses should be given during the initial resuscitation, within 1 hour of recognition of sepsis or septic shock. The choice of antibiotic can be narrowed once an organism is identified. In many cases of septic shock, especially in neutropenic patients, cultures are negative. Despite this, antibiotics are typically continued for up to 14 days. Early antifungal therapy should be considered in immunocompromised patients and in those who are unresponsive to antibacterial therapy with presumed sepsis.

Nutritional status. Nutritional support of a critically ill child has a role in maintaining stability, promoting healing, and improving the outcome from acute or chronic illness.[4,40] The goals of nutritional support are to promote these endpoints while simultaneously providing adequate metabolic substrate for the growth and development of the child.[40] The optimal balance is to maintain an anabolic state with positive nitrogen balance. Ideally enteral or, alternatively, parenteral nutrition should begin as soon as cardiovascular stability is obtained. Early enteral nutrition appeared to prevent gut mucosal atrophy and bacterial translocation.[39] Evaluation of vitamins, trace elements, and immune-modifying nutritional agents did not demonstrate clear benefit.

Extracorporeal membrane oxygenation. Patients remaining in shock despite supportive therapies may benefit from mechanical cardiac support, such as ECMO. ECMO is highly effective for cardiogenic shock because it helps support the ailing heart (e.g., in myocarditis), but it is less successful in septic shock, except possibly refractory low cardiac output

Table 30-2 Commonly Used Vasoactives and Key Characteristics

Dopamine	Systemic effect determined by dose range; causes splanchnic and renal vasodilation at low to moderate doses; higher doses result in alpha effects
Epinephrine	Causes increase in peripheral vascular resistance; at lower doses, β_2 effects of smooth muscle dilation predominate; useful for anaphylaxis and vasoconstrictive shock states
Norepinephrine	Augments systemic vascular resistance; best in vasodilatory shock states
Vasopressin	Systemic vasoconstriction
Milrinone	Inodilator; causes lusitropy (end-diastolic relaxation)

septic shock.[2] Patients may still require vasoactive agents (Table 30-2) for persistent hypotension, but less inotropic support, because the circuit provides inotropy.[15] Patients with septic shock may require central cannulation strategy with venoarterial ECMO to provide adequate flows. This is a high-risk strategy and may not be adequate for patients with refractory vasodilation.

MENINGITIS

Meningitis describes an inflammation of the overlying membranes of the brain and spinal cord, known as the meninges. The causes of meningitis are varied and include bacterial, viral, and other infectious causes; the natural history of the disease is equally diverse, with factors such as organism, age of patient, time to recognition, and other comorbidities affecting clinical outcome.

DEFINITION AND CLASSIFICATION

The common causative agents for meningitis are age-specific. For neonates, the primary bacterial agents include group B *Streptococcus, Escherichia coli, Listeria monocytogenes,* and other gram-negative bacilli. In older infants through the early toddler years, *Streptococcus pneumoniae, Neisseria meningitides,* and *Haemophilus influenzae* type b (Hib) are most likely, though the incidence of *Haemophilus* meningitis has fallen dramatically since the introduction of the conjugate Hib vaccine in 1990.[41] For specific circumstances such as after trauma or subsequent to neurosurgical procedures, staphylococcal species and gram-negative organisms may predominate. Antimicrobial therapy must thus be directed at the most likely causative agents. Universal vaccination programs have helped to substantially decrease the incidence of many types of bacterial meningitis.

Aseptic meningitis, meaning without an identified bacterial cause, typically follows a more indolent and benign course than bacterial, is often of viral origin, and may have delayed diagnosis. Infants are at particular risk for meningitis as a result of herpes simplex virus, enterovirus, or parechovirus infections. With the increased availability of viral and antigen testing, the causative organisms of aseptic meningitis are often now identified. Although less common, fungal, parasitic, and tuberculous meningitis can occur, with fulminant clinical courses.

PATHOPHYSIOLOGY

The key pathologic derangements of meningitis involve two primary components: disruption of the blood–brain barrier and resultant alteration of cerebral autoregulation. After typically hematogenous spread after nasopharyngeal colonization, the blood–brain barrier becomes disrupted by the pathogen, leading to meningeal invasion. Inflammation of the subarachnoid space ensues with an accompanying inflammatory cascade. The presence of these cytokines alters neural vasoregulation, resulting in abnormal cerebral blood flow and potential alterations in intracranial pressure.

MANAGEMENT AND TREATMENT

General Considerations

Infants and children with meningitis may present with acute alteration in mental status, usually with bacterial meningitis, although, especially in older children with viral infections, there may be a nonspecific prodrome before meningeal signs develop. Meningitis caused by bacterial infection such as *N. meningitides* may also present with multiorgan system dysfunction and characteristic signs such as purpura fulminans. If intracranial pressure is elevated, the patient may have vital sign abnormalities consistent with Cushing's triad—hypertension, bradycardia, and irregular respirations. Symptoms such as loss of consciousness and seizures are late clinical signs that may be preceded by headache, photophobia, emesis, meningismus, or alterations in mental status.

Laboratory Testing

Timely recognition and high index of suspicion for meningitis are essential to its successful management and treatment. Even with mere suspicion for meningitis, patients should receive early and aggressive antibiotic treatment given the relative low risk versus potential high value of antimicrobials. Cerebrospinal fluid (CSF) sampling should ideally occur before antibiotics are initiated; however, this should not delay therapy in circumstances when it is not possible. Observed pleocytosis within the CSF and antigen testing can reliably aid the diagnosis of meningitis even when antibiotics have been administered beforehand;

thus the goal is to treat without delay. CSF is commonly analyzed for cell count, presence of organisms by Gram stain, glucose, and protein; additional testing such as bacterial antigen panels, herpes simplex virus (HSV) antigen, and latex agglutination testing may also be sent.

The role of neurologic imaging before lumbar puncture is somewhat controversial. When patients have clear signs of intracranial hypertension or a focal neurologic deficit, imaging is warranted to assess for presence of mass lesion and the associated risk of herniation with lumbar puncture. There is yet to be a universal recommendation for preimaging in children, especially in consideration of the risks of childhood exposure to ionizing radiation.

In most cases, empiric antibiotic therapy with vancomycin and a third-generation cephalosporin (e.g., ceftriaxone) is recommended. When there is concern for HSV, acyclovir is included, and for neonates, ampicillin is routinely added because of the risk of *Listeria* infection. Dexamethasone is recommended as adjunctive therapy in cases of *H. influenzae* meningitis to reduce the incidence of hearing loss.[42] For aseptic meningitis, which typically follows a benign clinical course, supportive care is recommended.

The primary complications of meningitis include lasting neurologic impairment, seizures, brain abscess, disorders of sodium homeostasis, and cerebral edema. As discussed, timely diagnosis and therapy may help to mitigate the worst of the possible outcomes.

SUMMARY

Although most children remain healthy, medical conditions such as shock and meningitis still pose a significant risk to their well-being. The overview of these two disease processes provided here included specific attention to septic shock and anaphylaxis as two shock states that account for a substantial amount of pediatric morbidity. Through our discussion of these topics, we hope we have sufficiently underscored the value of thoughtful and timely clinical evaluation coupled with prompt institution of therapy in the care of pediatric patients.

Key Points

- Timely recognition and early treatment of shock can help mitigate the risk of its morbidity and mortality in children.
- The goal of all shock treatment is to optimize oxygen delivery.
- Judicious antimicrobial therapy is the mainstay of managing sepsis syndromes.
- Anaphylaxis should be primarily managed with epinephrine.
- Meningitis is still an important cause of neurologic disability in children, but again, timely recognition and early treatment are essential.

Assessment Questions

1. All but which of the following describes a shock state?
   A. Hemorrhagic
   B. Obstructive
   C. Hypovolemic
   D. Cardiogenic
   E. Oliguric
2. Cardiac output is determined by all of the following *except:*
   A. Afterload
   B. Inotropy
   C. Preload
   D. Heart rate
   E. Oxygen content
3. Which of the following is a correct statement about oxygen consumption?
   A. It depends on oxygen-carrying capacity.
   B. It can be measured directly from the pulmonary artery catheter.
   C. It is a measure of the oxygen utilized by the body.
   D. Oxygen consumption increases as cardiac output decreases.
   E. Lower oxygen consumption has been associated with improved survival.
4. How would shock from a burn be classified?
   A. Distributive
   B. Obstructive
   C. Cardiogenic
   D. Hypovolemic
   E. Anaphylactic
5. What should initial assessment of a patient in shock include?
   A. Attention to ABCs (airway, breathing, circulation)
   B. Examination of mental status
   C. Brief directed history
   D. Examination of the skin
   E. All of the above
6. Regardless of etiology, what is the first step in treatment of shock?
   A. Begin rapid fluid infusion.
   B. Establish and maintain an airway.
   C. Place a central line.
   D. Start dopamine.
   E. Give a shock dose of steroids.

7. Which of the following enhances inotropy and vasodilation?
   - **A.** Milrinone
   - **B.** Dopamine
   - **C.** Norepinephrine
   - **D.** Dobutamine
   - **E.** Phenylephrine
8. Which of the following is commonly seen as part of the shock state?
   - **A.** Adrenal insufficiency
   - **B.** Disseminated intravascular coagulation
   - **C.** Electrolyte abnormalities
   - **D.** Hyperglycemia
   - **E.** All of the above
9. What are the major components of sepsis?
   - **A.** Infecting organisms leading to direct tissue damage and organ dysfunction
   - **B.** An excessive host inflammatory response
   - **C.** A failure of counterregulatory mechanisms
   - **D.** All of the above
10. Which of the following is correct regarding the treatment of sepsis?
    - **A.** Limited volume resuscitation improves outcome.
    - **B.** Dopamine is the best initial vasoactive substance for the hypotensive patient.
    - **C.** Extracorporeal membrane oxygenation (ECMO) is a commonly used form of hemodynamic support.
    - **D.** Activated protein C is recommended for pediatric patients.
    - **E.** Early empiric antimicrobial therapy is critical in the treatment of sepsis.
11. Which patient group(s) have an increased risk of sepsis?
    - **A.** Oncology patients
    - **B.** Transplant patients
    - **C.** Patients with chronic diseases
    - **D.** Patients with indwelling central venous catheters
    - **E.** All of the above
12. Symptoms from anaphylaxis may be:
    - **A.** Immediate
    - **B.** Delayed
    - **C.** Cutaneous
    - **D.** Cardiovascular collapse
    - **E.** All of the above
13. The treatment of anaphylactic shock includes which of the following?
    - **A.** Epinephrine
    - **B.** Antihistamines
    - **C.** Steroids
    - **D.** Limiting antigen exposure
    - **E.** All of the above
14. Which of the following is true regarding meningitis?
    - **A.** Inflammation of the meninges is always caused by bacterial infection.
    - **B.** Meningitis does not cause cerebral edema.
    - **C.** Bacterial meningitis is most often the result of hematogenous spread.
    - **D.** There is little risk of chronic morbidity with bacterial meningitis.
    - **E.** Bacteria, the cause of meningitis, are always gram-positive organisms.
15. Which of the following is/are complications of bacterial meningitis?
    - **A.** Vision loss
    - **B.** Hearing loss
    - **C.** Mental retardation
    - **D.** Subdural empyema
    - **E.** All of the above

REFERENCES

1. Maticus TJ, Sanchez-Pinto LN. Adaptation and validation of a pediatric sequential organ failure assessment score and evaluation of the Sepsis-3 definitions in critically Ill children. *JAMA Pediatr*. 2017;171(10):e172352.
2. Seymour CW, Gesten F, Prescott HC, et al. Time to treatment and mortality during mandated emergency care for sepsis. *N Engl J Med*. 2017;376(23):2235-2244.
3. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. *Crit Care Med*. 2017;45(3):486-552.
4. Curley MA, Castillo L. Nutrition and shock in pediatric patients. *New Horiz*. 1998;6:212.
5. Balk RA, Ely EW, Goyette RE. *Sepsis Handbook*. Knoxville, TN: Thomson Healthcare Advanced Therapeutics Communications; 2004.
6. Schears GJ, Deutschman CS. Common nutritional issues in pediatric and adult critical care medicine. *Crit Care Clin*. 1997; 13(3):669.
7. Dibs SD, Baker MD. Anaphylaxis in children: a 5-year experience. *Pediatrics*. 1997;99:E7.
8. Lieberman P. Specific and idiopathic anaphylaxis: pathophysiology and treatment. In: Bierman CW, ed. *Allergy, Asthma, and Immunology From Infancy to Adulthood*. 3rd ed. Philadelphia: WB Saunders; 1996:297-319.
9. Gauthier PM, Szerlip HM. Metabolic acidosis in the intensive care unit. *Crit Care Clin*. 2002;18:289.
10. Ross J, Covell JW. Frameworks for analysis of ventricular and circulatory function: integrated responses. In: West JB, ed. *Best and Taylor's Physiological Basis of Medical Practice*. 12th ed. Baltimore: Williams & Wilkins; 1990.
11. Pollack MM, Fields AI, Ruttimann UE. Sequential cardiopulmonary variables in infants and children in septic shock. *Crit Care Med*. 1984;12:554.
12. Parillo JE. Approach to the patient with shock. In: Goldman, ed. *Cecil Textbook of Medicine*. 22nd ed. Philadelphia: WB Saunders; 2004:608.
13. Pollack MM, Fields AI, Ruttimann UE. Distributions of cardiopulmonary variables in pediatric survivors and nonsurvivors of septic shock. *Crit Care Med*. 1985;13:454.
14. Hazinski MF. Shock in the pediatric patient. *Crit Care Nurs Clin North Am*. 1990;2:309.

15. Ross J. The cardiac pump. In: West JB, ed. *Best and Taylor's Physiological Basis of Medical Practice*. 12th ed. Baltimore: Williams & Wilkins; 1990.
16. Carcillo JA, Fields AI. Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock. *Crit Care Med*. 2002;30:1365.
17. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005; 6(1)2-8.
18. Levy FH, O'Rourke PP. Topics in pediatric critical care. In: Barnhart S, Czervinske M, eds. *Perinatal and Pediatric Respiratory Care*. Philadelphia: WB Saunders; 1995.
19. West JB. Gas transport to the periphery. In: West JB, ed. *Best and Taylor's Physiological Basis of Medical Practice*. 12th ed. Baltimore: Williams & Wilkins; 1990.
20. Tobin JR, Wetzel RC. Shock and multi-organ system failure. In: Rogers MC, Nichols DG, eds. *Textbook of Pediatric Intensive Care*. 3rd ed. Baltimore: Williams & Wilkins; 1996.
21. Thomas NJ, Carcillo JA. Hypovolemic shock in pediatric patients. *New Horiz*. 1998;6:120.
22. Ross J. Intracardiac and arterial pressures and the cardiac output: cardiac catheterization. In: West JB, ed. *Best and Taylor's Physiological Basis of Medical Practice*. 12th ed. Baltimore: Williams & Wilkins; 1990.
23. Seear M, Wensley D, MacNab A. Oxygen consumption-oxygen delivery relationship in children. *J Pediatr*. 1993;123:208.
24. Carcillo JA, Cunnion RE. Septic shock. *Crit Care Clin*. 1997; 13:553.
25. Feltes TF, Pignatelli R, Kleinert S, Mariscalco MM. Quantitated left ventricular systolic mechanics in children with septic shock utilizing noninvasive wall stress analysis. *Crit Care Med*. 1994;22:1647.
26. Behrman RE, Kliegman RM, Jenson HB, eds. *Nelson's Textbook of Pediatrics*. 16th ed. Philadelphia: WB Saunders; 2000.
27. Carcillo JA, et al. Pediatric shock. In: Slonim, Pollack, eds. *Pediatric Critical Care Medicine*. Philadelphia: Lippincott Williams and Wilkins, in press.
28. Tibby SM, Hatherill M, Murdoch IA. Capillary refill and core-peripheral temperature gap as indicators of haemodynamic status in paediatric intensive care patients. *Arch Dis Child*. 1999;80:163.
29. Evans JM, Hertzig JS, Schenkman KA. Principles of invasive monitoring. In: Fuhrman BP, Zimmerman JJ, eds. *Pediatric Critical Care*. 3rd ed. St. Louis: Mosby-Elsevier; 2006: 251-264.
30. Perkin RM, Anas N. Pulmonary artery catheters. *Pediatr Crit Care Med*. 2011;12(suppl 4):S12-S20.
31. Ceneviva G, Paschall JA, Maffei F, Carcillo JA. Hemodynamic support in fluid-refractory pediatric septic shock. *Pediatrics*. 1998;102:E19.
32. Carcillo JA, Davis AL, Zaritsky A. Role of early fluid resuscitation in pediatric septic shock. *JAMA*. 1991;266:1242.
33. Kallen RJ, Lonergan JM. Fluid resuscitation of acute hypovolemic hypoperfusion states in pediatrics. *Pediatr Clin North Am*. 1990;37:287.
34. Saladino RA. Management of septic shock in the pediatric emergency department in 2004. *Clin Ped Emerg Med*. 2004; 5:20-27.
35. Morgan WM, O'Neill JA. Hemorrhagic and obstructive shock in pediatric patients. *New Horiz*. 1998;6:150.
36. Agus MS, Wypij D, Hirshberg EL, et al. Tight glycemic control in critically ill children. *N Engl J Med*. 2017;376(8): 729-741.
37. Smith L, Hernan L. Shock states. In: Fuhrman BP, Zimmerman JJ, eds. *Pediatric Critical Care*. 3rd ed. St. Louis: Mosby-Elsevier; 2006:394-410.
38. Burns JP. Septic shock in the pediatric patient: pathogenesis and novel treatments. *Pediatr Emerg Care*. 2003;19:112.
39. Swanson D. Meningitis. *Pediatr Rev*. 2015;36:514-524.
40. Odio CM, Faingezicht I, Paris M, et al. The beneficial effects of early dexamethasone administration in infants and children with bacterial meningitis. *N Engl J Med*. 1991;324(22): 1525-1531.

Pediatric Trauma

31

Leo Benedict, Christopher Weldon, Samuel Rice-Townsend

Outline

Learning Objectives

After completing this chapter the reader will be able to:

1. Discuss the primary survey of a trauma patient with prioritization of securing the airway.
2. Understand the importance of and the technique of protecting the cervical spine in a trauma patient.
3. Discuss imaging studies in a trauma patient and when to forgo them to go straight to the operating room.
4. Recognize the spectrum of thoracic injuries seen in children.
5. Recognize signs of traumatic tension pneumothorax and discuss management.
6. Discuss abdominal injuries and appreciate their effects on respiratory performance.
7. Recognize different types of head injuries in a trauma patient.
8. Understand how mental status is scored in a child and when the airway is at risk.
9. Discuss the basic management of thermal injury and smoke inhalation.
10. Recognize signs of smoke inhalation injury.
11. Discuss strategies for respiratory management of drowning victims.
12. Discuss strategies for injury prevention in children.

Key Terms

abdominal compartment syndrome
angioembolization
cerebral perfusion pressure
chylothorax
concussion
cricothyroidotomy
damage-control surgery
emergency department thoracotomy
escharotomy
FAST examination
Glasgow Coma Scale (GCS)
inhalation injury
level I trauma center
nonaccidental trauma
primary survey
SCIWORA
solid organ injury
tension pneumothorax
total body surface area burn
trauma resuscitation
traumatic brain injury

EPIDEMIOLOGY

Traumatic injury remains the leading cause of death for children ages 1 to 19 years old in the United States.[1] Major mechanisms that contribute to traumatic injury include motor vehicle accidents, falls, burns, and drowning. Blunt mechanisms of trauma are far more common than penetrating injuries in children. Other mechanisms include homicide and suicide that unfortunately contribute to a significant number deaths in this population each year. In teenagers, this is often gun related. For infants who die from homicide, the cause is usually abuse (nonaccidental trauma). Furthermore, nonaccidental trauma continues to be widespread with more than 1.2 million cases reported annually, many of these resulting in death.[2]

EARLY EVALUATION AND MANAGEMENT

The initial evaluation and resuscitation of a pediatric trauma patient directly affects outcomes and plays an important role in diagnosing life-threatening injuries requiring immediate intervention. The themes of management are similar to those of adult **trauma resuscitation;** however, there are unique physiologic, anatomic, and social considerations that make resuscitation in children challenging. Children have greater physiologic reserves that allow them to compensate for severe injuries, making it important for the treating clinicians to recognize these injuries early in their course. By the time alterations in physiology are appreciated (heart rate, blood pressure), the patient may be close to cardiovascular collapse. Furthermore, children have more pliable bones, and thus blunt force trauma may result in internal organ injury without overlying fracture. Additionally, visceral organs in children are relatively large compared with their body size and encroach more readily on one another, making multiple simultaneous organ injuries more common. Lastly, nonaccidental trauma must always be carefully considered as a possible mechanism of injury.

PREHOSPITAL CARE AND TRANSPORT

Prehospital care is a crucial aspect of the initial management of a pediatric trauma patient.[3] The goals of emergency medical services are to initiate resuscitation, stabilize to prevent further injury, and provide safe transport to a trauma center.[4] Prehospital interventions performed by responders in the field can include placement of venous access, endotracheal intubation, needle decompression of a pneumothorax, or application of a tourniquet to control hemorrhage. Patients are routinely "boarded and collared" (placed in a cervical spine collar and transported on a spine board) to stabilize the patient's body and prevent further injury during transport.

Patients are transported to the nearest appropriate trauma center, often based on the severity of injury and nearest appropriate center of expertise. Centers vary in their specific capabilities and are identified by level designation per the American College of Surgeons (ACS) Committee on Trauma, with level I being the highest and III the lowest. **Level I trauma centers** must demonstrate 24 hour–a–day availability of surgical specialists and the intensive resources necessary for the immediate treatment of severely injured patients. ACS-designated pediatric trauma centers have similar capabilities as adult trauma centers; however, they are certified to care for injured children. Despite the distinction between adult and pediatric trauma centers, most injured children are initially evaluated at adult trauma centers and then transported to pediatric trauma centers once stabilized.[5]

PRIMARY SURVEY

The initial assessment of children presenting with a traumatic injury is termed the **primary survey.**[6] It is the same for all pediatric patients who have sustained a traumatic injury regardless of mechanism. During this assessment, identification of life-threatening injuries and resuscitation are done simultaneously.[6] A cervical spine (C-spine) injury is always assumed, and necessary precautions are taken during the assessment to maintain in-line mobilization of the cervical spine. The head and neck are stabilized by placing a cervical collar or by assigning an individual to hold the neck in line with the patient's body to prevent unwanted rotational movements and possible secondary injuries. A simple mnemonic, *ABCDE*, is used as a memory aid for the order in which problems should be addressed. It stands for:

- *A*irway
- *B*reathing
- *C*irculation
- *D*isability
- *E*xposure

Airway

Confirming or establishing a patent airway is the first priority of the primary survey. A child who can speak or cry has a patent airway. If needed, a jaw thrust maneuver can be used to open the airway. It is important for this maneuver and any others to maintain cervical spine stabilization while aiding in respirations. A cervical spine injury must be presumed until it can be ruled out. This means not using head-tilt, sniff position, or chin-lift maneuvers, because these change the orientation of the spinal column and increase the risk of additional spinal injury. The jaw-thrust technique may be used in these children unless otherwise contraindicated, however. The head, neck, spine, and body should be treated as a single entity and moved in unison and in the same plane for any reason or purpose throughout the survey and resuscitation.

When a definitive airway is needed with endotracheal intubation, a rapid-sequence intubation is

preferred. An induction agent, such as etomidate or ketamine, is given along with a paralytic agent such as succinylcholine or rocuronium. Atropine may be given to infants in anticipation of bradycardia associated with laryngeal stimulation. (Please note that when and how to use any medication described in this chapter is beyond the scope of this work, and the reader is reminded to investigate when and how any specific drug should be used before its use.) Providers must understand the differences between adult and pediatric airways. Oral intubation in children can be more challenging because of increased soft tissue. The subglottic airway narrows in a child and can make passing a larger tube difficult even after it passes through the cords. In small infants, an uncuffed endotracheal tube may be preferred to allow a larger lumen tube. The tube size can be quickly estimated by the age of the child divided by 4, plus 4 (Age/4 + 4). If a patient cannot be intubated, adequate gas exchange can be achieved with bag–mask ventilation, and the medical providers caring for children must not lose sight of this fact. If an urgent surgical airway is needed, a **cricothyroidotomy** (window in the cricothyroid membrane in the midneck) can be performed in children 11 years or older. Younger children have a smaller cricothyroid membrane that puts the larynx at risk during a cricothyroidotomy. Hence a temporizing needle cricothyroidotomy is preferred in this population. Both these methods of accessing the trachea are temporary and should be revised to a formal tracheostomy as soon as it is feasible.

Breathing

Breath sounds are assessed bilaterally by auscultation. If the child is breathing, support may be provided in the form of supplemental oxygen by nasal cannula or mask delivery systems. Alternatively, breaths may need to be delivered to the patient by bag–mask and then endotracheal tube if he or she is not achieving sufficient breaths. Breath volumes are typically 4 to 6 mL/kg in a child with a normal rate ranging from 30 breaths/minute in a teenager to 60 breaths/minute in an infant. If respirations deteriorate or the patient's state of consciousness declines, mechanical ventilation should be instituted immediately.

If breath sounds are absent or significantly diminished on one side, a pneumothorax must be suspected and should be immediately evaluated and treated. An expanding collection of air in the chest will eventually lead to a **tension pneumothorax,** compressing the heart and great vessels and leading to cardiovascular collapse from a loss of venous return. To prevent this, a chest tube should be inserted and then placed to suction with position confirmed on a chest radiograph. In an emergent situation, in which cardiovascular collapse has already occurred or appears imminent, a large-bore angiocatheter may be placed in the midclavicular anterior chest to relieve tension physiology until a chest tube can be inserted.

Circulation

Placement of two large-bore peripheral intravenous lines should be placed on arrival to the emergency department (performed simultaneously to the primary survey). If unable to obtain intravenous access, intraosseous lines can be placed in the proximal or distal tibia, distal femur, or proximal humerus.[6,7]

The presence and strength of pulses and evidence of distal perfusion is the method for assessing the patient's circulation. Pulse oximetry can be a useful adjunct to assess distal perfusion. Capillary refill is a quick and specific method of checking the adequacy of peripheral circulation. Normal capillary refill time is less than 2 seconds. In pediatric patients in particular, a high level of suspicion must be maintained for internal bleeding. As mentioned, a child can physiologically compensate for significant blood loss, and initial vital signs may be misleading in the setting of occult hemorrhage. A child may lose up to half his or her blood volume before exhibiting hypotension (Table 31-1).[8]

The current ACS Advanced Trauma Life Support (ATLS) guidelines recommends a 20 mL/kg bolus of crystalloid solution for all pediatric trauma patients during the initial resuscitation.[6] A second bolus may be given if needed. If a third bolus is required for continued hypotension or tachycardia (signs of hypovolemia), blood products should then be administered. Persistent hemodynamic instability in a trauma patient should be assumed to be a result of hemorrhage until proven otherwise. Rapid transfusion systems may be used to accelerate resuscitation efforts. In select circumstances, vasopressors may be used to support blood pressure when hemorrhage is not suspected (e.g., spine injury).

Significant external bleeding should be controlled during this phase of the primary survey, with at least temporary measures (this may mean pressure tamponade of a wound or suture ligation of an exposed bleeding vessel). More definitive procedures such as a wash out of a complex laceration are likely better performed in the operating room setting.

Disability

Next, neurologic status should be assessed. Children have a larger brain-to-body ratio and have up to twice the relative cerebral perfusion of adults. For this reason, they have a higher risk of anoxic brain injury in the setting of trauma. Neurologic status can be quickly estimated with the **Glasgow Coma Scale (GCS)** score. It is a composite score based on three areas: eye opening, verbal response, and motor response. In younger children, particularly those who are nonverbal, GCS is scored by age-appropriate signs (Table 31-2).[9] A patient with a GCS less than 8 does not have the ability

Table 31-1 Classification of Hemorrhagic Shock in Pediatric Trauma Patients

	I	II	III	IV
Blood loss (% blood volume)	Up to 15	15-25	26-39	>40
Heart rate	Normal or mildly increased	Tachycardia	Significant tachycardia	Severe tachycardia
Blood pressure	Normal	Normal	Hypotension	Significant hypotension
Pulse exam	Normal pulses	Diminished peripheral pulses	Thready peripheral pulses	Thready peripheral pulses
pH	Normal	Normal	Metabolic acidosis	Significant acidosis
Respiratory rate	Normal	Tachypnea	Moderate tachypnea	Severe tachypnea
Urine output	Normal	Oliguria, increased specific gravity	Oliguria, increased blood urea nitrogen	Anuria
Mental status	Slightly anxious	Irritable, confused	Irritable or lethargic	Coma
Skin	Warm, pink	Cool extremities, mottling	Cool extremities, mottling or pallor	Cold extremities, pallor, or cyanosis
Capillary refill	Brisk	Delayed	Prolonged	Prolonged

Table 31-2 Pediatric Glasgow Coma Scale Score

	Child	Infant	Score
Eye opening	Spontaneous	Spontaneous	4
	To speech	To speech	3
	To pain only	To pain only	3
	No response	No response	1
Best verbal response	Oriented, appropriate	Coos and babbles	5
	Confused	Irritable cries	4
	Inappropriate words	Cries to pain	3
	Incomprehensible sounds	Moans to pain	2
	No response	No response	1
Best motor response	Obeys commands	Normal, spontaneous	6
	Localizes pain	Withdraws to touch	5
	Withdraws to pain	Withdraws to pain	4
	Abnormal flexion	Abnormal flexion	3
	Abnormal extension	Abnormal extension	2
	No response	No response	1

to protect his or her airway, and a definitive airway should be acquired.

Exposure

Last, the patient should be completely exposed to assess for injuries everywhere on the body. This often means cutting off clothes for quick and thorough assessment of the entire body. Once exposed, it is crucial to cover a pediatric patient with warm blankets to prevent hypothermia, which can exacerbate bleeding via induction or propagation of an underlying coagulopathy. Children have less fat insulation and increased surface area–to–mass ratios, placing them at higher risk for hypothermia, not to mention that room temperature or cooler resuscitation fluids may be administered that can also exacerbate ongoing temperature instability. Therefore intravenous fluids should also be warmed and a warm environment maintained in the trauma bay to prevent hypothermia. Furthermore, after completion of the secondary survey, a Foley catheter should be placed to guide the resuscitation by monitoring the urinary output and to evaluate for hematuria (signs of a kidney, bladder, or urethral injury).

SECONDARY SURVEY

When the primary survey is completed, resuscitation is underway, and the vital signs are normalizing, the secondary survey can begin. Although the primary survey serves to quickly identify life-threatening injuries and commence resuscitation efforts, the secondary survey is a thorough head-to-toe evaluation of the trauma patient, including a complete history and physical examination, with a reassessment of all vital signs. Each region of the body must be fully examined, and if at any time during the secondary survey the patient deteriorates, the primary survey must be performed again so that a life-threatening condition may be immediately addressed. The goal of this portion of the resuscitation is to identify all possible injuries to avoid missing any problems that would complicate care delivery. Occult injuries that go unrecognized can have a significant effect on the patient's overall outcome and recovery, and hence a high index of

suspicion must be maintained to identify all possible injuries. Finally, it is essential to understand "patterns of injuries" (injuries that "go together") in trauma patients so any associated problem can be suspected and identified.

IMAGING CONSIDERATIONS

Imaging is often performed in the trauma bay to identify significant injuries that may require immediate treatment. A portable chest radiograph will identify a clinically significant pneumothorax or hemothorax. In a hemodynamically unstable patient, a **FAST examination** (Focused Assessment with Sonography for Trauma) using ultrasound at the bedside may diagnose internal bleeding by visualizing blood in the peritoneal and pericardial spaces. Similarly, a radiograph of the pelvis may demonstrate a significant pelvic fracture and indicate pelvic hemorrhage as the source of hemodynamic instability. Although not comprehensive, these studies are quick to perform and do not require the unstable patient to be transported. In select patients who require immediate intervention in the operating room, they may be the only imaging studies needed. The timing of these studies is dependent on the patient's clinical condition and injuries suspected. A chest radiograph, for example, may be called for before the secondary survey if a pneumothorax is suspected.

In stable patients, more detailed imaging may be pursued, if indicated. Computed tomography (CT) scans are rapidly performed and provide detailed imaging to better define injuries. It is, however, important to highlight that CT should not be performed in unstable pediatric trauma patients (hypotension, tachycardia, tachypnea, etc.) because of the risk of decompensation during the imaging study. If a patient is unstable, he or she should be adequately resuscitated or treated (intubated, chest tube placed, etc.) before CT or taken directly to the operating room without a CT scan. For a pediatric trauma patient, indications for urgent surgery include hemodynamic instability that does not respond appropriately to resuscitation, particularly in the setting of a positive FAST examination.

Although CT provides detailed images and allows better characterization of injuries, it comes with cost and radiation exposure to the patient and should not be routinely used. Controversy exists regarding the use of imaging in pediatric trauma patients, particularly based on mechanism alone. In the adult literature, there may be mortality benefits to performing CT of the head, neck, chest, abdomen, and pelvis after what is considered a *significant* blunt injury.[10] However, evidence in the pediatric population is lacking, and what is considered a significant mechanism of injury is highly subjective.[11] Furthermore, radiation exposure associated with imaging studies has been linked to increased malignancy rates later in life.[12,13] In a patient with potential life-threatening injuries, this risk may be inconsequential. CT should be performed when the results are likely to change management and the benefits of the study are likely to outweigh the risks of radiation exposure.

THORACIC TRAUMA

Thoracic injuries in children result in significant morbidity and mortality compared with other types of traumatic injuries. They commonly result from mechanisms associated with high velocity and increased force.[14] However, the initial signs of a thoracic injury may be subtle. Practitioners must have a high index of suspicion for a thoracic injury in severely injured children, requiring intensive monitoring along with respiratory and hemodynamic support.[15] The most common thoracic injuries in pediatric patients are pulmonary contusion, pneumothorax and hemothorax, and rib fractures.[15,16] Thoracic injuries alone in children are associated with a 5% mortality but increase significantly with associated head or abdominal trauma.[17]

ANATOMIC CONSIDERATIONS

Children tend to have increased cartilage content with incomplete ossification of their ribs compared with adults. This makes their ribs more compliant and compressible, with pulmonary contusions without concomitant rib fracture more common in children.[18] Reports also indicate that flail segments (paradoxical movement of the chest during respiration) also become more common in adults as ossifications occurs.[19] In addition, the body wall thickness of a child is less than that of adults, making penetrating wounds to the thorax more likely to injure internal organs.[20]

Furthermore, the physiologic differences between adults and children must be considered. Young children are more prone to hypoxemia because they have both a lower functional residual capacity and higher metabolic rate with increased oxygen demand. Children also have a greater ability to compensate for excess blood loss before hypotension occurs. The resultant hypotension can occur rapidly and be profound because of the mobile mediastinum seen in young children.[14]

PENETRATING VERSUS BLUNT THORACIC TRAUMA

Most thoracic trauma in children is by blunt mechanism (motor vehicle collisions, falls, etc.); however, the incidence of penetrating trauma increases with age and is higher in adolescents than young children.[21] Penetrating thoracic injuries can injure a number of different vital structures, including the heart, great vessels, trachea, lung, chest wall, or diaphragm.

Whether there is blunt or penetrating trauma, the assessment for a pediatric trauma patient should follow the guidelines set forth by ATLS with a primary

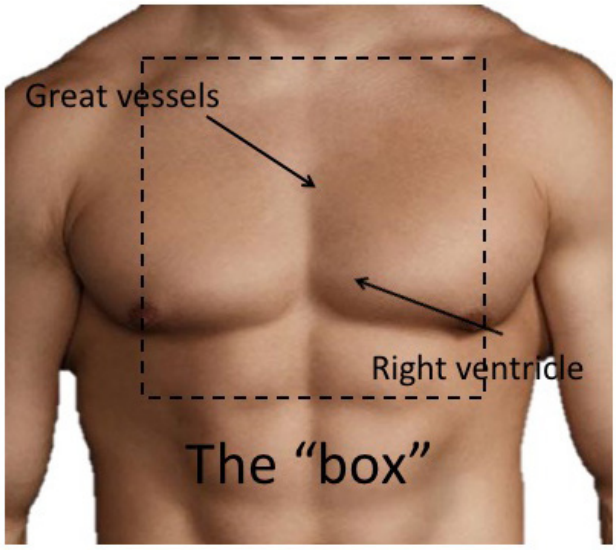


FIGURE 31-1 The cardiac box in thoracic trauma. Penetrating injuries to this area are at risk for injuries to the heart and great vessels.

survey to identify life-threatening injuries. Blunt trauma patients are at particular risk for pulmonary or cardiac contusion, rib fractures, and pneumothorax. Lateral penetrating injuries are at high risk for lung injury with pneumothorax, whereas penetrating injuries to "the box," defined as the area between the nipples, the manubrium, and the inferior costal margin, are often associated with life-threatening injuries to the heart and great vessels (Figure 31-1). Subcutaneous emphysema in the neck and upper chest may indicate an injury to the trachea or bronchial tree. Asymmetric breath sounds should be evaluated with a radiograph expeditiously to rule out pneumothorax before it progresses to compress the mediastinal vascular structures, creating tension physiology. Tracheal shift away from unilateral absent breath sounds, on the other hand, should indicate impending tension pneumothorax and requires immediate drainage by chest tube placement (or needle if chest tube is not immediately available). Penetrating wounds below the nipple should raise the suspicion for a concomitant abdominal injury.

INDICATIONS FOR EMERGENCY DEPARTMENT THORACOTOMY

Emergency department or resuscitative **thoracotomy** is a procedure used to gain immediate control of life-threatening cardiac injuries or control massive hemorrhage after trauma. Exposure gained during this procedure allows the clinician to treat injuries leading to cardiac tamponade, provide internal cardiac compressions, and cross-clamp the thoracic aorta to control hemorrhage in the abdomen.

The indication for resuscitative thoracotomy for pediatric trauma patients is a penetrating thoracic injury with no signs of life for less than 15 minutes.[6] Recent reports indicate no survival benefit for resuscitative thoracotomy in pediatric trauma patients who sustain blunt trauma with no signs of life or vital signs on arrival.[22] Outcomes among pediatric trauma patients are similar to adults; less than ten percent of such patients survive to hospital discharge.[22,23] The mechanism of penetrating injury impacts outcome: Patients with stab wounds have a higher survival rate compared with patients with gunshot wounds.[24]

IMAGING CONSIDERATIONS

The initial imaging technique used to evaluate a pediatric trauma patient for a thoracic injury is an anteroposterior chest radiograph. This test can be used to identify a pneumothorax, a hemothorax, pulmonary contusions, and rib fractures. In addition to chest radiography, CT is an important tool to diagnose an intrathoracic injury in patients with blunt trauma. However, it does not often change management of the patient and thus should not be used routinely because of the radiation exposure. A plain chest radiograph should be used to screen for significant thoracic injures in blunt pediatric trauma patients and to direct the selective use of thoracic CT scans.[25] Findings on chest radiograph that should prompt CT after blunt trauma are those that make an aortic injury more likely, including a widened mediastinum, blunting of the aortic knob, apical capping, and fracture of first or second ribs. Of note, thymic tissue can appear prominent in infants and cause the mediastinum to appear widened and serve as a confounder. Furthermore, a FAST examination should be performed to assess for pericardial blood.

MANAGEMENT CONSIDERATIONS

Upper Airway Injuries or Obstruction

Tracheobronchial injuries are extremely rare in the pediatric population and are usually associated with high-energy impact injuries.[26] Many tracheobronchial injuries are associated with other injuries, and they have a mortality rate of 30%.[27] The most common presenting signs and symptoms of a tracheobronchial injury are shortness of breath, sternal tenderness, and subcutaneous emphysema.[28] Typical radiographic findings include pneumomediastinum, subcutaneous emphysema, and pneumothorax.[29]

If a tube thoracostomy is placed and a persistent continuous air leak is identified, disruption of a major airway must be considered. In this event, a CT scan of the chest should be performed to confirm the location and extent of the airway disruption.[26] Small tracheobronchial tears can initially be managed without an operation; however, this approach is associated with high rates of stricture formation.[30] If an operation to repair the tracheobronchial injury is needed, the principles of surgery are to debride injured tissue and reapproximate the ends to prevent leakage of air. The site of injury will often dictate the choice of thoracotomy

incision. Injuries to the right mainstem bronchus and posterior aspect of the trachea will often require a right thoracotomy for exposure, whereas injuries to the left mainstem bronchus will require a left thoracotomy incision.

Complications in children with traumatic tracheobronchial injuries include bronchial stenosis, infections, or bronchopleural fistula.[18] Approximately 50% of children with tracheobronchial injuries die within the first hour of injury, with an overall mortality rate of 30%.[18]

Pneumothorax

Pneumothorax is defined as the presence of air within the pleural space and occurs in one-third of children who sustain a thoracic injury.[15,16] Air under pressure within the pleural space that is associated with hemodynamic instability from compression of the mediastinum is termed a *tension pneumothorax.* In the presence of trauma and concerns for possible cervical spine injury, the evaluation of a pediatric trauma patient is typically in the supine position, limiting the effectiveness of a chest radiograph to identify a pneumothorax, because the air will be located anteriorly to the lung.[31]

Pneumothorax after thoracic trauma is most commonly the result of small lung parenchymal tears and are effectively treated with a tube thoracostomy.[17] Small lung injuries typically heal over time without the need for direct repair. When a simultaneous hemothorax is not suspected, a small catheter (8-12 Fr) can be placed in the fourth intercostal space in the anterior axillary line. The presence of blood typically requires the placement of a larger tube for better drainage. A pneumothorax observed on CT scan of the chest and abdomen but not seen on chest radiograph may be safe to observe without intervention if small.[32] Serial radiographs should be performed to ensure that this collection of air does not expand over time.

Hemothorax

Hemothorax is defined as the presence of blood within the pleural cavity that hinders normal respiratory mechanics by interfering with lung expansion. Bleeding from tears in the lung parenchyma causing a hemothorax is typically low volume because of low pulmonary arterial pressures. Hemostasis is achieved by lung expansion. Prompt drainage of blood in the pleural cavity using a large chest tube is indicated to prevent lung entrapment and subsequent empyema and to quantify the amount of hemorrhage.[14]

Thoracotomy for the management of pulmonary injury is indicated when the initial thoracostomy tube output is greater than or equal to 20% to 30% of the calculated blood volume, which is 15 mL/kg. Thoracotomy is also indicated when the tube output is greater than 2 to 3 mL/kg/hour over the following 6 hours, or when there is significant hemodynamic compromise.

Pulmonary Contusion

Pulmonary contusion is defined as nonanatomic areas of consolidation on chest radiograph or CT after thoracic trauma.[33] It can occur in up to 48% of children with thoracic injuries, with motor vehicle crashes (MVCs) being the most common mechanism.[16] The flexible chest wall of pediatric patients allows contusion of the lung without associated rib fractures. The presence of pulmonary contusion contributes to a number of physiologic abnormalities such as decreased pulmonary compliance leading to hypoventilation, hypoxia, and ventilation–perfusion mismatch.

Treatment of pulmonary contusion is supportive, including appropriate fluid resuscitation, supplemental oxygen, and aggressive pain management strategies to prevent atelectasis and pneumonia. Approximately 20% of children with pulmonary contusion develop pneumonia with worsening respiratory compromise.[34] Patients with pulmonary contusion can also develop a pneumatocele. These are lung cysts that occur more commonly in children than adults as a result of lung laceration from the pliable chest wall compressing the lung. These lesions typically undergo slow resolution without need for surgical intervention.[35]

Rib Fractures

The increased cartilage content and incomplete ossification of ribs in children allows them to be more compliant and compressible than adults. This makes pulmonary contusion without concomitant rib fractures more common in children.[18] Rib fractures are an important marker of severe injury in children, with a mortality rate of 6% with just one rib fracture compared with 2% in children without any rib fractures.[36] The number of fractured ribs in both injured adults and children correlates directly with the severity of the injury, the likelihood of intrathoracic injury, and overall higher mortality rates. The presence of three or more rib fractures in a child is associated with a greater likelihood of organ involvement and death from injuries.[37]

The key to successful management of rib fractures is adequate pain control to promote effective gas exchange with the goal of preventing atelectasis and pneumonia. The use of regional anesthetic techniques such as intercostal nerve blocks and epidurals has increased and are considered essential adjuncts to traditional analgesia techniques.

Flail Chest

Flail segments result from multiple contiguous ribs with more than two points of fracture.[14] The flail segment retracts with inspiration and expands with expiration, resulting in paradoxical chest wall movement leading to hypoventilation and hypoxia. These types of injuries are very uncommon in children and the role of operative rib fixation in the setting of

flail chest has not been validated in the pediatric population.[38]

Cardiac Contusion

Children may be at greater risk for cardiac injury because of their pliable chest wall that permits the direct transfer of kinetic energy to their myocardium.[39] Children with blunt cardiac injury may have minimal or no symptoms or signs on physical examination. Injury can be suspected in the presence of chest wall ecchymosis, tenderness to palpation on the sternum or upper ribs, new murmur, or muffled heart sounds.[18] The diagnosis can present as supraventricular and ventricular arrhythmias, or it can resemble a myocardial infarction with decreased function. There is no gold standard diagnostic test; however, electrocardiogram (ECG) is considered a reliable screening tool. Findings may include sinus tachycardia, atrial fibrillation, premature ventricular contractions, right bundle branch block, and nonspecific ST changes.[40] Furthermore, obtaining serum troponin levels in addition to ECG can help identify children with acute cardiac injury.[40,41] Bedside ultrasound and echocardiography can also be used to diagnose cardiac contusion.

An asymptomatic patient with ECG and cardiac enzyme abnormalities should be observed in a monitored setting given the potential for arrhythmias. Patients with significant arrhythmias may require electrical cardioversion and inotropic support. Definitive treatment will depend on the specific injury identified during the workup.

Great Vessel Injuries

Major vascular injury is uncommon in children and occurs in approximately 0.6% of all pediatric trauma patients, with most injuries caused by a blunt mechanism.[42] Most thoracic aortic injuries occur in the descending aorta at the ligamentum arteriosum, which is the occluded ductus arteriosus. Children are often protected from this injury by the higher compliance of the chest well and more flexible vessel histology that tolerates greater tension of the aortic wall without tearing.[43] Signs and symptoms of an aortic injury in children can include back pain, unexplained hypotension, bilateral femoral pulse deficits, and upper extremity hypertension. Chest radiography may show a widened mediastinum, upward shift of the left mainstem bronchus, or blunting of the aortic knob.[44] CT aortography is considered the gold standard test to evaluate the aorta in injured children in addition to identifying other potential thoracic injuries. It is indicated for physical examination findings or chest x-ray abnormalities suggestive of a thoracic aorta injury.

Treatment priorities for a stable blunt pediatric trauma patient with an apparent aortic injury include strict blood pressure control in a monitored setting by using β-adrenergic antagonists. Traditional surgical options for repair of an aortic injury were thoracotomy with aortic cross clamping. The use of endovascular repair in adults makes this a potential option in children, with case reports using endovascular aortic stent grafts found in the literature.[45]

Diaphragmatic injury

The incidence of traumatic diaphragmatic injury is uncommon in the pediatric population, but it is most common after blunt trauma.[46] The transmission of blunt force from thoracic or intraperitoneal structures causes injury to the diaphragm. Left-sided injuries are more common, because the liver protects the right diaphragm from the direct force and limits herniation of intraperitoneal contents into the chest.[47] Many diaphragmatic injuries are initially asymptomatic; however, these injuries can cause immediate respiratory difficulty if they become symptomatic. Patients will have symptoms of shortness of breath and shoulder pain. Physical examination findings can include the absence of breath sounds on the affected side or the presence of bowel sounds within the chest. Chest radiograph is the initial diagnostic study used to screen for a potential thoracic injury in pediatric trauma. The most common findings that suggest a diaphragm injury include displacement of the nasogastric tube tip into the chest and the presence of bowel in the chest.[48] CT can also be used to diagnose a diaphragm rupture if findings on chest radiograph are inconclusive (Figure 31-2).

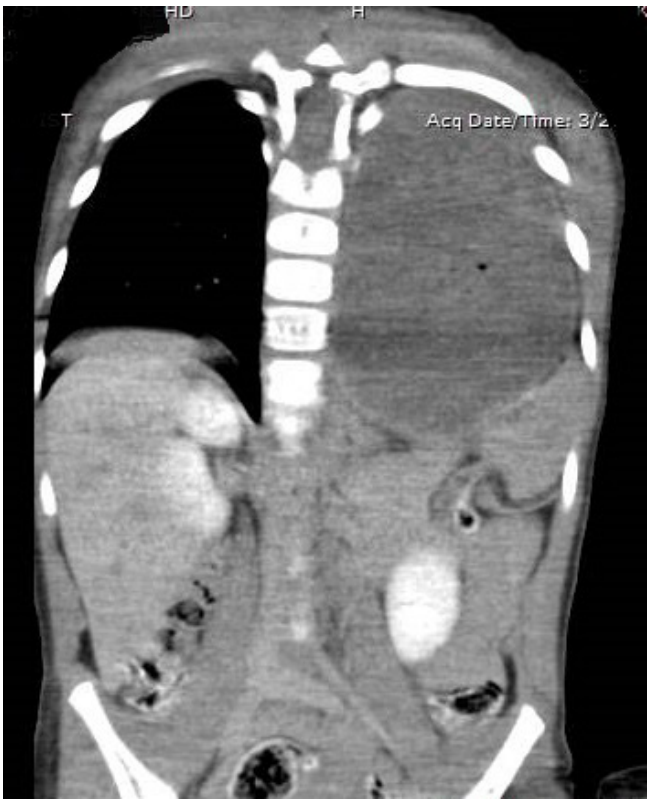


FIGURE 31-2 Computed tomography image demonstrating a left-sided diaphragmatic rupture with herniation of intraabdominal contents into the left chest.

The initial management of a diaphragm injury includes both resuscitation and appropriate operative intervention. Most diaphragm injuries are best repaired through the abdomen, with a midline incision or by minimally invasive techniques. If a thoracotomy is required to manage associated injuries such as a hemothorax, the diaphragm can also be repaired through the chest. After the diaphragm is repaired, a chest tube is placed for drainage.

Esophageal Injury

Pediatric trauma patients with evidence of pneumomediastinum (air within the mediastinum) on chest radiograph warrant a diagnostic work up for an esophageal injury (Figure 31-3). However, the presence of traumatic pneumomediastinum does not specifically correlate with esophageal perforation in the pediatric population.[49] Diagnostic studies used to identify an esophageal injury include water-soluble esophagram or esophagoscopy (Figure 31-4). The combination of these two studies to identify an injury is more than 90% accurate. If a perforation is found, the cervical and upper thoracic segments of the esophagus are the most common sites.

Small or contained esophageal perforations can be managed nonoperatively with intravenous fluids, nothing by mouth, and broad-spectrum antibiotics. Large or uncontained esophageal injuries require operative intervention. The lower thoracic esophagus is accessed through a left thoracotomy incision, and the midesophagus is accessed through a right thoracotomy incision. To obtain access to the cervical esophagus, a left neck incision is the best approach. For ruptures identified early (sooner than 6 hours), primary repair of the esophagus is possible. In the setting of a delayed diagnosis, an exclusion procedure must be considered. This is done with the use of a T-tube brought out from the perforation through the chest wall. Additionally, a cervical esophagostomy can be used to gain proximal control. After repair, esophageal strictures may develop, but these can be successfully managed with endoscopic dilation.

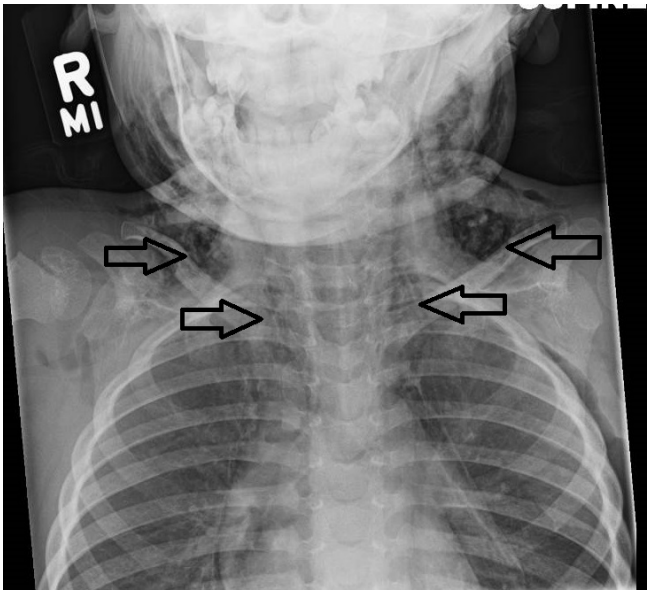


FIGURE 31-3 Chest radiograph showing evidence of pneumomediastinum. Note the *arrows* showing the presence of air within the mediastinum, which is a concern for an injury to the trachea or esophagus.

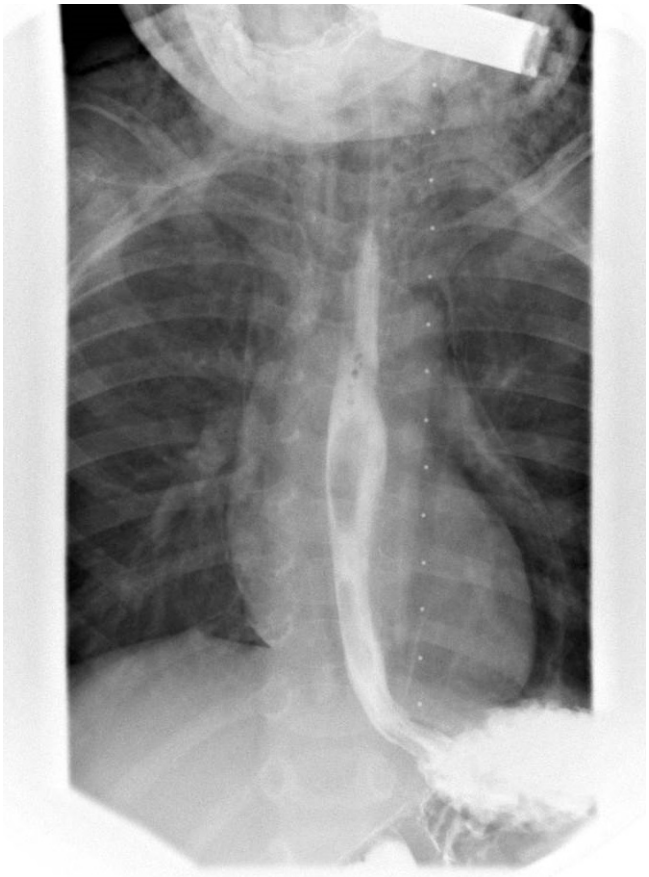


FIGURE 31-4 An esophagogram is used to identify an injury to the esophagus after thoracic trauma. In this case, there is no injury seen.

ABDOMINAL TRAUMA

The abdomen is the third most commonly injured anatomic region in children, with an incidence of 10% to 15%.[50] If unrecognized, injuries to abdominal contents can be fatal because of hemorrhage (immediate) or abdominal sepsis (early or late sequelae). Abdominal injuries affect approximately 10% of injured children, and the liver and spleen are the two most frequently injured organs. Falls and MVC (including pedestrians being struck) are the most common mechanisms of abdominal trauma in children. When assessing for an abdominal injury, laboratory studies in addition to physical examination help determine which patients might benefit from diagnostic imaging.[51] Bedside ultrasound, using the FAST examination, is the initial diagnostic tool to identify bleeding in the abdomen. In a patient who is hemodynamically unstable, this may be all the information needed to take the patient to the

operating room. However, the FAST examination is neither highly sensitive nor specific for identifying intraabdominal injuries in children, and results should be interpreted accordingly.[52] CT remains the gold standard for diagnosis of an intraabdominal injury; however, the detrimental effects of radiation exposure must be weighed.

ANATOMIC CONSIDERATIONS

There are unique anatomic features of children that make them more susceptible to abdominal injuries after trauma. The immaturity of their rib cage and their lack of soft tissue results in less protection of the upper abdominal viscera. The abdominal organs themselves are larger relative to the patient's overall size, with less "space" between them, making an organ injury more likely with any abdominal trauma.

PENETRATING VERSUS BLUNT ABDOMINAL TRAUMA

Most penetrating abdominal injuries in children are secondary to gunshot wounds and stabbings. In teenagers, gunshot injuries may be associated with intentional violence similar to adult patterns. Younger children are more commonly shot by accident, by an older sibling playing with a weapon at home, or as an innocent bystander. These patients can present with a number of clinical symptoms, from mild abdominal tenderness to rigidity and guarding on physical examination.[53] The trajectory of the penetrating object will determine other areas that need to be evaluated. Wounds that project toward the head can damage the diaphragm and enter the thoracic cavity, whereas wounds in the flank can injure the retroperitoneal structures (aorta, inferior vena cava, kidneys, small and large bowel). The diaphragm should be assumed to extend to the nipples, and thus a penetrating injury to the chest at the level of the nipples may have a concomitant abdominal injury. As per ATLS guidelines, patients must be fully exposed to identify both entrance and exit wounds during the trauma resuscitation to guide further management.[6]

Blunt abdominal trauma is more common than penetrating trauma in children, with injuries to the liver and spleen occurring most frequently. Injuries to hollow viscus organs (stomach, small bowel, and colon) can also occur after blunt abdominal trauma. Seatbelt-associated injuries can occur from abrupt deceleration during a MVC. The seatbelt sign is defined as an area of erythema across the abdomen, and intraabdominal injuries are more common in children with this finding.[54] Furthermore, a sheer injury caused by rapid acceleration/deceleration at a tethered point along the small bowel or its mesentery can occur. Child safety restraints are aimed to prevent these injuries, and the American Academy of Pediatrics recommends that toddlers stay in rear-facing car seats until the age of 2 and older children be kept in booster seats until they are 4 feet 9 inches in height.[55] Furthermore, regulations vary by state law, and hence there may be overarching legal considerations in regards to how a child should be protected until the appropriate age or size is reached.

INDICATION FOR LAPAROTOMY

Abdominal exploration in trauma is indicated when there is peritonitis on physical examination and free intraabdominal air. In addition, intraperitoneal fluid on FAST examination with hemodynamic instability not responsive to fluid and blood resuscitation is also an indication for exploratory laparotomy.

IMAGING CONSIDERATIONS

The diagnosis of an abdominal injury in pediatric trauma is best done using the physical examination during the secondary survey. Findings such as peritonitis or handlebar or seatbelt marks are suggestive of an underlying abdominal injury. These findings, combined with tachycardia, hypotension, and abdominal distension, should concern the clinician for significant intraabdominal bleeding. Abdominal imaging is reserved for stable pediatric trauma patients, without signs of shock. The FAST examination using bedside ultrasound is a rapid assessment of the abdomen and chest to diagnose bleeding. The FAST examination is neither sensitive nor specific for identifying injuries in children and is operator dependent; thus the results must be viewed with caution.[52] Furthermore, the vast majority of **solid organ injuries** to the liver and spleen in children can be managed nonoperatively. The FAST examination should be used as an adjunct to the history, mechanism of injury, and physical examination to guide further diagnostic workup.

Currently CT remains the gold standard for diagnosing solid organ injuries to the liver and spleen. However, concerns over the effects of radiation exposure have limited the enthusiasm for this diagnostic modality. Reports of increased rates of brain cancer and leukemia in children exposed to CT coincided with a movement within pediatrics to limit the number of CT scans to reduce unnecessary radiation exposure in children.[12] To help determine those children at very low risk for significant intraabdominal injury, the Pediatric Emergency Care Applied Research Network (PECARN) made a decision rule to help guide CT in pediatric abdominal trauma.[56] The model consists of GCS score, seatbelt sign, abdominal tenderness, decreased breath sounds, and vomiting. The authors concluded, based on their data, that CT can be used selectively in children with abdominal trauma.

MANAGEMENT CONSIDERATIONS

Solid Organ Injury

Injuries to the liver and spleen are characterized by a consensus grading system developed by the American Association for the Surgery of Trauma (AAST) (Tables 31-3 and 31-4).[57] The grades are assigned

Table 31-3 Spleen Injury Scale

GRADE	DESCRIPTION
I: Hematoma	Subcapsular, less than 10% surface area
Laceration	Capsular tear, less than 1 cm parenchymal depth
II: Hematoma	Subcapsular, 10%-50% surface area; intraparenchymal less than 5 cm in diameter
Laceration	1-3 cm parenchymal depth, which does not involve trabecular vessel
III: Hematoma	Subcapsular, greater than 50% surface or expanding; ruptured subcapsular or parenchymal hematoma Intraparenchymal greater than 5 cm in diameter or expanding
Laceration	Greater than 3 cm parenchymal depth or involving trabecular vessels
IV: Laceration	Involving segment of hilar vessels producing major devascularization (greater than 25% of the spleen)
V: Laceration	Completely shattered spleen
Vascular	Hilar vascular injury, which devascularizes the spleen

Table 31-4 Liver Injury Scale

GRADE	DESCRIPTION
I: Hematoma	Subcapsular, less than 10% surface area
Laceration	Capsular tear, less than 1 cm parenchymal depth
II: Hematoma	Subcapsular, 10%-50% surface area; intraparenchymal less than 10 cm in diameter
Laceration	1-3 cm parenchymal depth, less than 10 cm in length
III: Hematoma	Subcapsular, greater than 50% surface area or expanding; ruptured subcapsular or parenchymal hematoma Intraparenchymal greater than 10 cm in diameter or expanding
Laceration	Greater than 3 cm parenchymal depth
IV: Laceration	Parenchymal disruption involving 25%-75% of hepatic lobe or 1-3 Couinaud segments within a single lobe
V: Laceration	Parenchymal disruption involving greater than 75% of the hepatic lobe or more than 3 Couinaud segments within a single lobe
Vascular	Juxtahepatic venous injuries (i.e., retrohepatic vena cava/central major hepatic veins
VI: Vascular	Hepatic avulsion

according to the features found on CT imaging or intraoperative findings. Currently, management decisions in children are made according to hemodynamic status and signs of ongoing bleeding, not anatomic grade of injury.[58] Most blunt injuries to the liver and spleen are treated nonoperatively and based on physiologic parameters. During resuscitation, if the patient has signs of shock, which suggests ongoing bleeding, a 20 mL/kg bolus of crystalloid solution should be given. Nonresponders should then be given blood, and decisions regarding operative or interventional radiology should be discussed.

The presence of contrast extravasation on CT imaging in the pediatric patient with blunt liver and spleen injury may indicate patients who will benefit from **angioembolization.**[59] The technique of angioembolization of a splenic injury involves proximal main splenic artery embolization just distal to the pancreatic branches to stop bleeding.[60] In addition, selective angioembolization of liver injuries are an effective adjunct to nonoperative treatment of pediatric blunt liver injury.[61] The use of this modality for a contrast blush on CT in the presence of significant ongoing bleeding should be avoided, because patients with shock should not be transported to the interventional radiology suite.

Patients who fail nonoperative management are best treated by laparotomy. Signs of failure include persistent tachycardia, hypotension, falling hematocrit values despite blood transfusion, and peritonitis. Specific steps regarding operative intervention are beyond the scope of this work, but a brief description of general options for treatment at surgery will be reviewed. For bleeding splenic injuries requiring an operation, a midline incision is made where abdominal packing and control of the splenic hilum can be performed. The blunt force of the injury disrupts the usual splenic attachments, and the hilar vessels are ligated after the spleen is elevated into the wound. The surgeon must be careful to avoid injury to the tail of the pancreas that can lead to a pancreatic leak. Attempts at splenic salvage, such as partial splenectomy or splenorrhaphy, should be reserved for stable pediatric trauma patients without other associated serious injuries.[62] In addition, bleeding from the liver is best controlled using **damage-control surgery,** an abbreviated operation with the goal of controlling vascular injuries using perihepatic packing, and then resuscitation in the intensive care unit, typically with the abdomen left open. Once the patient has stabilized in 24 to 48 hours, definitive surgery is performed.[63]

Hollow Viscus Organ Injury

Injuries to the small bowel are also based on a classification system, and plain radiographs of the chest during the primary survey can help determine the presence of free air (Table 31-5).[64] Free air under the diaphragm is indicative of intestinal or colon injury; however, it is

Table 31-5 Small Bowel Injury Scale

GRADE	DESCRIPTION
I: Hematoma	Contusion or hematoma without devascularization
Laceration	Partial thickness, no perforation
II: Laceration	Laceration less than 50% circumference
III: Laceration	Laceration greater than 50% circumference without transection
IV: Laceration	Transection
V: Laceration	Transection with segmental tissue loss or devascularized segment

not always present. Despite concerns regarding the detrimental effects of radiation exposure, CT remains the best diagnostic tool short of surgical exploration to identify injury to the bowel and mesentery.[65] Findings on CT imaging concerning for a bowel injury are the presence of extraluminal air, intraperitoneal fluid, bowel dilation, and bowel wall thickening. Children with abdominal trauma, hemodynamic instability, and the presence of intraperitoneal fluid on FAST examination should undergo urgent exploratory laparotomy. Peritonitis on physical examination or progressive physical examination findings after a nondefinitive CT scan should also prompt surgical evaluation in the operating room.

Operative management of small bowel injuries will be briefly reviewed here, and the reader is referred to the article by Shilyansky and colleagues, which is an excellent review on the management of these injuries, specifically injuries involving the duodenum.[66] Bowel injuries are based on the grade of the injury, and every attempt at primary repair should be made to preserve bowel length. Higher-grade injuries are treated with bowel resection. Regarding injuries to the colon, operative repair also depends on the classification of the injury. Nondestructive colonic injuries affect less than 50% of the bowel wall without devascularization.[67] These types of colonic injuries are treated with primary repair without colonic diversion. Destructive colonic injuries are those that devascularize or transect the colon. These cases are best treated with resection and primary anastomosis. Children who are hypotensive in the operating room may be left in discontinuity with a temporary abdominal closure and delayed anastomosis when the child has been adequately resuscitated (usually 24-48 hours later).

Abdominal Compartment Syndrome

A compartment syndrome is a condition in which increased pressure in a confined space negatively affects circulation and threatens the viability of tissue within that space.[68] Compartment syndromes can occur in the extremities, orbital globe, head, and the abdominal cavity. **Abdominal compartment syndrome** refers to intraabdominal hypertension that reduces blood flow to abdominal organs. The definition of abdominal compartment syndrome is a pressure greater than 20 mm Hg with new onset of multiple organ failure (acute renal failure with oliguria, elevated peak inspiratory pressure on the ventilator with worsening pulmonary compliance).[69] Worsening abdominal compartment syndrome leads to fulminant multiple organ dysfunction and is fatal if left untreated. Risk factors include posttraumatic bleeding, patients who require vigorous fluid resuscitation from shock of any cause, and bleeding within the abdomen.[69]

Often the first sign of abdominal compartment syndrome is increasing peak inspiratory pressures on the ventilator in the setting of a tense abdomen. The best way to measure intraabdominal pressure is through the urinary bladder, by injecting saline through a Foley catheter into a fully drained bladder. The Foley is then clamped and connected to a transducer system, with intraabdominal hypertension defined as a reading greater than 20 mm Hg. Medical management of abdominal compartment syndrome is limited to sedation, paralysis, diuresis, fluid restriction, and gastric decompression via a nasogastric tube.[69] However, these measures are temporizing, and definitive surgical intervention is often needed. Decompression of the abdominal compartment can be done at the bedside in the ICU or in the operating room.

PELVIC FRACTURES

Pelvic fractures are uncommon injuries in children, occurring with an estimated incidence of 1 per 100,000 per year.[70] The pediatric pelvis is more resistant to fractures than the adult pelvis because of its intrinsic flexibility. Despite its rare occurrence overall, within the pediatric trauma population, pelvic fractures are identified in 2.4% to 7.5% of patients.[71] Common mechanisms for pediatric pelvic fractures include falls, bicycle accidents, and high-energy sports injuries.[71]

A pelvic fracture indicates a high-energy injury and is often associated with hemorrhage, which can be significant and life-threatening. If a traumatic pelvic fracture is suspected in a child, the patient can be quickly evaluated with a pelvis radiograph. In a hypotensive patient with a documented pelvic fracture, an injury to major pelvic vessels should be assumed, and stabilization of the pelvis should be initiated first using a pelvic binder. For those patients that remain hemodynamically unstable even after initial stabilization of the pelvis, bleeding is ideally controlled by angioembolization performed by an interventional radiologist.[71] If angioembolization is not immediately available or other significant injuries require urgent surgical exploration, pelvic bleeding can be temporized with extraperitoneal pelvic packing. A hybrid suite serves as the ideal arena to control pelvic hemorrhage, because it affords the possibility to perform both open operative maneuvers

and angioembolization to control bleeding in the same room. External fixation of the pelvis can be performed in the operating room to better stabilize the pelvis and reduce the risk of further injury.

GENITOURINARY TRAUMA

Genitourinary trauma most commonly occurs from a blunt mechanism, and the kidneys are the most commonly injured organ. Kidney injuries are associated with other solid organ or orthopedic injuries, and the clinician should maintain a high index of suspicion for a kidney injury with abdominal and pelvic trauma.[72] Renal injuries are graded from 1 to 5, with grade 1 being the least severe and grade 5 being the most serious. Renal injuries should be suspected with significant flank trauma and gross or microscopic hematuria. For definitive diagnosis, an ultrasound or CT is performed. If an injury is identified, up to 95% can be managed without an operation, with early operative management reserved for high-grade injuries with hemodynamic instability.[73] Bedrest is commonly recommended for a period after the injury to prevent inducing new bleeding. Surgical treatment of a kidney injury is rare, and every attempt should be made to salvage the kidney after trauma.

Bladder injuries most commonly are related to blunt trauma and can result from blunt force to a distended bladder or from a bony fragment from a pelvic fracture.[74] Bladder injuries can be either intraperitoneal or extraperitoneal, with extraperitoneal injuries occurring more commonly. Among both children and adults, pelvic fractures are commonly seen with bladder injuries.[75] A CT cystogram is the diagnostic imaging of choice to assess for a bladder injury; it requires injecting contrast directly into the bladder though a Foley catheter. An intraperitoneal bladder injury will show free contrast within the peritoneal cavity, and this will require an operation to repair the injury.[74] Uncomplicated extraperitoneal bladder injuries are managed by bladder drainage through a Foley catheter. The bladder will heal with sufficient time to drainage. Complications of a bladder injury are rare, but a delay in diagnosis can result in infection and abscess formation, urinary peritonitis, and sepsis.[74]

Pediatric urethral trauma is extremely rare, occurring in 3% of children with trauma to the genitourinary system.[76] Pelvic fractures are a common mechanism for a urethral injury. Blood at the urinary meatus along with gross hematuria are the most common presenting signs, and when this is seen a Foley should not be passed. For diagnosis of a urethral injury, a retrograde urethrogram (injecting water-soluble contrast using a small Foley catheter with the balloon slightly inflated outside the urethra) is performed. The initial management for most patients with a urethral injury is placement of a suprapubic catheter for bladder drainage along with definitive repair several weeks after the injury.[77] Complications after a urethral injury are infection, incontinence, impotence, and stricture formation.

HEAD INJURIES

Traumatic brain injuries (TBI) are a leading cause of morbidity and mortality in the pediatric population. In the United States, more than 37,000 children aged 14 years or younger are hospitalized for a TBI, with 3,000 deaths and 30,000 children suffering permanent disability.[78] Males younger than 4 years old have the highest rates of TBI-related emergency department visits, hospitalizations, and deaths. TBI is a contributing factor to a third (30.5%) of all injury-related deaths in the United States.[79] Most head injuries result from MVCs, falls, assaults, and child abuse. Improved outcomes after severe TBI result from better prehospital care and adherence to evidence-based practice guidelines.[80] The bimodal age distribution of TBI in children occurs between ages 0 to 4 and 15 to 19 years old, with males approximately two times more likely to suffer an injury.[81]

ANATOMIC CONSIDERATIONS

Children fall more than adults; this is related to several factors. They have an immature sense of balance and coordination, and children have heads that are larger than their bodies, shifting the center of gravity toward their head. When a young child falls, he or she is more likely to strike the head as a result of its relative size and weight compared to the body. This relative weight of the head also makes young children and particularly infants prone to inertial injuries, such as "shaken baby syndrome." With weak neck muscles, the force of shaking the head is absorbed by the brain itself impacting the sides of the skull.

Although they are more prone to injury, children are also better equipped to recover. The brains of infants and children have a large degree of plasticity in redistributing function from a damaged area to an undamaged area. In adults, the ability of the brain segments to adapt to new functions is rarely seen, because the maturing brain becomes locked into a specific distribution of functions. This plasticity in children enhances the ability to recover from even significant injuries.

The skull is more elastic in infants and children, offering protection against both fractures and the effects of closed head injuries. Prior to fontanels closing completely or the bones of the skull having ossified or fused completely, the cranial vault can allow more expansion than can an adult skull (Figure 31-5). This can be protective to the brain in the setting of a bleed within the confined space of the cranial vault. Elasticity of the skull is also protective against skull fracture. Children younger than 4 years may have a "ping-pong ball" skull injury that results in depression without fracture. On the other hand, diffuse cerebral edema is

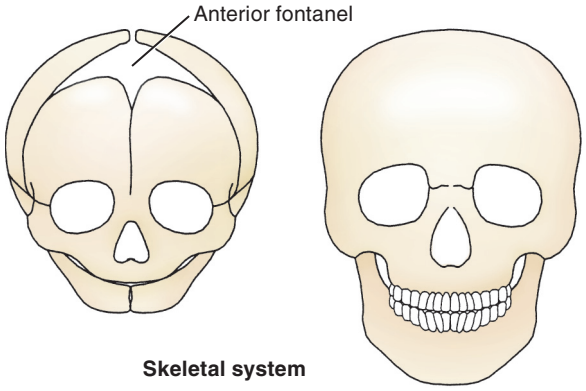


FIGURE 31-5 Image comparing the skulls between infant and adolescent children. The elasticity of the infant skull helps protect against the effects of closed head injuries and skull fractures. (From MacGregor J: *Introduction to the anatomy and physiology of children*, London, 2000, Routledge.)

more common in the pediatric population because of the smaller subarachnoid space.

IMAGING CONSIDERATIONS

For head trauma patients, the only imaging study typically needed is nonenhanced head CT. The study is quick to perform and highly sensitive to diagnose traumatic injuries that require emergent neurosurgical intervention. In addition, maxillofacial CT performed simultaneously to evaluate the brain and skull provides highly detailed images of the bones of the face, including the orbits and mandible. In select stable patients or those who require more detailed follow-up imaging after initial CT, magnetic resonance imaging (MRI) may have a role for providing detailed information regarding the presence of a contusion, intraparenchymal hemorrhage, extra axial hemorrhage, skull fractures, and diffuse axonal injury.[82]

MANAGEMENT CONSIDERATIONS

Airway Considerations

As in every other trauma patient, assessment must begin with the airway. Patients with head injuries are at particular risk for aspiration resulting from inadequate protection of the airway. At the same time, maintaining excellent oxygenation and ventilation is crucial in this patient group to prevent compounded injury to the brain. The primary survey includes a calculation of the GCS score (Table 31-2).[9] This score is also predictive of a patient's ability to protect his or her airway. If the GCS sore is less than 8, the airway must be secured with an endotracheal tube (or surgical airway if needed). Nasotracheal intubation is not preferred because of the risk to the cervical spine and direct injury in cases of skull fracture. The need for endotracheal intubation is otherwise based on the ability of the patient to both adequately oxygenate and ventilate. For patients with TBI, a low threshold for intubation should be maintained to avoid hypoxia and hypercarbia. Both result in cerebral vasodilation, which leads to an increase in cerebral pressure and potentially ischemia to an already injured brain. On the other hand, hyperventilation ($Paco_2$ less than 35 mm Hg) leads to cerebral vasoconstriction and decreased flow, and this should also be avoided except when there is concern for brainstem herniation. The medications administered for intubation should be selected and dosed to avoid hypotension and increased intracranial pressure.

Acute Brain Injuries

Once the airway is established, an efficient neurologic evaluation should be included in the survey of every patient in the trauma bay. The pediatric GCS should be estimated and the pupils examined. If there is suspicion for intracranial injury, noncontrast head CT should be performed, often in combination with other imaging studies needed such as evaluation of the spine. Timing of this study should not be delayed when a closed head injury is suspected, because findings such as epidural hematomas can require emergent neurosurgical intervention.

Intracranial hemorrhage is classified as a subdural, epidural, or intraparenchymal hematoma. Subdural hematomas occur when blood accumulates in the subarachnoid space, the area between the arachnoid membrane and the pia mater surrounding the brain. They appear as a crescent-shaped lesion at the surface of the brain that can be associated with mass effect and cerebral edema. Often subdural hematomas do not require surgical intervention, and patients can be closely monitored in an intensive care unit with serial examinations and imaging to watch for progression. If ongoing bleeding leads to significant compression of the brain, surgery may be needed. Epidural hematomas are caused by a middle meningeal artery injury or a bleeding skull fracture that allows blood to collect between the skull and the dura. They appear as a lens-shaped hematoma on head CT (Figure 31-6). Unlike subdural hematomas, epidural hematomas do not cross suture lines and more commonly require decompression. Patients who present with epidural hematomas may have a "lucid interval" for a period of several hours after initial loss of consciousness. Thus a conscious patient cooperating with physical examination in the trauma bay may still have an expanding epidural hematoma. This must be suspected based on the mechanism of injury accompanied by initial loss of consciousness. Intraparenchymal hematomas result from acceleration–deceleration injuries as the brain ricochets off the inside of the skull. This may result in focal injury to the underlying brain (coup) and also damage the other side (contrecoup) from rebound movement of the brain within the skull. Like epidural and subdural hematomas, bleeds can enlarge over time, and patients must be monitored closely for signs of neurologic deterioration. Each of the three entities can

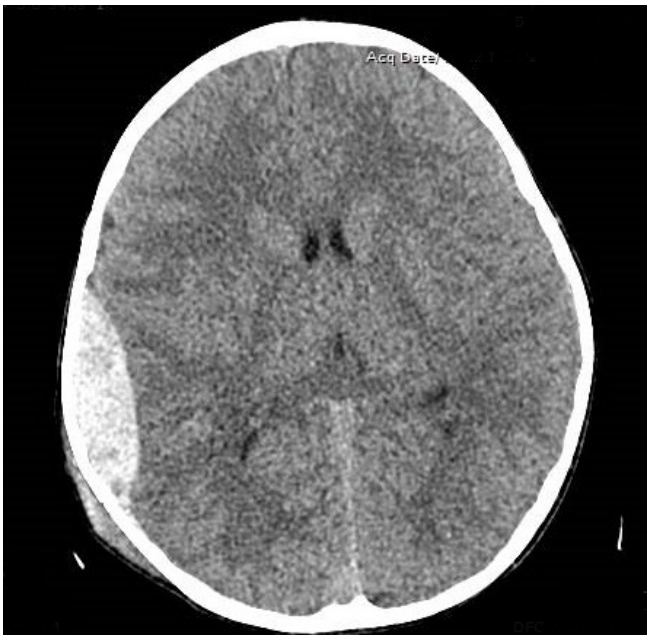


FIGURE 31-6 Computed tomography image of the head demonstrating a right-sided epidural hematoma. Note the lens-shaped appearance of blood.

progress rapidly and may require emergent surgical evacuation.

Nonaccidental trauma should always be considered in a pediatric patient with an acute brain injury. A history of trauma may not be reported. Symptoms such as lethargy, vomiting, and seizures should raise suspicion for this possibility. A combination of retinal hemorrhages seen on ophthalmologic examination and subdural hematoma should prompt a thorough investigation into this possibility.

Intracranial Pressure Monitoring and Treatment

Acute TBIs require careful monitoring to avoid secondary brain injury after the initial insult. Maintaining an adequate **cerebral perfusion pressure** (CPP) is crucial. CPP is calculated as the difference between the systemic mean arterial pressure (MAP) and the intracranial pressure (ICP). Current methods are aimed at maintaining a CPP of 40 mm Hg in infants and 50 mm Hg in older children. Thus maintaining an adequate perfusion pressure relies on maintaining adequate systemic blood pressure to perfuse the brain and controlling ICP. In a trauma patient, maintaining adequate systemic blood pressure typically equates to controlling hemorrhage in other anatomic sites. For example, although splenectomies in pediatric trauma are performed less commonly, this procedure may be indicated in the setting of a concurrent head trauma if it is leading to persistent systemic hypotension.

Like systemic blood pressure, the ICP can be measured to calculate the CPP, in this case by neurosurgical placement of an ICP monitor. Elevated ICP is defined as a pressure over 20 mm Hg, and these patients are at increased risk of decreased cerebral perfusion. Any child with a GCS of 8 or less should be considered for an ICP monitor. An intraventricular drain can often be placed at the bedside by neurosurgery and serves the dual function of measuring ICP and also decreasing it by allowing drainage of cerebrospinal fluid (CSF).[80]

Treatments aimed at lowering ICP can begin with simple interventions such as raising the head of the bed to 30 degrees to promote venous drainage from the brain and limiting fever, which tends to raise ICP. Mechanical ventilation should be achieved with the lowest peak pressures possible, because increases in intrathoracic pressure can impact cerebral venous drainage and consequently raise ICP. Sedation has been shown to decrease ICP, with both etomidate and barbiturates showing beneficial effects.[83] Hypertonic saline (3%) is used as a mainstay of treatment to decrease cellular edema by shifting water into the intravascular space. A serum sodium concentration of 150 to 170 mEq/L and a serum osmolarity of 360 mOsm/L are often used as targets.[84] Other methods to decrease ICP such as hyperventilation and hypothermia have not shown overall beneficial effects but are occasionally used in patients with elevated ICP refractory to standard treatments.[85,86] Hyperventilation to $Paco_2$ below 30 mm Hg causes a rapid decrease in ICP and can be life-saving for a patient with impending brainstem herniation. This should only be used as a temporizing maneuver until the patient can be definitively treated with surgery. When efforts to control ICP nonsurgically fail, decompression of the brain with craniectomy is indicated.

Skull Injuries

Skull fractures are common in pediatric patients admitted with TBI. Likewise, up to 21% of pediatric patients diagnosed with a skull fracture have a concomitant underlying parenchymal injury.[87] The three major types of skull fractures are linear, depressed, and basilar skull fractures. The most common is a linear fracture, which typically does not require any intervention. Skull base fractures are uncommon in children but have specific clinical signs such as mastoid ecchymosis (battle sign), periorbital ecchymosis (raccoon eyes), and hemotympanum.[88] When a basilar skull fracture is present, it should raise concern about possible associated injuries. For example, a skull base fracture can extend into the auditory canal and cause hearing loss. It can be associated with a CSF leak or extension into the sinuses. Involvement of the petrous bone can result in a carotid artery dissection and require medical therapy (antiplatelet therapy) or even endovascular intervention. Facial nerve injuries have also been described.

Surgical intervention is often indicated for depressed skull fractures. Indications for intervention include CSF leak, open fracture with contamination, a

neurologic deficit related to depression site, or hematoma. Surgical intervention involves elevation of the depressed segment of bone. In children younger than 4 years old, the skull may be depressed without fracture resulting in a ping-pong ball injury. These often require no intervention and resolve with skull remodeling over time.

Concussion

Concussion is an injury to the brain that results in characteristic neurologic impairment. Loss of consciousness may only occur in 10% of cases, and thus the diagnosis should be considered in any patient with a history of significant head strike or one who shows impairment after a more minor injury. Neurologic impairment usually appears within minutes but can also be delayed, manifesting up to a day after the event. Initial symptoms typically include inability to concentrate, confusion, delayed response to questions, and disorientation. Concussion is distinguished from other acute TBIs by characteristic neurologic impairment without any brain injury seen on imaging. Acute brain injuries need to be ruled out with imaging, and the patient should be managed initially as any other trauma patient, with a primary and secondary survey.

This injury occurs in two phases, one resulting from the trauma to the brain itself and the second as a product of the body's inflammatory response to trauma. The end result is a high metabolic demand by neurons attempting to repair themselves, and a mismatch of blood supply to meet these demands.[89] For this reason, physical and mental rest is typically prescribed to concussion patients to afford the body the greatest opportunity to feed and heal these recovering cells.

Patients who suffer from concussion can be evaluated using neurocognitive examinations to quantify levels of impairment in different capacities. These tests can be used to measure improvement over time. This is especially important for children as they return to their normal lives and school. Follow up is imperative, as is preventing a subsequent concussion in the period of healing.

NECK AND SPINE INJURIES

Neck trauma is fortunately uncommon in children. However, a missed injury can have devastating consequences for the patient. Traumatic injuries of the larynx and trachea occur in only 20 pediatrics patients per year in the United States but have a mortality of 8%.[90] Most (more than 80%) are caused by blunt disruption, not penetrating trauma. Spinal injuries occur more commonly with an incidence of 2% but with an associated mortality of 4% to 20%.[91] Eighty percent of spinal injuries in children occur in the cervical spine. Motor vehicle accidents are the cause of injury in more than half of cases. Nonaccidental trauma and falls account for a large portion of the remainder, as do sports-related injuries in teenagers. Upper cervical spine injuries are more common in younger children, with the highest rates involving the occiput through C3. In teenagers, lower cervical spine injuries are more common.

ANATOMIC CONSIDERATIONS

There are key anatomic differences between an adult and child neck that come to bear in assessment and management of pediatric trauma patients. First, a smaller caliber airway means that swelling and edema caused by trauma is more likely to threaten the lumen in a significant way. The larynx sits more protected behind the mandible and is less likely to be injured because of its location. In addition, the larynx and tracheal rings are more pliable and less likely to fracture. Similarly, bones of the neck are more pliable and less likely to fracture than adult bones. This does not however decrease the potential for ligamentous injury of the cervical spine. Moreover, decreased muscle mass in the neck overall equates to greater transmission of force to internal structures. Lastly, the relatively larger sized head in young children results in a specific pattern of cervical spine injury.

CERVICAL SPINE PROTECTION AND CLEARANCE

As in adult trauma patients, a child should always be assumed to have a cervical spine injury until proved otherwise. Pediatric patients who suffer from blunt trauma are placed in collars to help protect the cervical spine in case of an injury. A range of manufactured rigid collars are available, but all comprise a firm plastic shell secured with straps and padded liners. The most frequently prescribed collars are the Aspen, Malibu, Miami J, and Philadelphia collars. These collars can be used with additional head and chest extenders for further stability if needed.

The cervical spine may be "cleared" and the collar removed without need for imaging confirmation in a patient with a negative and reliable physical examination. This means no midline neck tenderness or neurologic concerns on examination in a child who is alert and without a distracting injury. In a young child, documenting a reliable examination can of course be more challenging. In a patient who is unable to be clinically cleared for one reason or another, an injury to the cervical spine must be assumed until imaging studies can be performed or the patient can be clinically cleared at a later time. When imaging is indicated, plain radiographs of the cervical spine can detect most bony injuries, reserving CT for patients with equivocal or inadequate radiographs. MRI can be used when the cervical spine cannot be cleared because a patient has altered mental status or when there is a concerning mechanism of injury.[92] A recent study performed at Boston Children's Hospital validated a pediatric cervical spine clearance algorithm that was

associated with both low missed injury rates and low use of CT for clearance (Figure 31-7).[93]

In the initial management of a trauma patient, maintaining cervical spine protection has particular relevance to management of the airway, because establishing an airway can be made significantly more challenging. Nasal intubation should be avoided. Inline stabilization of the neck should be provided during intubation if the collar is removed.

IMAGING CONSIDERATIONS

For diagnosing cervical spine injuries, practice guidelines have been developed for imaging pediatric patients after blunt injury. The Canadian cervical spine guidelines, validated for children older than 4 years, determine risk factors such as mechanism of injury and ability to rotate the neck to help guide the use of cervical spine radiography for trauma.[94] Plain films offer less exposure to radiation, cost less, and are yet quite sensitive in detecting cervical spine injuries (more than 90%). In a child considered low risk for cervical spine injury, this is the preferred modality of imaging. When there is higher degree of concern for injury on examination or plain films raise suspicion for injury, CT provides detailed visualization of structures of the neck. Radiation exposure in children is a growing concern, and the use of MRI avoids the exposure while providing superior evaluation of soft tissue structures including ligaments. Because of the time required for the study, cost, and common need for sedation and intubation in a child, it is not typically preferred over CT (however, for an ICU patient who is already intubated and whose cervical spine cannot be clinically cleared, MRI may be preferred and should be performed within 48 hours of injury).

Spinal cord injuries without radiographic abnormality, or **SCIWORA,** are defined as "neurologic examination or symptoms indicating a spinal cord injury without any correlated finding seen on plain film or CT." This is more common in younger children, up to

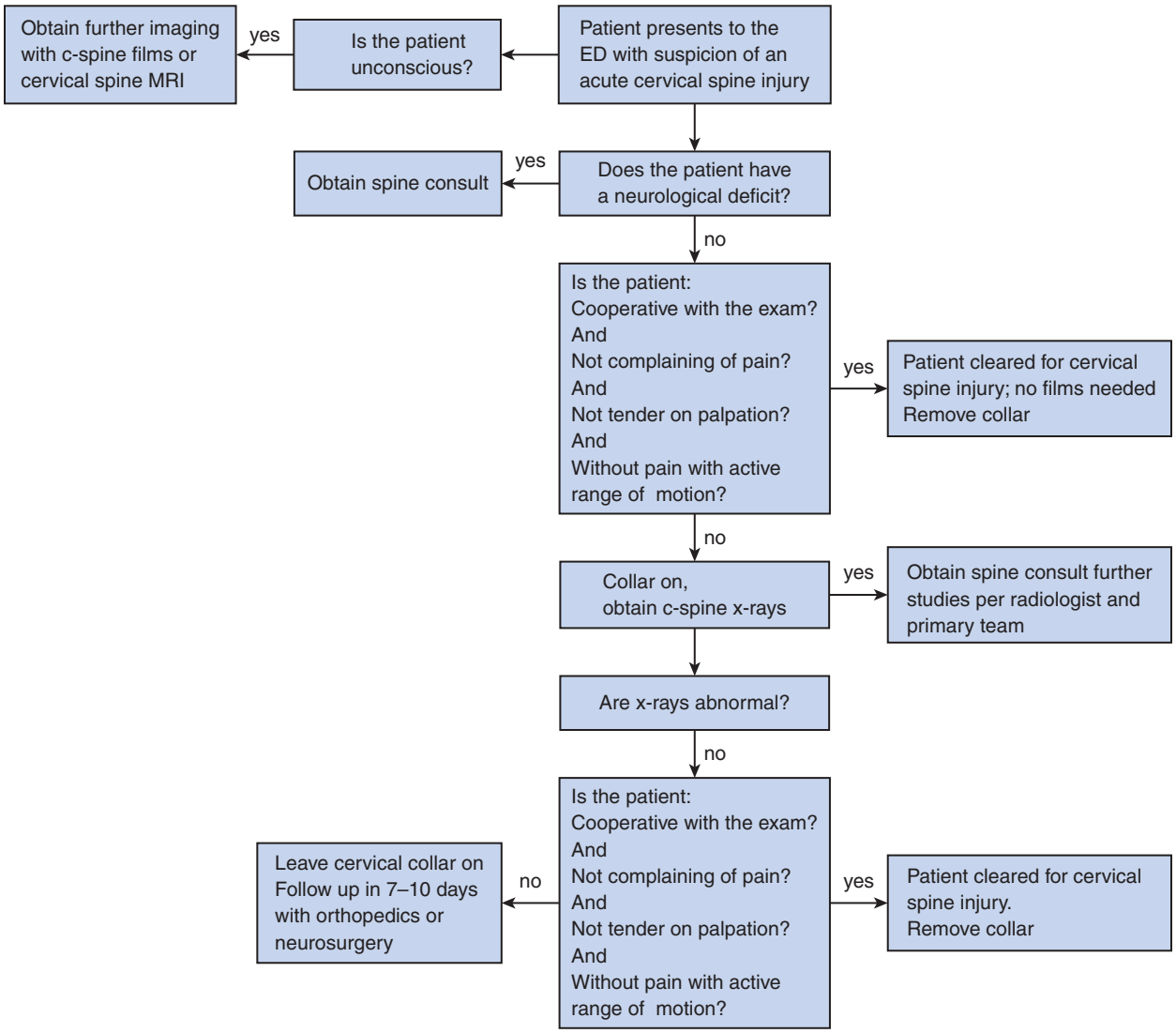


FIGURE 31-7 Algorithm for cervical spine clearance. *MRI,* Magnetic resonance imaging. (Adapted from Arbuthnot M, Mooney DP: *J Ped Surg* 52[1]:130-135, 2017.)

20%, and rare in adults. It is proposed that hypermobility in the pediatric neck allows dislocation related to hyperextension with immediate reduction resulting in a cord injury without associated fracture. In most of these cases, MRI will detect an injury unseen with other imaging studies. Thus, even with reassuring plain films or CT, any concern on physical examination or history should prompt MRI evaluation. In such cases or other complex scenarios, a low threshold should be maintained to involve orthopedic spine surgeons or neurosurgeons in the decision making.

MANAGEMENT CONSIDERATIONS

Neck Injuries

Like any other trauma patient, management of a child with a neck injury should begin with a critical assessment of the airway. If there is direct trauma to the neck or even the airway itself, intubation should be performed by the most experienced person available. In the rare circumstance that an oral airway cannot be established, a needle cricothyroidotomy with a 12- or 14-gauge angiocatheter attached to high-flow oxygen is a quick option to temporize and allow immediate transport to the operating room for a tracheostomy. The finding of crepitus on physical examination may indicate an airway injury but can also be seen with an injury to the esophagus or even with rupture of lung alveoli tracking into the neck. Subcutaneous emphysema is a marker of other injuries and should be investigated but rarely threatens the airway itself and is not an indication for intubation or surgical exploration.

The mechanism of injury and location with relation to the airway, major vessels, and esophagus informs early management. A blunt hanging injury should be evaluated by CT for hyoid bone fracture or trauma to the larynx or trachea and endoscopic evaluation for glottic or subglottic injuries. A penetrating injury to the neck is evaluated and managed based on anatomic zones I to III (Figure 31-8). Zone I spans from the thoracic inlet to the cricoid cartilage. Zone II extends from the cricoid cartilage to the angle of the mandible, and zone III starts at the angle of the mandible and extends to the skull base. Need for imaging or urgent operative exploration and timing depends on the structures at risk. A cervical collar is often not needed in a patient with a penetrating neck wound and should be removed to facilitate care. Classic teachings indicated that all penetrating zone II injuries should be explored surgically. In practice, many cases can be managed expectantly, and operative exploration is used as a means to treat rather than rule out injury. A stable patient with a penetrating neck injury should have a CTA to evaluate for vascular injury (zone III should include chest, and zone I should include head), followed by a panendoscopy evaluation in the operating room (laryngoscopy, bronchoscopy, esophagoscopy) to evaluate the aerodigestive tract. Some select patients

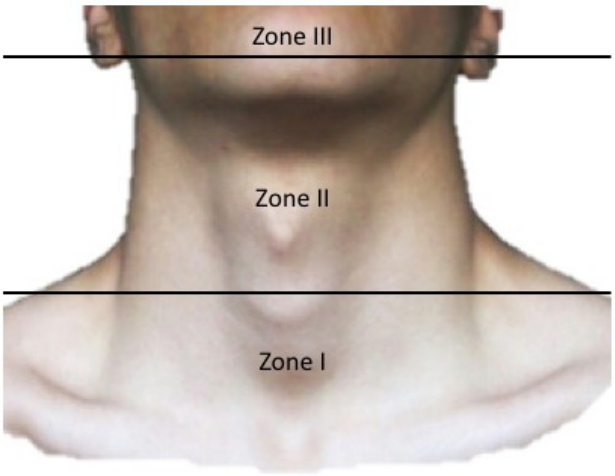


FIGURE 31-8 The anterior portion of the neck is divided into three zones to guide investigation and management after penetrating neck trauma.

may be adequately evaluated with observation and esophageal contrast study, or even observation alone. Vascular injuries in zone I or zone III and involving the vertebral arteries are often better managed with interventional radiology techniques than by operative exploration. Blunt injuries to the carotid and vertebral arteries are rare in children but can be investigated with a CTA in patients who meet one of the Memphis criteria (anisocoria, basilar skull fracture, cervical spine injury, soft tissue injury, Le Fort II or III facial fracture, or concerning neurologic findings on examination inconsistent with imaging).

Spine Injuries

Injuries to the cervical spine in pediatric trauma patients are commonly managed with immobilization through bracing. Types of injury include compression fractures, burst fractures, dislocations, ligamentous injuries, and injuries to the cord itself. Cervical spine injuries in children are more likely to be associated with a spinal cord injury. Findings on a neurologic examination suggesting cord injury include paralysis, asymmetry of reflexes, and numbness or weakness. Symptoms can be delayed in onset, sometimes appearing days after the event. Similarly, neurologic findings on initial examination may improve over the subsequent days. A spinal cord injury can also be associated with "spinal shock" with hypotension without bleeding and inappropriately warm and perfused extremities. Vasopressors such as phenylephrine are useful in such cases to support systemic blood pressure. Corticosteroids are currently not recommended for acute spinal cord injuries, with continued debate among clinicians regarding its clinical benefit.[95] An atlantooccipital spine injury is often fatal at the scene because of respiratory arrest. The force required for the injury is often associated with severe injuries to the brain and brainstem as well as the spinal cord. Odontoid

fractures may occur with only minor trauma in children but usually heal with immobilization alone. A custom collar in young children is favored over halo-traction.

Thoracic and lumbar spine injuries are less common than cervical injuries in children. When they occur, it is commonly at the junction of the thoracic and lumbar spine and related to seatbelt restraint. A Chance fracture involves all three columns of the vertebra and occurs as a flexion injury across a fulcrum, like a seatbelt. Small bowel injury or a vascular injury are not uncommonly associated with this type of fracture. Abdominal bruising and back pain should prompt an investigation into the possibility of both a spine injury and an occult abdominal injury.

SPECIAL CONSIDERATIONS

BIRTH INJURIES

The flexibility of the fetal skeleton exposes the fetus to injuries through the birth canal during vaginal delivery, resulting in trauma that can affect respiration.[16] The following section will outline specific injuries that can occur during birth including nerve injuries that result in paralysis of the diaphragm, lymph leak leading to **chylothorax,** and injury resulting in a pneumothorax.

Nerve Injury

During delivery the phrenic nerve, arising from the C4 level in the neck and controlling function of the diaphragm, can be damaged, impairing respiratory mechanics in the newborn.[96] Flexion and extension of the neck can stretch the origin of the phrenic nerve and lead to diaphragmatic paralysis. Diagnosis is suggested by a plain film of the chest but confirmed on a dynamic study such as fluoroscopy or ultrasound in which the movement of the diaphragm can be visualized. A paralyzed diaphragm may cause significant respiratory embarrassment in a newborn, who relies heavily on the diaphragm to generate the negative thoracic pressure to draw air. In addition, the paralyzed diaphragm elevates into the chest and compresses the ipsilateral lung, worsening function (Figure 31-9). The infant may require intubation and mechanical ventilation to support respiratory mechanics. The surgical therapy for persistent diaphragm paralysis consists of diaphragmatic plication, performed either through an open thoracotomy or by minimally invasive techniques.[97] The goals of surgery are to flatten the diaphragm to allow for better expansion of the ipsilateral lung and movement of the mediastinum to a more central position. It is not to restore function. Surgical therapy is typically deferred after the injury, allowing the phrenic nerve the opportunity to gain back its function. This can occur over weeks to even months.

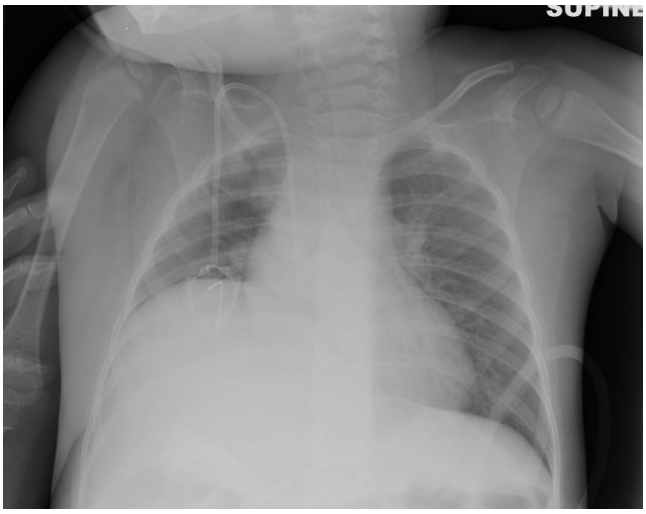


FIGURE 31-9 Chest radiograph showing elevation of the right hemidiaphragm, which is a concern for a phrenic nerve injury.

Chylothorax

Chyle is a noninflammatory, alkaline, and bacteriostatic fluid composed of fat, cholesterol, electrolytes, protein, glucose, and abundant lymphocytes.[98] Infants with chylothorax present with respiratory distress after birth and are noted to have significant pleural effusions on imaging. When the fluid is drained, it is found to be a milky white color. One proposed mechanism for this condition is the elevation of thoracic duct pressure as a result of thoracic compression during birth. The thoracic duct may rupture into the chest, leading to an ongoing lymph leak. Alternatively, congenital malformations that allow chyle to leak into the thoracic cavity can also cause a chylothorax. Once the diagnosis is established, treatment consists of immediate chest tube drainage and nothing by mouth to minimize the production of thoracic duct lymph. Nutrition is supplied by total parenteral nutrition until the chyle leak ceases. Furthermore, octreotide, which is a somatostatin analogue, is often used as an adjunct in the management of chylothorax with varying results.[98] Refractory cases will require surgical treatment (usually after several weeks of failed nonoperative management). Typically, thoracoscopic or open ligation of the duct at the diaphragm is performed. If this fails, a pleuroperitoneal shunt to drain the fluid into the peritoneal cavity is a last resort but can be effective. Between these two techniques, there is an approximately 80% success rate in managing infants with persistent congenital chylothorax.[99,100]

NONACCIDENTAL TRAUMA

There are approximately 1.2 million cases of **nonaccidental trauma** (NAT) reported annually, with an increased risk of death occurring among abused children.[2] Race and gender affects the prevalence of NAT, where females and minority children display higher rates of abuse.[101] Other risk factors include young age,

firstborn children, prematurity and low birth weight, children with speech or learning disabilities, low income homes, single parent homes, and substance abuse in the home. NAT represents a significant concern, with approximately 2% to 10% of children visiting emergency departments being victims of abuse or neglect.[102] It is important for members of the care team to recognize suspicious injuries by correlating the injury with the child's developmental age and clinical history. Physical signs such as bite marks, cigarette burns, unexplained bruises, multiple bruises in different stages of healing, belt marks, burns, lacerations, or abrasions should prompt a more detailed evaluation for NAT.

BITES

Most animal bites in the United States are from dogs, and approximately 4.5 million incidents occur each year, with children accounting for half of the cases.[103] Dog bites can result in significant morbidity in pediatric patients. Injuries can range from superficial wounds to life-threatening head and neck injuries, with reports of death occurring in the literature.[104] The psychological insult can have an adverse effect on quality of life for both the victim and their family. A single center case series at a level I pediatric trauma center identified 68.4% of dog bite victims requiring surgical intervention. Most operative procedures were performed by plastic surgeons 129 of 193 (66.8%), followed by pediatric surgeons (17.6%), ophthalmologists (10.4%), and hand surgeons (6.2%).[105] Cat bites are the second most common type of animal bite in the United States, with an estimated annual incidence of 400,000.[106] Cat bites are more likely to penetrate deep into tissue, particularly into the bones and joints. Thus deep abscesses and osteomyelitis are also more common with cat bites.[106]

Management of animal bite wounds should begin with a thorough inspection of the wound to identify deep injuries and devitalized tissue. Irrigation is one of the most important means of infection prevention. The bite wound should be rinsed with isotonic sodium chloride and covered with a sterile dressing. For all animal bite wounds, tetanus and rabies prophylaxis should be considered and patients should be treated with a 3- to 5-day course of antibiotics. The choice of antibiotics may vary, but they always should cover anaerobes, Staphylococcus, Streptococcus, and *Pasteurella* species.[106]

BURNS

Pediatric burns are a significant cause of injury-related mortality and are the third leading cause of death in children, following MVCs and drowning (safe kids worldwide, DC 2011). There is a bimodal distribution, with one peak occurring in children younger than 5 years and the second peak occurring during teenage years. Children younger than 5 years of age account for 50% to 78% of burn injuries, with burns more commonly found in males.[107] There is also seasonal variation in the incidence of burns, with the highest peak occurring in the winter months. Furthermore, children of young mothers (younger than 25 years) and mothers of low socioeconomic status have an increased risk of burn injury.[107] Scald injuries are the most common type of burn and occur most commonly in children younger than 5 years. Hospital admissions costs in the United States for pediatric burn patients average nearly 15 thousand dollars per case.[108] Prevention remains the best way to decrease thermal injury in children. Important measures in preventing pediatric thermal-related injuries are having working smoke detectors, keeping matches out of reach, lowering hot water temperatures, covering electrical outlets, and using flame-resistant children's clothing.[108]

With improved treatment of thermal injury, advancements in early wound repair techniques, effective antibiotics, appropriate fluid resuscitation, and avoidance of high pulmonary pressure and oxygen concentrations, the pediatric mortality rate and outcomes continue to improve. With these advances, the likelihood that a child will survive a burn exposure of up to 60% of the body surface area has increased.[109]

The skin is composed of two layers, the epidermis and dermis, and is an essential organ for survival. It protects against both infection and injury, maintains fluid homeostasis by preventing excess fluid loss, regulates body temperature, and provides sensory input from the environment. The epidermis is the thin outer layer and the dermis is the thicker, deeper layer. The dermis contains hair follicles, sweat glands, sebaceous glands, and sensory fibers for touch, pain, pressure, and temperature. Beneath the dermis lies the subcutaneous tissue, which is composed of connective tissue and fat.

Burn injuries are classified by the depth of the injury and are dependent on the temperature and duration of contact with the skin. Superficial burns involve only the epidermis, with the skin appearing erythematous similar to a sunburn. Blisters may or may not be present, and superficial burns are not included in the estimation of **total body surface area of a burn.**[110] Superficial partial-thickness burns involve the epidermis and the superficial part of the dermis. These burns contain blisters and are painful because nerve endings in the middle and superficial dermal layer survive the injury. Healing generally occurs quickly, because epithelial cells survive in deeper portions of hair follicles and migrate to the surface. Deep partial-thickness burns involve the epidermis and the entire dermis. These burns vary in pain because they involve some superficial nerve endings. They also include dermal appendages such as hair follicles and sweat glands. These burns do not typically blanch with pressure and may take longer than 14 days to heal.[110] Full-thickness burns involve injury and necrosis beyond the depths

of the hair follicles, through the entire thickness of the skin, and into the subcutaneous tissue. The area is usually blanched in appearance with destruction of sensory nerves, causing local anesthesia.

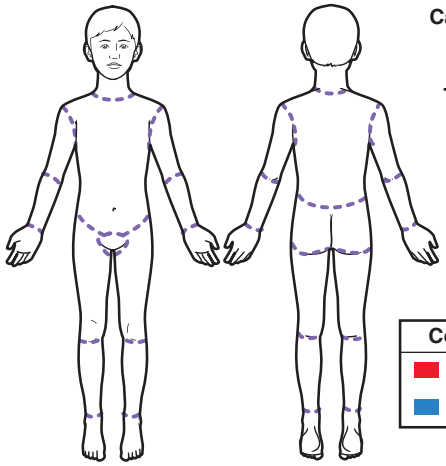
Estimating burn size and depth of injury assists the clinician to determine the severity, prognosis, and disposition of the patient. This is critical because fluid resuscitation requirements, nutritional support, and surgical interventions are all based on the size and percentage of body surface area burned. The size of the burn wound is described as a percentage of total body surface area. The rule of nines is the method most often used to estimate percent body surface area burned.[110] This estimate is based on various anatomic regions representing 9% of body surface area, or a multiple of nine. However, infants and young children have body proportions different from those of an adult, and a modified estimating rule is used (Figure 31-10).[111]

An essential component of burn wound care is initiating accurate fluid resuscitation after the injury. The primary goal of fluid resuscitation is to achieve organ and tissue perfusion while minimizing soft tissue edema. The Parkland formula (4 mL × kg × percent total body surface area burn) is used to guide resuscitation efforts in a pediatric burn patient over the first

Burn Estimate: Age Versus Area

Area	Birth 1 yr	1–4 yr	5–9 yr	10–14 yr	15 yr	2 degrees	3 degrees	Total
Head	19	17	13	11	9			
Neck	2	2	2	2	2			
Anterior Trunk	13	13	13	13	13			
Posterior Trunk	13	13	13	13	13			
Right Buttock	2½	2½	2½	2½	2½			
Left Buttock	2½	2½	2½	2½	2½			
Genitalia	1	1	1	1	1			
Right Upper Arm	4	4	4	4	4			
Left Upper Arm	4	4	4	4	4			
Right Lower Arm	3	3	3	3	3			
Left Lower Arm	3	3	3	3	3			
Right Hand	2½	2½	2½	2½	2½			
Lower Hand	2½	2½	2½	2½	2½			
Right Thigh	5½	6½	8	8½	8			
Left Thigh	5½	6½	8	8½	8			
Right Leg	5	5	5½	6	5½			
Left Leg	5	5	5½	6	5½			
Right Foot	3½	3½	3½	3½	3½			
Left Foot	3½	3½	3½	3½	3½			
					Total			

Burn Diagram



Cause of burn _____

Date of burn _____

Time of burn _____

Age _____

Sex _____

Weight _____

Color code
3rd degree
2nd degree

FIGURE 31-10 Table demonstrating body surface area estimates of burn size based on age. Correct assessment of burn wound size guides fluid resuscitation and nutritional support. (From Robert L. Sheridan : Burn care for children, *Pediatr Rev*, Jun 2018, 39 (6) 273-286; DOI:10.1542/pir.2016-0179.)

24 hours. Isotonic fluids (normal saline and lactated Ringer) are the most common fluids used, and the addition of dextrose for children younger than 5 years reduces the incidence of hypoglycemia caused by their limited glycogen stores.[112] Overaggressive fluid resuscitation may result in increased extravascular hydrostatic pressure, pulmonary edema, and soft tissue swelling, which can occur after inaccurate measurement of burn wound size.[113] The best measure of adequate fluid resuscitation is the urine output. Careful hemodynamic monitoring is required, along with intubation for most patients with severe burns.

Surgical intervention for burn wounds depends on the depth of injury. Superficial burns often heal spontaneously, usually within 2 weeks, and do not require surgical intervention.[110] Excision and early grafting of partial- and full-thickness burns, along with topical antimicrobial therapy, have decreased the incidence of burn wound sepsis.[110] Topical agents most commonly used include sulfadiazine (Silvadene), silver nitrate, and mafenide acetate (Sulfamylon). The dead skin after a burn injury forms an eschar, which is tough and leathery. Because the eschar layer does not expand well, circumferential burns of the limbs often swell and occlude perfusion to peripheral portions of the extremities. In the same manner, circumferential burns of the thorax can restrict ventilation. This can lead to severe restrictive disease requiring surgical release of the tissues by **escharotomy** (Figure 31-11).

The metabolic rate can increase as much as two to three times normal after a burn injury and is related to the size of the burn. There are elevations in stress hormones, cortisol and glucagon, that result in protein wasting, insulin resistance, and multisystem organ failure.[114] Nutritional support remains essential, because carbohydrates provide a caloric source for healing, decreasing the need to break down proteins for fuel. Pharmacologic support of the hypermetabolic response consists of using arginine; glutamine; vitamins A, C, and D; and anabolic agents such as insulin to alleviate muscle wasting and preserve lean body mass.

INHALATION INJURY

Inhalation injury has now emerged as the most common cause of death in patients with severe burns.[115] Inhalation injury impairs the mucociliary transport mechanism in the lung, predisposing the patient to retain secretions, which leads to pneumonia and atelectasis. The subsequent increased permeability leading to edema and mucosal sloughing can clinically manifest as bronchospasm, small airway occlusion, and decreased pulmonary compliance.[116]

Airway injury after smoke inhalation occurs at any level of the respiratory system, resulting in impaired ventilation and oxygenation. Direct thermal trauma to the upper airway results in obstruction from edema, hemorrhage, and ulceration of the mucosa.

Carbon monoxide poisoning is a serious consequence of smoke inhalation and has been implicated in up to 80% of smoke inhalation–related deaths. Other sources of carbon monoxide include malfunctioning heating systems, improperly ventilated motor vehicles, generators, grills, and stoves.[117] Combustion of furniture and household items can also result in cyanide poisoning. This should be suspected in a house fire and can be detected on laboratory evaluation. Antidote therapies are commercially available. Burn victims suspected to have inhalation injury should have carbon monoxide levels measured in addition to concurrently receiving 100% oxygen. Supplemental oxygen decreases the half-life of carbon monoxide from 90 minutes on room air to 20 to 30 minutes with high-flow oxygen. The formation of carboxyhemoglobin leads to a reduction in the oxygen-carrying capacity of

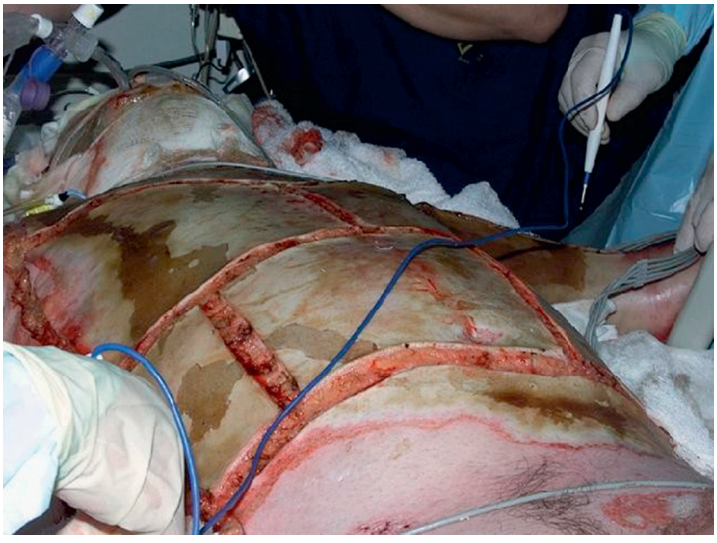


FIGURE 31-11 An escharotomy aimed at improving ventilation after a significant burn to the chest. (Courtesy University of Michigan Trauma Burn Center, Ann Arbor, MI. From Sole et al.: *Introduction to critical care nursing,* ed 6, Philadelphia, 2013, Saunders.)

the blood, shifting the oxyhemoglobin dissociation curve to the left. The major detrimental effects of carboxyhemoglobin are to organs that rely on a high supply of oxygen to support metabolism, such as the brain and heart.

Soot around the mouth may suggest the diagnosis, but the standard for the diagnosis of inhalation injury is fiberoptic bronchoscopy.[118] Furthermore, spirometry can also be used to diagnose an inhalation injury. Reductions in the forced expiratory volume in 1 second (FEV_1) and the ratio of FEV_1 to vital capacity (FEV1/VC) are seen within 24 hours of injury.[119]

The initial management of a suspected inhalation injury is to provide 100% oxygen therapy to increase the oxygen content of the blood. Oxygenation is monitored by arterial blood gas analysis, and COHb levels are analyzed with cooximetry.

Inhalation injury to the lower airways results in bronchospasm and wheezing. This is best managed with aerosolized bronchodilators that provide bronchial smooth muscle relaxation while stimulating mucociliary clearance. However, when using these agents, it is important to remember that they also increase overall metabolic rates. Racemic epinephrine may be used as an aerosolized vasoconstrictor, bronchodilator, and secretion bond breaker. The vasoconstrictive action of racemic epinephrine is useful in reducing mucosal and submucosal edema within the walls of the pulmonary airways. Furthermore, the use of inhalational heparin and N-acetylcysteine has been advocated as an adjunct to clear secretions, resulting in a reduction in reintubation rates and mortality.[120] The prophylactic use of antibiotics is not recommended. Instead, antibiotic therapy is directed by sputum Gram stain and blood cultures, with culture specimens obtained when infection or pneumonia is suspected.

Patients with moderate or severe inhalation injury may develop respiratory failure and require mechanical ventilation with an increased risk for iatrogenic, ventilator-induced lung damage.[120] The increased resistance often requires higher airway pressures to maintain sufficient flow to support minute ventilation. Conventional volume-limited ventilation in patients with inhalation injury is usually instituted at a tidal volume of 6 to 8 mL/kg. Lung compliance, system resistance, compressive volume loss, oxygenation, and ventilation must be considered when tidal volumes are selected. PEEP is added to recruit lung volumes, elevate mean airway pressures, and improve oxygenation. Consensus on the optimal mode of ventilation for inhalation injury is lacking; however, a review article by Peck and colleagues discusses the most commonly used strategies. [121]

The most common complications after an inhalation injury are infection and respiratory failure. Patients with inhalation injury have a high incidence of pneumonia, and immediate recognition of these complications is imperative so that appropriate treatment can begin promptly. In addition, barotrauma can result from a variety of injuries caused by mechanical ventilation, especially when high peak inspiratory pressures are maintained. Patients with inhalation injury often develop sloughing of the tracheobronchial mucosa, which results in a ball valve–type obstruction. This type of obstruction acts as a one-way valve. The volume from the mechanical ventilator is allowed to enter the lungs; however, expiration is only allowed to partially occur. If this problem is left untreated, further barotrauma may occur, resulting in a pneumothorax.

Tracheobronchitis can occur after an inhalation injury with the diagnosis suggested by fever, leukocytosis, and productive cough. A Gram stain showing white blood cells can also be suggestive. Treatment is supportive with antibiotics specific to the organism found on cultures.

ELECTRICAL INJURIES

Electric injuries in children rarely result in significant disability, tissue damage, or death. Low voltage injuries are most commonly sustained at home by toddlers inserting an object or fingers into an electric outlet or touching an exposed wire. Most low-voltage injuries are asymptomatic; however, children will often complain of pain, numbness, and tingling when symptoms do occur. In addition, children can develop a superficial or partial-thickness burn at the injury site and be managed in a similar way. During the workup, a baseline ECG should be obtained to evaluate for arrhythmias, and patients should be admitted and monitored for any abnormal results.

High-voltage injuries result from exposure to over 1000 volts and can occur from sources such as power lines. These injuries are extremely uncommon and usually occur when older children and teenagers climb trees near power lines. Patients sustaining these injuries are at high risk for extremity compartment syndrome, and serial clinical examinations should be performed. Indications for immediate fasciotomy are similar to abdominal compartment syndrome, and rates of amputation range from 20% to 40%.[122] Wounds should be promptly debrided of all necrotic tissue to reduce systemic and hypermetabolic responses. Tissue coverage can be achieved with cadaveric skin, flaps, or autografts.

Direct muscle injury from electrical burns can cause rhabdomyolysis, with the diagnosis based on elevated serum creatinine kinase levels. A consequence of rhabdomyolysis is the development of acute renal failure caused by the leakage of intracellular components such as myoglobin that obstruct the renal tubules. Early aggressive resuscitation with either normal saline or lactated Ringer to maintain an adequate urine output helps prevent the development of renal failure. Treatment is aimed at aggressive correction of hypovolemia, the prevention of oliguria using loop diuretics, and normalization of serum electrolytes.[123]

DROWNING

Drowning is the process of experiencing respiratory impairment from submersion or immersion in a liquid medium. It is classified as "witnessed" when the episode is observed from onset, or "unwitnessed" if the victim is found in the water. *Immersion* means to be covered in water—that is, the face and airway are immersed for a drowning to occur. *Submersion* occurs when the entire body is under water. Injuries may be further classified as cold-water or warm-water drowning. Warm-water drowning occurs at water temperatures of 20° C (68° F) or higher, and cold-water drowning occurs at water temperatures of less than 20° C (68° F).

According to the Centers for Disease Control and Prevention, from 2005 to 2014, there were an average of 3536 fatal unintentional drownings (non–boating related) annually in the United States. About one in five people who die from drowning are children 14 years and younger. More than 50% of drowning victims treated in emergency departments require hospitalization or transfer for further care (compared with a hospitalization rate of about 6% for all unintentional injuries).[124]

Males and children between the ages of 1 and 4 have the highest rates of drowning. In 2014, among children 1 to 4 years old who died from an unintentional injury, one-third died from drowning, with the majority occurring in home swimming pools. Drowning is responsible for more deaths among children aged 1to 4 years than any other cause except congenital anomalies (birth defects). Among children 1 to 14 years old, fatal drowning remains the second-leading cause of unintentional injury–related death, behind MVCs.[124] Furthermore, between 1999 and 2010, the fatal unintentional drowning rate for African Americans was significantly higher than that of whites across all ages.[125] African American children 5 to 19 years old drown in swimming pools at rates 5.5 times higher than those of Western European ancestry. This disparity is greatest among those 11 to 12 years old, at which age African Americans drown in swimming pools at rates 10 times those of children with Western European ancestry. Factors such as access to swimming pools, the lack of desire to learn how to swim, and choosing water-related recreational activities may contribute to the racial differences in drowning rates.[125]

During an episode of drowning, the victim's airway moves below the surface of the liquid and a period of voluntary apnea, or breathholding, occurs. An involuntary period of laryngospasm secondary to the presence of liquid in the oropharynx or larynx occurs next, and the victim becomes hypercarbic, hypoxemic, and acidotic. As hypoxia worsens, the laryngospasm relaxes, and the victim actively breathes in liquid. Aspiration of water leads to destruction of surfactant, impaired alveolar capillary gas exchange, and pulmonary edema.[126] Victims will then become hypothermic, leading to extravascular fluid shifts and decreased systemic perfusion. Death occurs from tissue hypoxia and multisystem organ failure.[127]

Central nervous system injury is the major determinant of survival and long-term morbidity in cases of near drowning. If the period of hypoxia and ischemia is brief, primary injury may be limited. However, submersion injuries that are associated with prolonged hypoxia or ischemia lead to both significant primary injury and secondary injury from reperfusion, sustained acidosis, and cerebral edema.[126] Furthermore, autonomic instability (diencephalic or hypothalamic storm) can occur after severe TBI, presenting with signs of hyperstimulation of the sympathetic nervous system (tachycardia, hypertension, tachypnea, diaphoresis, agitation, and muscle rigidity).[126]

Aspiration of either fresh water or saltwater destroys surfactant, impairs alveolar–capillary gas exchange, and increases intrapulmonary shunt, leading to profound hypoxia and increased pulmonary vascular resistance. In addition, acute respiratory distress syndrome (ARDS) from altered surfactant function and neurogenic pulmonary edema are common complications among survivors of submersion injury.[128]

Hypoxia and acidosis during the drowning event can lead to cardiac arrhythmias and impaired myocardial function. Asystole is the first recorded rhythm in 61% of patients, ventricular tachycardia or fibrillation in 20%, and bradycardia in 16%.[129] Pulmonary hypertension can result from the release of pulmonary inflammatory mediators and increasing right ventricular afterload. This leads to a decrease in both pulmonary perfusion and left ventricular preload. Hypotension may also occur during and after the initial resuscitation period, especially when vasodilation occurs as the patient is rewarmed. Long-term cardiovascular complications are exceedingly rare if the patient is rescued at the time of drowning.

The focus of treatment at the time of drowning is ensuring appropriate resuscitation with cardiopulmonary resuscitation (CPR) starting as soon as an adequate surface is available (Figure 31-12). Care should be taken to stabilize the cervical spine if there is any risk of cervical spine injury. As soon as trained emergency personnel are available, techniques such as endotracheal intubation, positive-pressure ventilation, and intravenous access should be initiated. A response to resuscitation may occur at the scene and result in the return of spontaneous heart rate and respirations; however, the need for continued assisted ventilation should be expected. Cardiac monitoring and management of arrhythmia along with correction of hypothermia should be made a priority before transfer to the nearest emergency department.

In the emergency department, stability of the airway and adequacy of ventilation should be assessed. Patients who require intubation should have

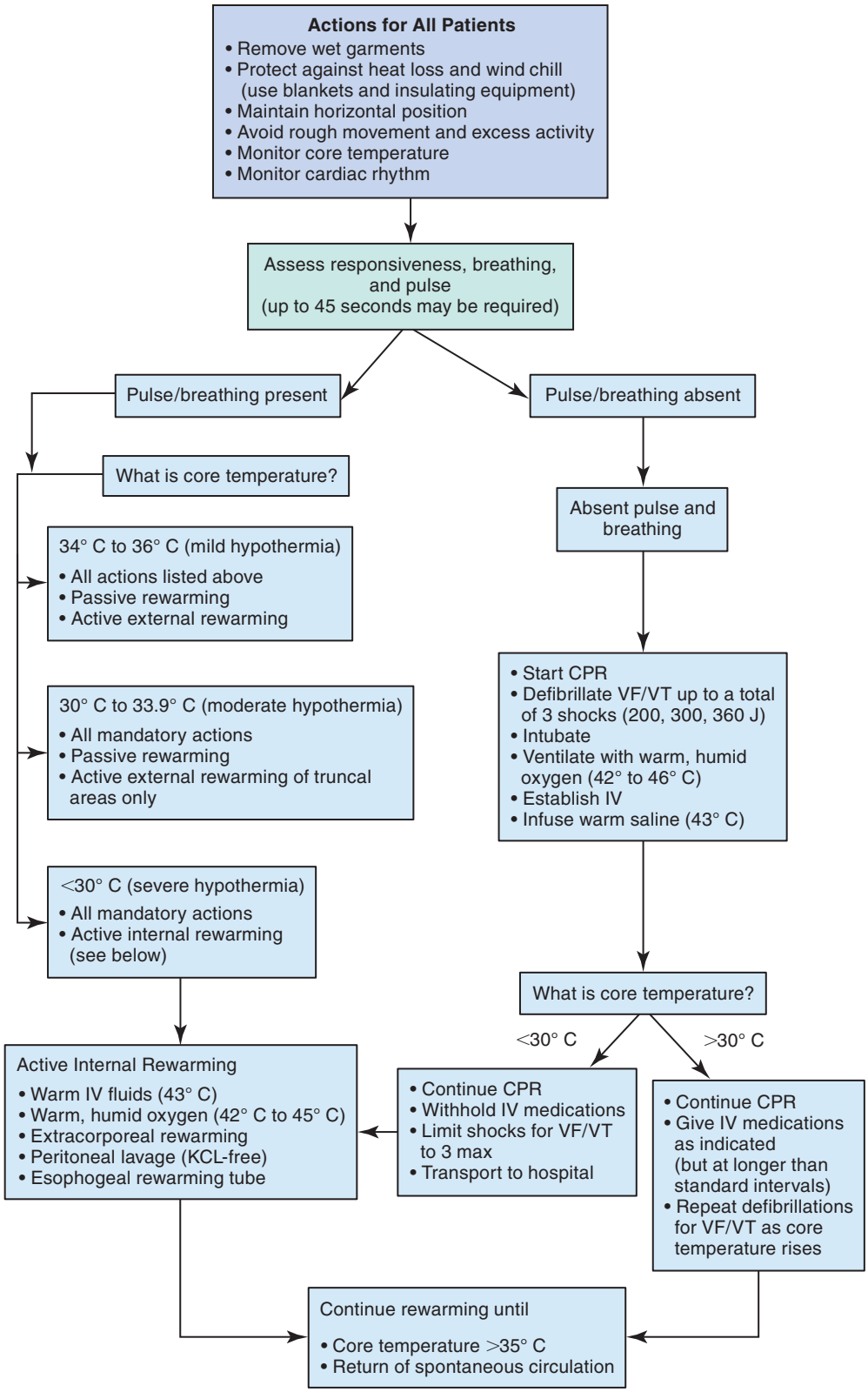


FIGURE 31-12 Treatment algorithm for initial resuscitation after drowning. *CPR,* Cardiopulmonary resuscitation; *IV,* intravenous line. (Data from Weinberg AD: Hypothermia. *Ann Emerg Med* 22 (Pt 2):370-377, 1993.)

a rapid-sequence induction performed with minimal bag–mask ventilation. Positive end-expiratory pressure should be initiated at 5 cm H_2O and increased in 2- to 3-cm H_2O increments to 15 cm H_2O as cardiac output and blood pressure allow.[130] Tissue perfusion and blood pressure should be assessed to determine the adequacy of cardiac output along with expansion of intravascular volume using crystalloid solution. Severe hypothermia (core temperature less than 35° C) is treated with rewarming the

patient 1° C to 2° C per hour to a range of 33° C to 36° C.[131] Aggressive rewarming above this range worsens underlying cerebral injury in post–cardiac arrest patients.[132] Methods to warm the patient include warm intravenous fluids and warm ventilator gases. Irrigation of the stomach, urinary bladder, and peritoneal cavity with warmed saline is effective and relatively low risk. Extracorporeal bypass is the most effective means of increasing body temperature for patients presenting with temperature less than 28° C, and in some cases this technique should be considered early in the course of management. Patients evaluated in the emergency department with no loss of consciousness, no altered mental status, and no respiratory signs and symptoms may be observed for a period of hours in the emergency department and discharged home if no complications are present.

INJURY PREVENTION

With the ongoing burden associated with traumatic injuries, prevention of trauma remains an important aspect of health care in the United States. Injury prevention strategies cover a variety of approaches, many of which are classified as falling under the "3 Es" of injury prevention: education, engineering modifications, and enforcement/enactment. Organizations such as Safe Kids Worldwide have expanded the list to six Es, adding evaluation, economic incentives, and empowerment. Examples of education include ways to promote seatbelt use, discourage impaired driving, and encourage parents to use child safety seats. Engineering includes vehicle crash worthiness, seatbelts, airbags, and locking seatbelts for child seats. Enforcement includes passage and enforcement of primary seatbelt laws and speed limits, along with impaired driving enforcement.

Health care professionals play a major role in educating patients and families about injury prevention either in the pediatrician's office or in the emergency department.[133]. Efforts to prevent deaths from drowning should focus on improved supervision, proper fencing around pools, and CPR training. Training families in CPR may decrease the duration of hypoxia experienced by a submersion victim. Of the 3Es previously mentioned, education is the strategy that health care providers can easily use in their daily practice. These measures require national, state, local, and individual support to maximize effectiveness for decreasing the incidence of unintentional injuries in children.

Key Points

- Systemic standardized evaluation of pediatric trauma patients using the primary and secondary surveys allows early identification and management of life-threatening injuries.
- A cervical injury should be assumed in blunt trauma victims and the cervical spine immobilized during manipulation of the airway.
- A tension pneumothorax can result in hemodynamic collapse and should be treated immediately by either needle decompression of the chest or tube thoracostomy.
- The Glasgow Coma Scale score can be modified for children to provide an assessment of mental status and can indicate whether the patient can protect his or her own airway.
- Hemodynamically unstable patients should either be adequately resuscitated in the trauma bay or taken directly to the operating room.
- The key tenet of rib fracture management is sufficient pain control to allow adequate respiratory mechanics.
- Solid organ injuries involving the liver and spleen are relatively common in children after blunt trauma and can often be managed nonoperatively.
- Signs of abdominal compartment syndrome include rising peak inspiratory pressures in the setting of a tense abdomen.
- Pelvic fractures can result in significant hemorrhage and may require angioembolization of bleeding vessels when pelvic stabilization does not result in improved stability.
- Monitoring and controlling intracranial pressure and cerebral perfusion pressure is essential to limit further injury in patients with closed head injuries.
- Nonaccidental trauma should always be considered in pediatric trauma patients, particularly in cases when the reported mechanism does not align well with observed injuries.
- Early debridement and proper wound care is essential to limit infectious complications of significant burns.
- Aspiration of water during drowning destroys surfactant and impairs alveolar–capillary gas exchange.
- Strategies for injury prevention often incorporate the 3 Es: education, engineering modifications, and enforcement.

Assessment Questions

1. Which of the following is not a characteristic of a level I trauma center?
   - **A.** 24-hour availability of surgical specialists
   - **B.** Intensive care capabilities
   - **C.** Part-time emergency medicine physicians
   - **D.** 24-hour access to imaging resources
2. What is the purpose of the primary survey?
   - **A.** Identify life-threatening injuries and resuscitation of the patient
   - **B.** Determine mechanism of the trauma
   - **C.** Determine disposition of the patient
   - **D.** Summarize injuries with the family members

3. What is a major risk of computed tomography (CT) in children?
   A. Delay in definitive treatment
   B. Expensive
   C. Radiation exposure and malignancy risk
   D. Potential for sedation
4. Why are children less likely to develop rib fractures after thoracic trauma compared with adults?
   A. Their ribs are smaller.
   B. They have higher cartilage content and incomplete ossification.
   C. They are less likely to be deficient in vitamin D.
   D. Their lungs are stiff.
5. Which of the following is an indication for an emergency department thoracotomy for pediatric trauma?
   A. Blunt injury with no signs of life for less than 15 minutes
   B. Blunt injury with no signs of life for less than 5 minutes
   C. Penetrating injury with no signs of life for less than 5 minutes
   D. Penetrating injury with no signs of life for less than 15 minutes
6. What is the definition of a tension pneumothorax?
   A. Air within the pleural space
   B. Air within the pleural space associated with hemodynamic instability
   C. Blood within the pleural cavity
   D. Nonanatomic area of consolidation
7. What percentage of children with a pulmonary contusion develop pneumonia?
   A. Less than 5%
   B. 50%
   C. 95%
   D. 20%
8. What is the most common location for a traumatic esophageal injury?
   A. Upper
   B. Middle
   C. Lower
9. What are the two most frequently injured abdominal organs in children?
   A. Colon and rectum
   B. Esophagus and stomach
   C. Liver and spleen
   D. Kidneys and bladder
10. Which of the following is not a characteristic of abdominal compartment syndrome?
    A. Intraabdominal pressure greater than 20 mm Hg
    B. Increasing peak inspiratory pressures
    C. Hypertension
    D. Low urine output
11. Which of the following is not a method aimed at lowering intracranial pressure after head trauma?
    A. Use of hypotonic saline
    B. Raising the head of bed to 30 degrees
    C. Sedation
    D. Hyperventilation
12. What is the first diagnostic imaging study used to rule out a cervical spine injury in children?
    A. Magnetic resonance imaging
    B. Radiography
    C. CT
    D. Ultrasound
13. What are the anatomic boundaries for a zone II neck injury?
    A. Thoracic inlet to the cricoid cartilage
    B. Angle of the mandible to the base of the skull
    C. Cricoid cartilage to the angle of the mandible
    D. Below the thoracic inlet
14. What is a proposed mechanism for a chylothorax?
    A. Rupture of the thoracic duct into the chest
    B. Blood accumulation into the pleural space
    C. Decrease in thoracic duct pressure during birth
    D. Air accumulation into the pleural cavity
15. What organisms must antibiotics cover after an animal bite?
    A. *E. coli*
    B. *Pasteurella*
    C. *Klebsiella*
    D. *Candida*
16. Which of the following is not a function of the skin?
    A. Maintains fluid homeostasis
    B. Regulates body temperature
    C. Has motor function
    D. Protects against infection
17. Estimating percent of body surface area burned is based on what?
    A. Anatomic regions representing multiples of nine
    B. Depth of the burn
    C. Presence of blisters
    D. Pain on clinical examination
18. What is the Parkland formula used for?
    A. Estimates body surface area burned
    B. Guides resuscitation over the first 24 hours after a burn
    C. Determines depth of injury
    D. Used as a measure of adequate fluid resuscitation
19. What findings on spirometry are not associated with an inhalation injury?
    A. Reduced FEV_1
    B. Elevated TLC
    C. Reduced FEV_1/vial capacity ratio
20. Which of the following are not part of the 6 Es of injury prevention?
    A. Economic incentives
    B. Education
    C. Enforcement
    D. Exposure

REFERENCES

1. Centers for Disease Control and Prevention. Vital signs: unintentional injury deaths among persons aged 0-19 years - United States, 2000-2009. *MMWR Morb Mortal Wkly Rep*. 2012;61:270-276.
2. Putnam-Hornstein E. Report of maltreatment as a risk factor for injury death: a prospective birth cohort study. *Child Maltreat*. 2011;16(3):163-174.
3. Seid T, Ramaiah R, Grabinsky A. Pre-hospital care of pediatric patients with trauma. *Int J Crit Illn Inj Sci*. 2012;2(3): 114-120.
4. Bankole S, Asuncion A, Ross S, et al. First responder performance in pediatric trauma: a comparison with an adult cohort. *Pediatr Crit Care Med*. 2011;12(4):e166-170.
5. Potoka DA, Schall LC, Gardner MJ, Stafford PW, Peitzman AB, Ford HR. Impact of pediatric trauma centers on mortality in a statewide system. *J Trauma*. 2000;49(2):237-245.
6. Subcommittee ATLS, American College of Surgeons' Committee on Trauma, ATLS working group. Advanced trauma life support (ATLS(R)): the ninth edition. *J Trauma Acute Care Surg*. 2013;74(5):1363-1366.
7. Greene N, Bhananker S, Ramaiah R. Vascular access, fluid resuscitation, and blood transfusion in pediatric trauma. *Int J Crit Illn Inj Sci*. 2012;2(3):135-142.
8. Soud T, Pieper P, Hazinski MF. *Nursing Care of the Critically Ill Child*. 2nd ed. Mosby Year Book; 1992.
9. Borgialli DA, Mahajan P, Hoyle Jr JD, et al. Performance of the Pediatric Glasgow Coma Scale Score in the Evaluation of Children With Blunt Head Trauma. *Acad Emerg Med*. 2016; 23(8):878-884.
10. Huber-Wagner S, Lefering R, Qvick LM, et al. Effect of whole-body CT during trauma resuscitation on survival: a retrospective, multicentre study. *Lancet*. 2009;373(9673): 1455-1461.
11. Jindal A, Velmahos GC, Rofougaran R. Computed tomography for evaluation of mild to moderate pediatric trauma: are we overusing it? *World J Surg*. 2002;26(1):13-16.
12. Pearce MS, Salotti JA, Little MP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. *Lancet*. 2012;380(9840):499-505.
13. Mathews JD, Forsythe AV, Brady Z, et al. Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. *BMJ*. 2013;346:f2360.
14. Bliss D, Silen M. Pediatric thoracic trauma. *Crit Care Med*. 2002;30(11 suppl):S409-S415.
15. Pearson EG, Fitzgerald CA, Santore MT. Pediatric thoracic trauma: current trends. *Semin Pediatr Surg*. 2017;26(1):36-42.
16. Nakayama DK, Ramenofsky ML, Rowe MI. Chest injuries in childhood. *Ann Surg*. 1989;210(6):770-775.
17. Peclet MH, Newman KD, Eichelberger MR, Gotschall CS, Garcia VF, Bowman LM. Thoracic trauma in children: an indicator of increased mortality. *J Pediatr Surg*. 1990;25(9): 961-965; discussion 965-966.
18. Sartorelli KH, Vane DW. The diagnosis and management of children with blunt injury of the chest. *Semin Pediatr Surg*. 2004;13(2):98-105.
19. Snyder CL, Jain VN, Saltzman DA, Strate RG, Perry Jr JF, Leonard AS. Blunt trauma in adults and children: a comparative analysis. *J Trauma*. 1990;30(10):1239-1245.
20. Sandler G, Leishman S, Branson H, Buchan C, Holland AJ. Body wall thickness in adults and children—relevance to penetrating trauma. *Injury*. 2010;41(5):506-509.
21. Peterson RJ, Tepas JJ, Edwards FH, Kissoon N, Pieper P, Ceithaml EL. Pediatric and adult thoracic trauma: age-related impact on presentation and outcome. *Ann Thorac Surg*. 1994;58(1):14-18.
22. Allen CJ, Valle EJ, Thorson CM, et al. Pediatric emergency department thoracotomy: a large case series and systematic review. *J Pediatr Surg*. 2015;50(1):177-181.
23. Nicolson NG, Schwulst S, Esposito TA, Crandall ML. Resuscitative thoracotomy for pediatric trauma in Illinois, 1999 to 2009. *Am J Surg*. 2015;210(4):720-723.
24. Rhee PM, Acosta J, Bridgeman A, Wang D, Jordan M, Rich N. Survival after emergency department thoracotomy: review of published data from the past 25 years. *J Am Coll Surg*. 2000;190(3):288-298.
25. Holscher CM, Faulk LW, Moore EE, et al. Chest computed tomography imaging for blunt pediatric trauma: not worth the radiation risk. *J Surg Res*. 2013;184(1):352-357.
26. Baumgartner F, Sheppard B, de Virgilio C, et al. Tracheal and main bronchial disruptions after blunt chest trauma: presentation and management. *Ann Thorac Surg*. 1990;50(4): 569-574.
27. Hancock BJ, Wiseman NE. Tracheobronchial injuries in children. *J Pediatr Surg*. 1991;26(11):1316-1319.
28. Pate JW. Tracheobronchial and esophageal injuries. *Surg Clin North Am*. 1989;69(1):111-123.
29. Unger JM, Schuchmann GG, Grossman JE, Pellett JR. Tears of the trachea and main bronchi caused by blunt trauma: radiologic findings. *AJR Am J Roentgenol*. 1989;153(6): 1175-1180.
30. Wood JW, et al., Traumatic tracheal injury in children: a case series supporting conservative management. *Int J Pediatr Otorhinolaryngol*. 2015;79(5):716-720.
31. Hehir MD, Hollands MJ, Deane SA. The accuracy of the first chest X-ray in the trauma patient. *Aust N Z J Surg*. 1990;60(7):529-532.
32. Fulton C, Bratu I. Occult pneumothoraces in ventilated pediatric trauma patients: a review. *Can J Surg*. 2015;58(3): 177-180.
33. Schild HH, Strunk H, Weber W, et al. Pulmonary contusion: CT vs plain radiograms. *J Comput Assist Tomogr*. 1989; 13(3):417-420.
34. Allen GS, Cox Jr CS. Pulmonary contusion in children: diagnosis and management. *South Med J*. 1998;91(12):1099-1106.
35. Galea MH, Williams N, Mayell MJ. Traumatic pneumatocele. *J Pediatr Surg*. 1992;27(12):1523-1524.
36. Rosenberg G, Bryant AK, Davis KA, Schuster KM. No breakpoint for mortality in pediatric rib fractures. *J Trauma Acute Care Surg*. 2016;80(3):427-432.
37. Lee RB, Bass SM, Morris JA Jr, MacKenzie EJ. Three or more rib fractures as an indicator for transfer to a Level I trauma center: a population-based study. *J Trauma*. 1990;30(6): 689-694.
38. Ceran S, Sunam GS, Aribas OK, Gormus N, Solak H. Chest trauma in children. *Eur J Cardiothorac Surg*. 2002;21(1):57-59.
39. Maron BJ, Gohman TE, Kyle SB, Estes NA, Link MS. Clinical profile and spectrum of commotio cordis. *JAMA*. 2002; 287(9):1142-1146.
40. Talving P, Demetriades D. Cardiac trauma during teenage years. *Pediatr Clin North Am*. 2014;61(1):111-130.
41. Hirsch R, Landt Y, Porter S, et al. Cardiac troponin I in pediatrics: normal values and potential use in the assessment of cardiac injury. *J Pediatr*. 1997;130(6):872-877.
42. Barmparas G, Inaba K, Talving P, et al. Pediatric vs adult vascular trauma: a National Trauma Databank review. *J Pediatr Surg*. 2010;45(7):1404-1412.
43. Tashiro J, Hannay WM, Naves C, et al. Mechanism and mortality of pediatric aortic injuries. *J Surg Res*. 2015;198(2): 456-461.
44. Yanchar NL, Woo K, Brennan M, et al. Chest x-ray as a screening tool for blunt thoracic trauma in children. *J Trauma Acute Care Surg*. 2013;75(4):613-619.
45. Brinkman AS, Rogers AP, Acher CW, et al. Evolution in management of adolescent blunt aortic injuries—a

single institution 22-y experience. *J Surg Res*. 2015;193(2):523-527.
46. Okur MH, Uygun I, Arslan MS, et al. Traumatic diaphragmatic rupture in children. *J Pediatr Surg*. 2014;49(3):420-423.
47. Hanna WC, Ferri LE. Acute traumatic diaphragmatic injury. *Thorac Surg Clin*. 2009;19(4):485-489.
48. Patlas MN, Leung VA, Romano L, Gagliardi N, Ponticiello G, Scaglione M. Diaphragmatic injuries: why do we struggle to detect them? *Radiol Med*. 2015;120(1):12-20.
49. Pryor SD, Lee LK. Clinical outcomes and diagnostic imaging of pediatric patients with pneumomediastinum secondary to blunt trauma to the chest. *J Trauma*. 2011;71(4):904-908.
50. Gaines BA. Intra-abdominal solid organ injury in children: diagnosis and treatment. *J Trauma*. 2009;67(2 suppl):S135-S139.
51. Mahajan P, Kuppermann N, Tunik M, et al. Comparison of Clinician Suspicion Versus a Clinical Prediction Rule in Identifying Children at Risk for Intra-abdominal Injuries After Blunt Torso Trauma. *Acad Emerg Med*. 2015;22(9):1034-1041.
52. Scaife ER, Rollins MD, Barnhart DC, et al., The role of focused abdominal sonography for trauma (FAST) in pediatric trauma evaluation. *J Pediatr Surg*. 2013;48(6):1377-1383.
53. Cotton BA, Nance ML. Penetrating trauma in children. *Semin Pediatr Surg*. 2004;13(2):87-97.
54. Borgialli DA, Ellison AM, Ehrlich P, et al., Association between the seat belt sign and intra-abdominal injuries in children with blunt torso trauma in motor vehicle collisions. *Acad Emerg Med*. 2014;21(11):1240-1248.
55. American Academy of Pediatrics. *AAP Recommendation on Car Seats*. 2011. Available at: https://www.aap.org/en-us/about-the-aap/aap-press-room/pages/aap-updates-recommendation-on-car-seats.aspx.
56. Holmes JF, Lillis K, Monroe D, et al. Identifying children at very low risk of clinically important blunt abdominal injuries. *Ann Emerg Med*. 2013;62(2):107-116.e2.
57. Moore EE, Cogbill TH, Jurkovich GJ, Shackford SR, Malangoni MA, Champion HR. Organ injury scaling: spleen and liver (1994 revision). *J Trauma*. 1995;38(3):323-324.
58. Notrica DM, Eubanks JW, Tuggle DW, et al. Nonoperative management of blunt liver and spleen injury in children: Evaluation of the ATOMAC guideline using GRADE. *J Trauma Acute Care Surg*. 2015;79(4):683-693.
59. van der Vlies CH, Saltzherr TP, Wilde JC, van Delden OM, de Haan RJ, Goslings JC. The failure rate of nonoperative management in children with splenic or liver injury with contrast blush on computed tomography: a systematic review. *J Pediatr Surg*. 2010;45(5):1044-1049.
60. Schnüriger B, Inaba K, Konstantinidis A, Lustenberger T, Chan LS, Demetriades D. Outcomes of proximal versus distal splenic artery embolization after trauma: a systematic review and meta-analysis. *J Trauma*. 2011;70(1):252-260.
61. Fallon SC, Coker MT, Hernandez JA, et al. Traumatic hepatic artery laceration managed by transarterial embolization in a pediatric patient. *J Pediatr Surg*. 2013;48(5):E9-E12.
62. William C, Asensio J. In: Evers BM, Townsend C, eds. *Atlas of Trauma/Emergency Surgical Techniques*. Saunders; 2013:368.
63. Sharrock AE, Barker T, Yuen HM, Rickard R, Tai N. Management and closure of the open abdomen after damage control laparotomy for trauma. A systematic review and meta-analysis. *Injury*. 2016;47(2):296-306.
64. Moore EE, Cogbill TH, Malangoni MA, et al. Organ injury scaling, II: Pancreas, duodenum, small bowel, colon, and rectum. *J Trauma*. 1990;30(11):1427-1429.
65. Fang JF, Wong YC, Lin BC, Hsu YP, Chen MF. Usefulness of multidetector computed tomography for the initial assessment of blunt abdominal trauma patients. *World J Surg*. 2006;30(2):176-182.
66. Shilyansky J, Pearl RH, Kreller M, Sena LM, Babyn PS. Diagnosis and management of duodenal injuries in children. *J Pediatr Surg*. 1997;32(6):880-886.
67. Miller PR, Fabian TC, Croce MA, et al. Improving outcomes following penetrating colon wounds: application of a clinical pathway. *Ann Surg*. 2002;235(6):775-781.
68. Kirkpatrick AW, Roberts DJ, De Waele J, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. *Intensive Care Med*. 2013;39(7):1190-1206.
69. Roberts DJ, Ball CG, Kirkpatrick AW. Increased pressure within the abdominal compartment: intra-abdominal hypertension and the abdominal compartment syndrome. *Curr Opin Crit Care*. 2016;22(2):174-185.
70. Amorosa LF, Kloen P, Helfet DL. High-energy pediatric pelvic and acetabular fractures. *Orthop Clin North Am*. 2014;45(4):483-500.
71. DeFrancesco CJ, Sankar WN. Traumatic pelvic fractures in children and adolescents. *Semin Pediatr Surg*. 2017;26(1):27-35.
72. Grimsby GM, Voelzke B, Hotaling J, Sorensen MD, Koyle M, Jacobs MA. Demographics of pediatric renal trauma. *J Urol*. 2014;192(5):1498-1502.
73. LeeVan E, Zmora O, Cazzulino F, Burke RV, Zagory J, Upperman JS. Management of pediatric blunt renal trauma: a systematic review. *J Trauma Acute Care Surg*. 2016;80(3):519-528.
74. Gomez RG, Ceballos L, Coburn M, et al. Consensus statement on bladder injuries. *BJU Int*. 2004;94(1):27-32.
75. Myers JB, Taylor MB, Brant WO, et al. Process improvement in trauma: traumatic bladder injuries and compliance with recommended imaging evaluation. *J Trauma Acute Care Surg*. 2013;74(1):264-269.
76. Tarman GJ, Kaplan GW, Lerman SL, McAleer IM, Losasso BE. Lower genitourinary injury and pelvic fractures in pediatric patients. *Urology*. 2002;59(1):123-126; discussion 126.
77. Pichler R, Fritsch H, Skradski V, et al. Diagnosis and management of pediatric urethral injuries. *Urol Int*. 2012;89(2):136-142.
78. Rutland-Brown W, Langlois JA, Thomas KE, Xi YL. Incidence of traumatic brain injury in the United States, 2003. *J Head Trauma Rehabil*. 2006;21(6):544-548.
79. Coronado VG, Xu L, Basavaraju SV, et al. Surveillance for traumatic brain injury-related deaths—United States, 1997-2007. *MMWR Surveill Summ*. 2011;60(5):1-32.
80. Adelson PD, Bratton SL, Carney NA, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents. Chapter 10. The role of cerebrospinal fluid drainage in the treatment of severe pediatric traumatic brain injury. *Pediatr Crit Care Med*. 2003;4(3 suppl):S38-S39.
81. Andersson EE, Sejdhage R, Wage V. Mild traumatic brain injuries in children between 0-16 years of age: a survey of activities and places when an accident occurs. *Dev Neurorehabil*. 2012;15(1):26-30.
82. Mehta H, Acharya J, Mohan AL, Tobias ME, LeCompte L, Jeevan D. Minimizing Radiation Exposure in Evaluation of Pediatric Head Trauma: Use of Rapid MR Imaging. *AJNR Am J Neuroradiol*. 2016;37(1):11-18.
83. Bramwell KJ, Haizlip J, Pribble C, VanDerHeyden TC, Witte M. The effect of etomidate on intracranial pressure and systemic blood pressure in pediatric patients with severe traumatic brain injury. *Pediatr Emerg Care*. 2006;22(2):90-93.
84. Khanna S, Davis D, Peterson B, et al. Use of hypertonic saline in the treatment of severe refractory posttraumatic intracranial hypertension in pediatric traumatic brain injury. *Crit Care Med*. 2000;28(4):1144-1151.
85. Curry R, Hollingworth W, Ellenbogen RG, Vavilala MS. Incidence of hypo- and hypercarbia in severe traumatic brain injury before and after 2003 pediatric guidelines. *Pediatr Crit Care Med*. 2008;9(2):141-146.

86. Hutchison JS, Ward RE, Lacroix J, et al. Hypothermia therapy after traumatic brain injury in children. *N Engl J Med*. 2008;358(23):2447-2456.
87. Bin SS, Schutzman SA, Greenes DS. Validation of a clinical score to predict skull fracture in head-injured infants. *Pediatr Emerg Care*. 2010;26(9):633-639.
88. Liu-Shindo M, Hawkins DB. Basilar skull fractures in children. *Int J Pediatr Otorhinolaryngol*. 1989;17(2):109-117.
89. Giza CC, Hovda DA. The Neurometabolic cascade of concussion. *J Athl Train*. 2001;36(3):228-235.
90. Cheng J, Cooper M, Tracy E. Clinical considerations for blunt laryngotracheal trauma in children. *J Pediatr Surg*. 2017;52(5):874-880.
91. Shin JI, Lee NJ, Cho SK. Pediatric cervical spine and spinal cord injury: a National Database Study. *Spine (Phila Pa 1976)*. 2016;41(4):283-292.
92. Nigrovic LE, Rogers AJ, Adelgais KM, et al. Utility of plain radiographs in detecting traumatic injuries of the cervical spine in children. *Pediatr Emerg Care*. 2012;28(5):426-432.
93. Arbuthnot M, Mooney DP. The sensitivity and negative predictive value of a pediatric cervical spine clearance algorithm that minimizes computerized tomography. *J Pediatr Surg*. 2017;52(1):130-135.
94. Stiell IG, Wells GA, Vandemheen KL, et al. The Canadian C-spine rule for radiography in alert and stable trauma patients. *JAMA*. 2001;286(15):1841-1848.
95. Hurlbert RJ, Hadley MN, Walters BC, et al. Pharmacological therapy for acute spinal cord injury. *Neurosurgery*. 2013;72(suppl 2):S93-S105.
96. Schullinger JN. Birth trauma. *Pediatr Clin North Am*. 1993;40(6):1351-1358.
97. Rodgers BM, Hawks P. Bilateral congenital eventration of the diaphragms: successful surgical management. *J Pediatr Surg*. 1986;21(10):858-864.
98. Tutor JD. Chylothorax in infants and children. *Pediatrics*. 2014;133(4):722-733.
99. Johnstone DW, Feins RH. Chylothorax. *Chest Surg Clin N Am*. 1994;4(3):617-628.
100. Wolff AB, Silen ML, Kokoska ER, Rodgers BM. Treatment of refractory chylothorax with externalized pleuroperitoneal shunts in children. *Ann Thorac Surg*. 1999;68(3):1053-1057.
101. Wildeman C. Emanuel N, Leventhal JM, Putnam-Hornstein E, Waldfogel J, Lee H. The prevalence of confirmed maltreatment among US children, 2004 to 2011. *JAMA Pediatr*. 2014;168(8):706-713.
102. Leetch AN, Woolridge D. Emergency department evaluation of child abuse. *Emerg Med Clin North Am*. 2013;31(3):853-873.
103. Gilchrist J, Sacks JJ, White D, Kresnow MJ. Dog bites: still a problem? *Inj Prev*. 2008;14(5):296-301.
104. Lang ME, Klassen T. Dog bites in Canadian children: a five-year review of severity and emergency department management. *CJEM*. 2005;7(5):309-314.
105. Garvey EM, Twitchell DK, Ragar R, Egan JC, Jamshidi R. Morbidity of pediatric dog bites: a case series at a level one pediatric trauma center. *J Pediatr Surg*. 2015;50(2):343-346.
106. Aziz H, Rhee P, Pandit V, Tang A, Gries L, Joseph B. The current concepts in management of animal (dog, cat, snake, scorpion) and human bite wounds. *J Trauma Acute Care Surg*. 2015;78(3):641-648.
107. Laitakari E, Koljonen V, Rintala R, Pyörälä S, Gissler M. Incidence and risk factors of burn injuries among infants, Finland 1990-2010. *J Pediatr Surg*. 2015;50(4):608-612.
108. Worldwide SK, 2015.
109. Kraft R, Herndon DN, Al-Mousawi AM, Williams FN, Finnerty CC, Jeschke MG. Burn size and survival probability in paediatric patients in modern burn care: a prospective observational cohort study. *Lancet*. 2012;379(9820):1013-1021.
110. Patel PP, Vasquez SA, Granick MS, Rhee ST. Topical antimicrobials in pediatric burn wound management. *J Craniofac Surg*. 2008;19(4):913-922.
111. Block L, King TW, Gosain A. Debridement Techniques in Pediatric Trauma and Burn-Related Wounds. *Adv Wound Care (New Rochelle)*. 2015;4(10):596-606.
112. Schulman CI, King DR. Pediatric fluid resuscitation after thermal injury. *J Craniofac Surg*. 2008;19(4):910-912.
113. Goverman J, Bittner EA, Friedstat JS, et al. Discrepancy in Initial Pediatric Burn Estimates and Its Impact on Fluid Resuscitation. *J Burn Care Res*. 2015;36(5):574-579.
114. Jeschke MG. Postburn Hypermetabolism: Past, Present, and Future. *J Burn Care Res*. 2016;37(2):86-96.
115. Sheridan, RL, Schnitzer JJ. Management of the high-risk pediatric burn patient. *J Pediatr Surg*. 2001;36(8):1308-1312.
116. Walker PF, Buehner MF, Wood LA, et al. Diagnosis and management of inhalation injury: an updated review. *Crit Care*. 2015;19:351.
117. Wu PE, Juurlink DN. Carbon monoxide poisoning. *CMAJ*. 2014;186(8):611.
118. Marek K, Piotr W, Stanislaw S, et al. Fibreoptic bronchoscopy in routine clinical practice in confirming the diagnosis and treatment of inhalation burns. *Burns*. 2007;33(5):554-560.
119. Moylan Jr JA, Wilmore DW, Mouton DE, Pruitt Jr BA. Early diagnosis of inhalation injury using 133 xenon lung scan. *Ann Surg*. 1972;176(4):477-484.
120. Desai MH, Mlcak R, Richardson J, Nichols R, Herndon DN. Reduction in mortality in pediatric patients with inhalation injury with aerosolized heparin/N-acetylcystine [correction of acetylcystine] therapy. *J Burn Care Rehabil*. 1998;19(3):210-212.
121. Peck MD, Harrington D, Mlcak RP, Cartotto R. Potential studies of mode of ventilation in inhalation injury. *J Burn Care Res*. 2009;30(1):181-183.
122. Arnoldo B, Klein M, Gibran NS. Practice guidelines for the management of electrical injuries. *J Burn Care Res*. 2006;27(4):439-447.
123. Coban YK. Rhabdomyolysis, compartment syndrome and thermal injury. *World J Crit Care Med*. 2014;3(1):1-7.
124. Centers for Disease Control and Prevention. N.C.f.I.P.a.C.W.-b.I.S.Q.a.R.S.W. 2015. Available at: http://www.cdc.gov/injury/wisqars.
125. Gilchrist J, Parker EM. Racial and ethnic disparities in fatal unintentional drowning among persons less than 30 years of age–United States, 1999-2010. *J Safety Res*. 2014;50:139-142.
126. Bierens JJ, Knape JT, Gelissen HP. Drowning. *Curr Opin Crit Care*. 2002;8(6):578-586.
127. Brenner RA. Prevention of drowning in infants, children, and adolescents. *Pediatrics*. 2003;112(2):440-445.
128. Modell JH. Drowning. *N Engl J Med*. 1993;328(4):253-256.
129. Donoghue AJ, et al. Out-of-hospital pediatric cardiac arrest: an epidemiologic review and assessment of current knowledge. *Ann Emerg Med*. 2005;46(6):512-522.
130. Leroy P, Smismans A, Seute T. Invasive pulmonary and central nervous system aspergillosis after near-drowning of a child: case report and review of the literature. *Pediatrics*. 2006:118(2):e509-513.
131. Nolan JP, Morley PT, Vanden Hoek TL, et al. Therapeutic hypothermia after cardiac arrest: an advisory statement by the advanced life support task force of the International Liaison Committee on Resuscitation. *Circulation*. 2003;108(1):118-121.
132. Hickey RW, Kochanek PM, Ferimer H, Graham SH, Safar P. Hypothermia and hyperthermia in children after resuscitation from cardiac arrest. *Pediatrics*. 2000;106(1 Pt 1):118-122.
133. Zonfrillo, MR, Melzer-Lange M, Gittelman MA. A comprehensive approach to pediatric injury prevention in the emergency department. *Pediatr Emerg Care*. 2014;30(1):56-62.

Disorders of the Pleura

32

Paul C. Stillwell, Oren Kupfer

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. Describe the normal function of the pleural space in healthy children.
2. List the causes of pneumothorax in neonates and children.
3. Recognize the causes of pleural effusions and empyema in children of all ages.
4. Discuss the principles of managing abnormal air or fluid in the pleural space in children.

Key Terms

chest tube
empyema
pleural effusion
pneumomediastinum
pneumothorax
thoracotomy
video-assisted thoracoscopic surgery (VATS)

The pleura surround the outer surface of the lungs and the mediastinum and the inner surface of the chest wall and the diaphragm. This sliding surface provides minimal resistance between the lung and chest wall during respiratory movements. The pleural "space" is generally only a *potential* space with a normal fluid volume of 1 to 5 mL. The pleural membranes, however, are very thin and permeable to both liquid and gas; an estimated 5 to 10 L of fluid per day cross from the parietal pleura to the visceral pleura in a normal adult.[1-3]

The pleura lining the chest wall, mediastinum, and diaphragm is called the *parietal pleura.* Its blood supply is from the systemic circulation, and its venous drainage is through the azygos, hemiazygos, and internal mammary veins into the superior vena cava. The *visceral pleura* covers the surface of the lungs including the fissures, with its blood supply from bronchial arteries and its venous drainage through the pulmonary veins.[1] In a healthy subject a positive 9 cm H_2O of hydrostatic pressure drives fluid from the parietal pleura capillary bed into the pleural space, and a negative 10 cm H_2O of hydrostatic pressure favors absorption of fluid into the visceral pleura capillaries.[1-3]

Several factors determine the amount of fluid in the pleural space. The *intracapillary* hydrostatic pressures tend to drive fluid out of the capillaries, whereas the *pericapillary* hydrostatic pressures tend to counterbalance this force. The *plasma* colloid osmotic pressures exert a force to retain fluid within the capillaries, whereas the *pericapillary* colloid osmotic pressure tends to favor fluid movement out of the capillaries. Changes in the balance of these forces determine how much fluid is retained within the pleural space. Increased capillary permeability (e.g., acute respiratory distress syndrome), decreased intravascular colloid osmotic pressure (e.g., low serum albumin), and increased pulmonary venous pressure (e.g., heart failure) are common contributors to accumulation of fluid in the pleural space. Obstructed lymphatic drainage is another factor that favors accumulation of fluid in the pleural space.[1,2] Chylothorax, a collection of lymphatic fluid in the pleural space, is an uncommon cause of pleural effusion in children, except when they have undergone thoracic surgery with interruption of the thoracic duct. [1,2,4]

In healthy individuals the chest radiograph seldom demonstrates any pleural fluid.[5] An estimated 4% of normal adults may have minor radiographic evidence of pleural fluid if the films are taken in the decubitus or Trendelenburg position. A pleural effusion has typical radiographic features (Figures 32-1 to 32-3). Ultrasound examination or computed tomography (CT) of the chest may be more sensitive in identifying small

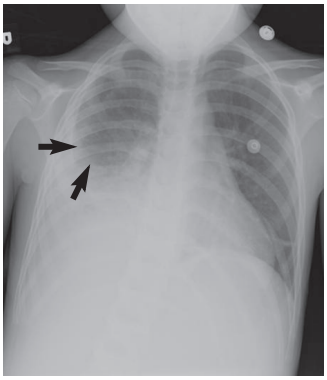


FIGURE 32-1 Upright chest radiograph of a 7-year-old child with a large pleural effusion on the right. The bottom third of the right hemithorax is white with a rounded superior margin (meniscus sign, *arrows*). The diaphragm is obscured, and there are air bronchograms in the right lower lung zone. This parapneumonic effusion was an empyema caused by streptococcal pneumonia.

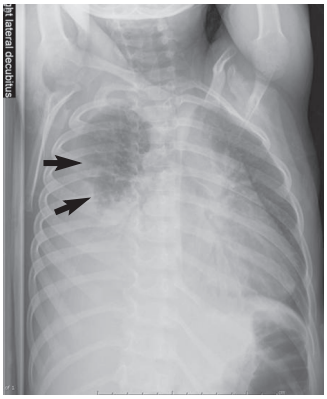


FIGURE 32-2 Right-side-down decubitus radiograph of the child in Figure 32-1. The fluid is more prominent on the lateral chest wall margin, indicating free movement of the fluid in the pleural space *(arrows).*

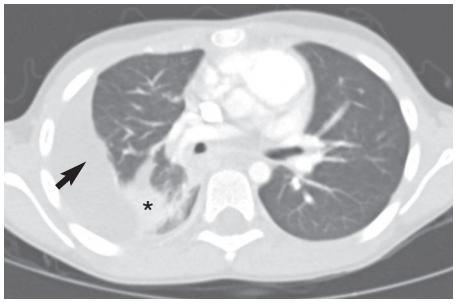


FIGURE 32-3 Chest computed tomography image showing a right-sided empyema along the right lateral wall *(arrow)* and a right lower lobe infiltrate between the empyema and the spinous process *(asterisk).*

accumulations of pleural fluid. [2,5] CT may also provide more information about the underlying lung parenchyma than is available from plain chest radiography, especially when large amounts of fluid are present. However, ultrasound and CT usually are not required to identify a clinically significant effusion. Ultrasound may be used to facilitate finding the optimal location to perform a thoracentesis.[5]

PLEURAL EFFUSIONS

Pleural effusions may be suspected clinically when there is an area of decreased-intensity breath sounds on chest auscultation with an associated dullness to percussion over the corresponding area.[2,3] Comparison with the contralateral lung can help distinguish the normal boundaries of the thoracic cavity unless the effusion is bilateral. The patient may experience few symptoms from a small pleural effusion but usually has symptoms of respiratory distress with larger accumulations. Chest pain, chest wall tenderness, dyspnea, and pain with coughing or deep breathing are often associated with pleural effusions. In addition to decreased intensity of breath sounds with dullness to percussion, crackles may be appreciated immediately superior to the effusion, where the lung may be involved with underlying pneumonia, or the normal lung may be partially compressed by the effusion. The location of these abnormal examination findings may change when the position of the patient is changed if the fluid is flowing freely within the pleural space. The respiratory care practitioner may be the first to detect the findings of a pleural effusion during auscultation.[3]

When a suspected effusion is confirmed by a chest radiograph, the initial decision is whether it should be drained, either for diagnostic purposes or for therapeutic purposes or both. In adult medicine and with older, cooperative children, a thoracentesis is often the initial approach to drainage.[3,6] This diagnostic procedure consists of placing a needle into the pleural space and withdrawing the pleural fluid. On occasion an underlying disease such as overt heart failure or nephrotic syndrome will leave little doubt as to the cause and nature of the pleural effusion, thereby decreasing the need for a diagnostic thoracentesis.[6] The pleural fluid is generally categorized as either a transudate or an exudate on the basis of specific criteria (Table 32-1 and Box 32-1). Disease processes associated with transudates and exudates in children are listed in Boxes 32-2 and 32-3.[2,3,6] In pediatric patients for whom prolonged drainage may be required, such as an **empyema,** a chest tube may be placed initially either by an interventional radiologist or by a surgeon, often after performing a video-assisted thoracoscopic surgery (VATS). If this is the case, thoracentesis is usually foregone and the fluid analysis is sent on a sample from the chest tube. In most children's hospitals the pleural drainage is

Table 32-1 Distinguishing Transudate from Exudate

MEASUREMENT	TRANSUDATE	EXUDATE
Protein (g/dL)	<3	>3
Effusion/serum protein ratio	<0.5	>0.5
LDH (units/L)	<250	>250
Effusion/serum LDH ratio	<0.6	>0.6

LDH, Lactate dehydrogenase.

Box 32-1 Common Pleural Fluid Analyses

- Total protein
- Lactate dehydrogenase (LDH)
- Cell counts and differential cell count
- pH
- Cytology
- Studies for infection
- Gram stain, bacterial culture
- Acid-fast stain and culture
- Fungal stains and culture
- Glucose
- Amylase

Box 32-2 Causes of Transudative Pleural Effusions

- Congestive heart failure
- Nephrotic syndrome
- Cirrhosis or liver failure
- Acute glomerulonephritis
- Hypoproteinemia
- Myxedema
- Sarcoidosis
- Peritoneal dialysis

Box 32-3 Causes of Exudative Pleural Effusions

- Parapneumonic effusion or empyema
- Pulmonary embolism
- Neoplasm
- Collagen vascular disease
- Trauma
- Drug hypersensitivity
- Lung transplant rejection
- Chylothorax
- Gastrointestinal diseases
- Lymphatic disease
- Postcardiac surgery syndrome
- Acute chest syndrome (sickle cell disease)

increasingly done by an interventional radiologist with ultrasound guidance.[7]

Complications of thoracentesis include pneumothorax, hemorrhage, and infection. A **pneumothorax** may be created by nicking the lung with the needle or by not maintaining a closed system and allowing air to enter the chest cavity from the atmosphere. Hemorrhage may result from nicking a vessel or the lung during needle insertion.[3] If sterile technique is not followed, infection can be introduced into the pleural space, or the sample sent for microbiology evaluation may be contaminated, or both. Other complications include an allergic reaction to the sedating medicines or hypoventilation resulting from oversedation. Because most pediatric patients receive sedation or anesthesia for chest tube placement and thoracentesis, a person skilled at providing and monitoring their sedation is usually in attendance. However, it is important for the respiratory care practitioner to be familiar with these complications, because he or she may be monitoring the patient's cardiovascular and pulmonary status after completion of the procedure. Rapid drainage of the pleural space (either effusion or pneumothorax) can result in reexpansion pulmonary edema.[8] Though rare in pediatrics, this complication can lead to acute respiratory failure and death. The mechanism is unclear but is probably related to rapid changes in intrapleural pressures. Any deterioration in the patient's clinical status after the procedure immediately should be called to the attention of the appropriate care team for further assessment.

Several laboratory tests are performed on the pleural fluid to identify the cause of effusion.[2,3,6] The most common type of pleural effusion in pediatrics is a parapneumonic effusion,[9] which indicates that the pleural fluid is the result of an underlying pneumonia. Although typically a bacterial pneumonia, parapneumonic effusion can also result from a viral, fungal, or parasitic infection or from tuberculosis (Box 32-4).[6,9] If the pneumonia extends to infect the pleural space as well, the effusion is then termed an **empyema.**[6,9] The effusion is characterized as an empyema by the presence of frank pus in the pleural space,

Box 32-4 Causative Organisms in Parapneumonic Pleural Effusions

Aerobic Bacteria
- *Streptococcus pneumoniae*
- *Staphylococcus aureus* (both methicillin sensitive and resistant)
- *Haemophilus influenzae*
- *Streptococcus pyogenes*
- Group A, β-hemolytic streptococci

Anaerobic Bacteria
- *Bacteroides* species
- *Peptostreptococcus* species
- *Peptococcus* species
- *Fusobacterium* species

Tuberculosis
- *Mycobacterium tuberculosis*

Viruses/Mycoplasma
- Adenoviruses
- Parainfluenza viruses
- *Mycoplasma pneumoniae*

Fungi/Fungal Organisms
- *Coccidioides immitis*
- *Actinomyces* species
- *Nocardia* species

Parasites
- *Paragonimus* species
- *Cysticercus* species
- *Entamoeba histolytica*
- *Echinococcus multilocularis*

by a positive culture of the pleural fluid, by a positive Gram stain of the pleural fluid, or by a pleural fluid white blood cell count greater than 15,000 cells/mm^3. *Streptococcus pneumoniae* is the most common organism causing parapneumonic effusion and empyema in children. [9,10]

In adult patients the presence of an empyema suggests that a chest tube should be placed to prevent subsequent fibrous entrapment of the lung.[6] In children, lung entrapment seldom occurs after empyema. It is becoming less common for physicians to perform repeated thoracenteses or to wait for the antibiotic therapy alone (without chest tube drainage) to resolve both the pneumonia and the empyema (see Surgery in the Pleural Space later in this chapter).[9-11] In addition to chest tube drainage, prolonged antibiotic therapy is often administered (e.g., 4 to 6 weeks).[9-11] The availability of long-term indwelling intravenous catheters allows transition of intravenous therapy from hospital to home. The duration of combined intravenous and oral antibiotics necessary for successful resolution of an empyema is not well defined. Eventual healing of the pneumonia and pleural space with normal lung function, a normal chest radiograph, and good exercise tolerance is the usual outcome for children, although the chest radiograph may not return to normal for several months.[9-12] In addition to chest tube drainage alone, insertion of fibrinolytic agents (e.g., urokinase, tissue plasminogen activator, dornase alpha) into the pleural space to enhance drainage and perhaps hasten healing has been tried.[13] Studies in adults do not show a consistent benefit,[15] but there are no large controlled studies in children. In small series of pediatric patients for whom intrapleural fibrinolytic therapy has been tried, it has been achieved safely.[14,15] Because of the wide variation in success with different management strategies, management should be individualized.[9,13,14]

Although less common, other causes of exudative pleural effusion besides infection should be considered; malignancy, acute chest syndrome from sickle cell disease, and postsurgical effusions can also create exudative effusions. [2,3]

Additional studies besides total protein and lactate dehydrogenase levels may help identify the cause of the effusion. Cell counts and special stains may be helpful. Malignant cells are found in 60% to 90% of effusions caused by malignancy. [2,3,6] The respiratory care practitioner may be asked to determine the pleural fluid pH, using a blood gas machine. The specimen must be collected anaerobically in a heparinized syringe and kept on ice until it is analyzed. A pH less than 7.0 or less than 0.15 pH unit below the arterial pH in a patient with parapneumonic effusion may indicate that the patient is at risk for prolonged effusion and subsequent lung entrapment. This has not been extensively studied in children.[2,3,6]

PNEUMOTHORAX

Air in the pleural space is called a *pneumothorax*.[16-19] It is termed a *tension pneumothorax* if the volume of intrapleural air increases with each breath, subsequently pushing the heart and mediastinal structures into the opposite hemithorax. This is generally a life-threatening situation unless the tension is relieved. A patient with a tension pneumothorax will subsequently go into shock from decreased venous return to the heart and from compromised cardiac output caused by the shift of the mediastinum.[2,16] Sometimes the pleural air is not under tension and causes only minimal or moderate respiratory distress. A small percentage of patients with a pneumothorax are asymptomatic or have only mild and vague symptoms; however, it is much more common for chest pain and shortness of breath to accompany the pneumothorax.[16] On examination, breath sounds will have decreased intensity on the affected side, and the percussion note will be hyperresonant. With a mediastinal shift, the location of the heart's point of maximal impulse may change, and the patient is usually cyanotic with severe respiratory distress. Air under the skin is called *subcutaneous emphysema*, which usually indicates a pneumothorax or pneumomediastinum.[16,17]

A pneumothorax has a characteristic radiographic appearance (Figures 32-4 and 32-5). Lung markings are lost toward the peripheral chest wall, with evidence of a collapse of the underlying lung. In diseases in which the lung is stiff from underlying disease, such as respiratory distress syndrome of the newborn or cystic fibrosis, the lung may stay partly expanded (see Figures 32-4 and 32-5). A pneumothorax is considered *spontaneous* if no trauma or procedural intervention preceded its occurrence. A primary spontaneous pneumothorax occurs in patients without known underlying lung

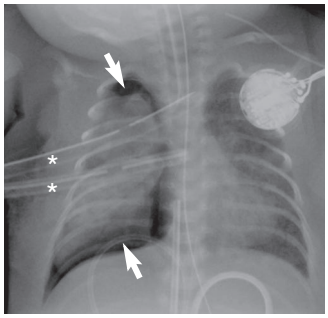


FIGURE 32-4 Chest radiograph from an extremely premature infant who has a right-sided pneumothorax *(arrows)* that persists despite two chest tubes *(asterisks).* The lung stays partially expanded because it has poor compliance (i.e., it is too stiff to collapse completely). The outline of the visceral pleura and lung is clearly visible because of air in the pleural space. An endotracheal tube and umbilical venous catheter are also present.

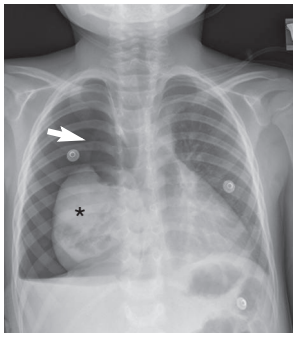


FIGURE 32-5 Chest radiograph of a 5-year-old boy with a right-sided pneumothorax caused by necrotizing pneumonia. There is a large volume of free air in the right pleural space *(arrow)*, and the right lung is deflated and collapsed *(asterisk)*. The right hemidiaphragm is flattened, and the pneumothorax can be seen extending into the left chest. A chest tube has not yet been inserted.

disease, and a secondary spontaneous pneumothorax occurs in patients with known lung disease (such as cystic fibrosis).[16-18] The common causes of pneumothorax in neonates and children are listed in Boxes 32-5 and 32-6. Other air leaks that may be associated with pneumothorax are listed in Box 32-7.

Treatment of the pneumothorax depends on whether it is under tension.[16-18] Tension pneumothorax is an emergency and should be relieved as soon as possible. The pleural space is drained by thoracentesis with a large-bore needle while awaiting more definitive therapy (see the next section). Some small pneumothoraces in patients with chronic lung disease (e.g., cystic fibrosis) might only be observed if there is no clinical deterioration. If the patient is stable, noninvasive therapy with 100% oxygen by nonrebreathing mask may be given a brief trial before a more definitive therapy is considered. This therapy is not well studied in children or adults. In rare cases it may be appropriate to withdraw the air by thoracentesis, similar to removing pleural fluid but without resorting to thoracostomy tube drainage.[18]

Box 32-5 Causes of Pneumothorax in Neonates

- Respiratory distress syndrome (hyaline membrane disease)
- Meconium aspiration
- Barotrauma
- Spontaneous onset
- First breath
- Congenital anomaly (congenital pulmonary airway malformation)
- Congenital diaphragmatic hernia
- Pulmonary hypoplasia
- Congenital lobar overdistention or emphysema
- Iatrogenic

Box 32-6 Causes of Pneumothorax in Children

- Chronic obstructive lung disease
- Cystic fibrosis
- Bronchopulmonary dysplasia
- Asthma
- Trauma
- Surgery
- Foreign body with ball-valve effect
- Tumor
- Infection
- Pneumatocele
- Barotrauma
- Spontaneous onset
- Congenital anomaly
- Bronchogenic cyst
- Iatrogenic

Box 32-7 Conditions Associated with Air Leakage in Pneumothorax

- Interstitial emphysema
- Pneumomediastinum
- Pneumopericardium
- Pneumoperitoneum
- Subcutaneous emphysema

THORACOSTOMY DRAINAGE

Tube thoracostomy drainage, or chest tube drainage, is the placement of a tube in the pleural space to drain air or fluid, or both, out of the pleural space. **Chest tubes** are routinely placed after many thoracic surgeries to ensure appropriate drainage of air, fluid, or blood.[20,21] A chest tube is usually placed to drain an empyema in adults, and they are often placed to drain empyemas in children as well.[10] The decision to place a chest tube for drainage of a pleural effusion is based on the patient's clinical status. Tension pneumothoraces almost always require chest tube drainage.

Insertion of a chest tube outside the operating room is generally done in an intensive care unit or in a specialized treatment area because of the seriousness of the underlying illness and the risk of complication. Sedation or anesthesia is usually needed, so a person skilled in providing these services (such as an anesthesiologist) is usually present during the procedure. The complications of chest tube insertion are similar to those of thoracentesis and may occur more commonly in small premature infants.[2] Some patients require more than one chest tube per side, especially if the pleural fluid is very viscous or loculated or if a pneumothorax persists.[22]

Once the chest tube is in the appropriate intrapleural location, the end is connected to commercially available devices that provide both a water seal and a collection chamber, the basic principles of which are demonstrated in Figure 32-6. Continuous negative pressure (suction) is provided via a port for wall suction to help evacuate pleural contents. The level of

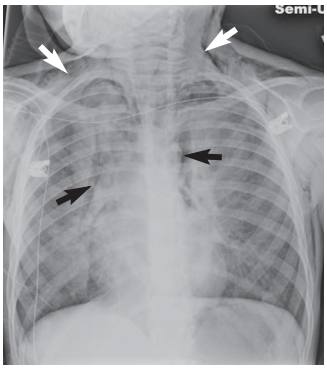


FIGURE 32-6 Chest radiograph of an 8-year-old asthmatic taken during an acute exacerbation. There is extensive mediastinal air evident around his heart and tracking upward into his neck and supraclavicular soft tissues *(arrows)*.

water in the suction control chamber determines the amount of negative pressure applied to the pleural space. Bubbling in the water seal chamber indicates ongoing air leaks, which are usually from the pleural space but can be from loose connections.[20,21] Modern pleural collection systems contain all three components in a single system that may not have liquid in the "suction control chamber" or in the "water seal chamber" (dry system). Students interested in learning more about chest tubes and drainage systems can view one of many animated discussions found on youtube.com (search Chest Tubes).

Respiratory care practitioners should be familiar with the features of the chest tube collection equipment commonly used in his or her institution to help monitor ongoing air leak and to ensure patient safety. While caring for the patient, the practitioner must not disrupt the chest tube and its attachments. A change in the patient's clinical status during evaluation by the respiratory care practitioner may indicate either a new problem with the lung or a malfunction of the chest tube system, which demands immediate evaluation. The practitioner should also anticipate patient discomfort at the site of the chest tube while manipulating the patient or surrounding equipment during chest physical therapy or ventilator tubing changes.[21]

Bronchopleural fistula presents a difficult management problem. When the integrity of the lung is not reestablished after an air leak or injury, a large portion of the volume of inspired gases may pass directly through the air leak, thus bypassing the gas-exchanging units of the lung. This can cause hypoventilation in the affected lung and a very large air leak through the chest tube. The bronchopleural fistula may be so severe that hypoventilation occurs despite increasing mechanical ventilatory support and the presence of several chest tubes.[22] Spontaneous healing of a bronchopleural fistula may take several days or even weeks. Surgical intervention may be required to oversew the air leak. In the interim, every attempt is made to reexpand the affected lung and minimize the interference with ventilation. In extreme cases, independent lung ventilation may be required or special valves inserted between the chest tube and wall suction to occlude the chest tube drainage intermittently during the inspiratory cycle of the mechanical ventilator.[22] Autologous blood patch pleurodesis and special glues and patches have been used to seal bronchopleural fistulas. [22,23]

PNEUMOMEDIASTINUM

When air leaks into the mediastinum rather than the pleural space it is called a pneumomediastinum[17,24] (Figure 32-7). The patient usually experiences chest, back, or neck pain and, if the pneumomediastinum is large, shortness of breath. The most common finding on examination is subcutaneous emphysema (crepitus). Pneumomediastinum is caused by a high-pressure Valsalva maneuver such as occurs during violent coughing or lifting heavy objects. They occur most commonly in patients with underlying asthma. Other causes of air in the mediastinum include esophageal injury or infection in the mediastinum.[17,24] The chest radiograph (see Figure 32-7) demonstrates air in the mediastinum, which often tracks upward into the neck. Intervention is seldom needed, but treatment of any underlying predisposing condition (such as asthma) should be offered.

SURGERY IN THE PLEURAL SPACE

The indications for surgery in the pleural space in pediatric patients with empyema are less well established than in adults.[25,26] Basic infectious disease tenets state that pus in a closed space should be drained. This is the basis for recommending closed-tube thoracostomy drainage (e.g., chest tube) for an empyema. Failure to drain an empyema increases the risk of developing a trapped lung, which subsequently may require pleural decortication.[25] In children, treatment with appropriate antibiotic therapy decreases the need for subsequent decortication.[9,10,12] Surgical decortication may reduce hospital length of stay in children with slow response to broad-spectrum intravenous antibiotics. [25] The use of intrapleural fibrinolytics with complex septated effusions is being used more commonly in an effort to avoid a surgical intervention. [12,13]

No clear consensus exists on the most appropriate management of the difficult problem of surgery in the pleural space, so each patient should receive the benefit of an individualized multidisciplinary therapeutic plan with flexibility to change depending on therapeutic success or failure.[9]

If a chest tube placed to drain an empyema stops functioning, often the empyema fluid is loculated in the pleural space or the chest tube is not in the ideal location. Repositioning the chest tube or adding another may allow better drainage. Injecting fibrinolytics (urokinase, dornase alpha, or tissue plasminogen activator)

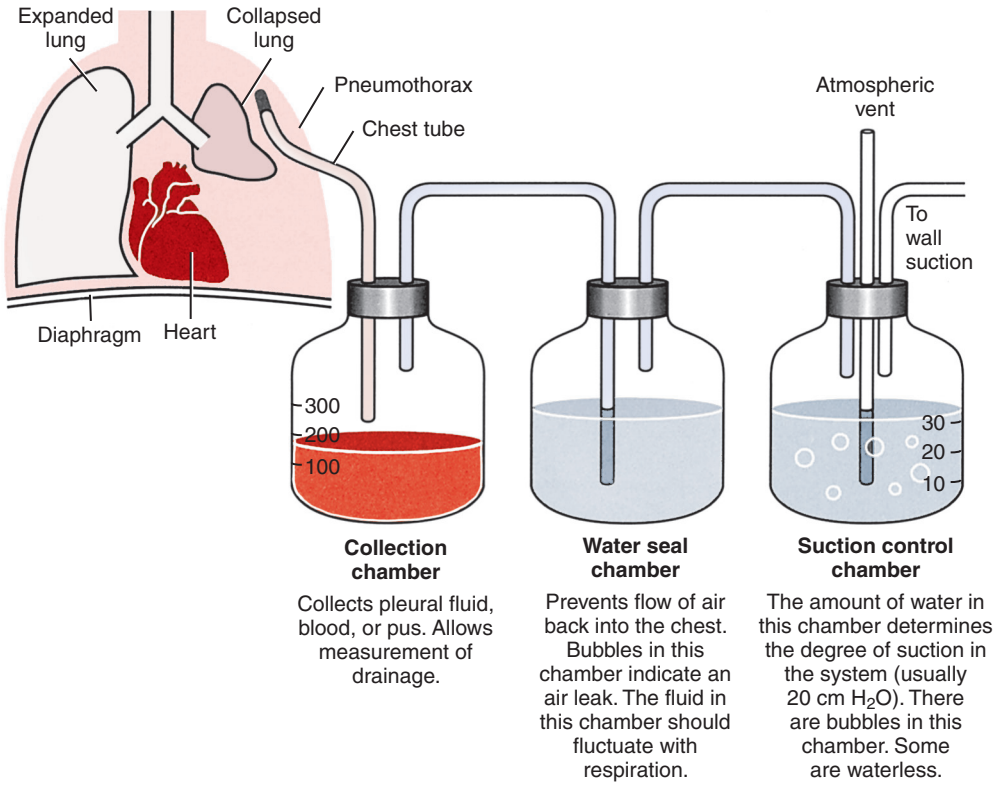


FIGURE 32-7 Example of the three-bottle system for thoracostomy drainage. Most current systems include all three components in a single plastic container rather than three separate bottles. Not all systems include the three components, and occasionally two components are combined (collection chamber and water seal chamber).

into the pleural cavity may facilitate drainage by liquefying the organizing empyema and dissolving the fibrin septations that are causing loculation of fluid.

Thoracoscopy is the direct visualization of the pleural space through either rigid or flexible surgical equipment.[26] This technique has had increasing indications for a variety of pediatric pulmonary problems since the initial use nearly 45 years ago.[25] Video-assisted thorascopic surgery technology is now commonly used for the following[25,26]:

- Biopsy in patients with diffuse lung disease
- Evaluation and biopsy of mediastinal masses
- Diagnosis and management of pleural disease
- Treatment of spontaneous pneumothorax
- Intrathoracic resections
- Evacuation of empyema fluid

In larger children, some surgical interventions are possible through the thoracoscope.[25] The major advantage of this approach is the avoidance of a **thoracotomy,** resulting in less postoperative pain and a shorter recovery period. Because the surgeon inserts a video camera into the pleural space to allow visualization of the surgical field, the procedure is called **video-assisted thoracoscopic surgery (VATS).**

Current size limitations of the equipment may limit the usefulness of thoracoscopy in premature infants and neonates, and some have recommended that it not be used in children younger than 6 months of age or in those who weigh less than 8 kg.[25] General anesthesia is required, and unilateral lung ventilation must be used. This may be accomplished by using a double-lumen endotracheal tube in larger patients (adolescents) or by performing mainstem intubation or bronchial blocking with a balloon catheter in a smaller child.[25] However, some children younger than 4 years of age cannot tolerate unilateral ventilation and become hypoxic because of their relatively limited respiratory reserve. Pneumothorax, infection, and bleeding are the most often reported complications, although complications often depend on the patient's preoperative condition.[25]

Surgical intervention is seldom needed for persistent pneumothorax or bronchopleural fistula in children. Borrowing from the experience with malignant pleural effusions, chemical pleurodesis has been attempted in children who have persistent pneumothorax or recurrent pneumothorax related to cystic fibrosis.[26,27] This procedure uses agents such as tetracycline or talc to produce a pleural abrasion that results in the adhesion of pleural surfaces. There has been no clear consensus as to whether surgical intervention or chemical pleurodesis is the most appropriate approach to this problem, and both may be performed in some patients.[26,27] An individualized patient management plan should be offered, with flexibility to consider alternative options if the initial plan is unsuccessful. The use of chemical or surgical pleurodesis may complicate or prohibit consideration of subsequent lung transplantation.

The respiratory therapist should be aware of the variety of pleural space diseases that might compromise the patient's respiratory function. Familiarity with these diseases will help the practitioner understand the reason for the patient's deterioration or improvement and will contribute to the health care team's management of these problems.

Case Study

A premature infant born at 24 weeks of gestation suffers immediate respiratory distress in the delivery room. She is intubated and given endotracheal surfactant replacement immediately. Despite the surfactant therapy and mechanical ventilation, she continues to have respiratory distress. Her chest radiograph demonstrates air in the right pleural space that persisted despite placement of two chest tubes (see Figure 32-4). The persisting air leak into the pleural space is likely from either tracheal trauma from intubation or pleural disruption from chest tube insertion in addition to hyaline membrane disease (respiratory distress syndrome) and mechanical ventilation.

Because her air leak has persisted despite chest tube placement, the next most appropriate intervention is:

A. Rigid bronchoscopy
B. Alteplase instilled in the pleural space
C. Pneumonectomy
D. Chest tube replacement

See Evolve Resources for answers.

Case Study

A 7-year-old girl complains of cough, right-sided chest pain, and fever. She has previously been well. Examination by her pediatrician reveals inspiratory crackles over the right lower lobe, so amoxicillin is prescribed for presumed bacterial pneumonia. Two days later her fever has persisted and she is increasingly short of breath. A chest radiograph (see Figure 32-1) demonstrates a right lower lobe infiltrate with right-sided pleural effusion. The right-side-down lateral decubitus radiograph (see Figure 32-2) confirms the effusion. Video-assisted thoracoscopic surgery (VATS) is performed to sample the pleural effusion and place a chest tube for drainage. Analysis of the pleural fluid reveals a white blood cell count of 22,000 cells/mm^3 with 96% segmented neutrophils. The total protein is 5.4 mg/dL, and the lactate dehydrogenase (LDH) is 425 IU. Although the Gram stain and culture of the fluid is negative, a blood culture is positive for *Streptococcus pneumoniae.* In addition to chest tube drainage she is treated with intravenous ampicillin. After 3 days the chest tube is removed and she completes a 10-day course of intravenous ampicillin followed by 7 days of oral amoxicillin. She makes a full recovery and her chest radiograph returns to normal.

The most appropriate label for this patient's pleural fluid is:

A. Empyema
B. Chylothorax
C. Hemithorax
D. Transudative effusion

See Evolve Resources for answers.

Key Points

- The pleural space is normally only a potential space that has a small amount of fluid and no air. The pleura facilitates movement between the lung and chest wall during respiration.
- When air accumulates in the pleural space (a pneumothorax), it usually requires drainage.
- When fluid accumulates in the pleural space (a pleural effusion), the cause of the fluid accumulation should be sought.
- Treatment of air or fluid in the pleural space often requires drainage by a chest tube, especially if the fluid is an empyema.
- If surgery is required in the pleural space, it is often achieved by VATS.

Assessment Questions

See Evolve Resources for answers.

1. Which of the following statements regarding the pleural space in a normal child is *true?*
   A. There is usually no fluid in the pleural space.
   B. There is normally a small amount of free air in the pleural space that can be seen only on a decubitus chest radiograph.
   C. There is a small amount of fluid in the pleural space that represents a balance of the fluid flux between the parietal and visceral pleura.
   D. The parietal pleura is thick and leathery to prevent penetration by sharp objects.
2. What is the most common cause of pneumothorax in a small premature infant with respiratory distress syndrome (hyaline membrane disease)?
   A. Neonatal pneumonia
   B. Barotrauma from mechanical ventilation
   C. Complication from subclavian intravenous line placement
   D. Meconium aspiration
3. The lung disease that is most commonly associated with spontaneous pneumothorax in adolescents is:
   A. Langerhans cell histiocytosis (eosinophilic granuloma)
   B. Pulmonary alveolar proteinosis
   C. Congenital tracheoesophageal fistula
   D. Cystic fibrosis
4. Which of the following pleural fluid measurements indicates the fluid is an exudate rather than a transudate?
   A. Total protein of 5.0 g/dL
   B. Lactate dehydrogenase (LDH) of 120 IU/L
   C. White blood cell count (WBC) of 860 cells/mm^3
   D. pH 7.30

5. When assessing the function of a chest tube draining air from the pleural space of a pediatric patient, which of the following suggests an ongoing intrapleural air leak?
   A. Bubbling in the water seal chamber
   B. Fluid in the collection chamber
   C. Fluctuating fluid in the chest tube
   D. Bubbling in the suction control chamber
6. Which of the following organisms most commonly causes empyema in toddlers and school age children?
   A. *Mycobacterium tuberculosis*
   B. Adenovirus
   C. *Streptococcus pneumoniae*
   D. *Aspergillus fumigatus*
7. Which of the following characteristics determines that the pleural fluid is an empyema?
   A. Appearance of thin, amber-colored fluid
   B. WBC count greater than 15,000 cells/mm^3
   C. pH equal to 7.32
   D. Lactic dehydrogenase of 150 U/dL
8. Which of the following statements about video-assisted thoracoscopic surgery (VATS) in the management of empyema is *true?*
   A. VATS often hastens the resolution of empyema compared with chest tube drainage alone.
   B. VATS requires the same skill level and equipment as standard chest tube insertion.
   C. VATS has been shown to be superior to the instillation of fibrinolytic agents (e.g., urokinase, streptokinase, or tissue plasminogen activator) in the management of pediatric empyema.
   D. VATS should be performed early in the evaluation and management of pleural effusion regardless of whether the fluid is a transudate, an exudate, or an empyema.
9. Which congenital anomaly is commonly associated with a pneumothorax in a neonate?
   A. Congenital diaphragmatic hernia
   B. Pulmonary sequestration
   C. Unilateral absence of the pulmonary artery
   D. Esophageal atresia

REFERENCES

1. Pleura, lungs, trachea and bronchi. In: Standring S, Borley NR, Collins P, et al, eds. *Gray's Anatomy: The Anatomical Basis of Clinical Practice*. Spain: Churchill Livingstone Elsevier; 2008:989-991.
2. Montgomery M. Air and liquid in the pleural space. In: Wilmott RW, Chernick V, Boat TF, Deterding RR, Bush A, Ratjen F, eds. *Kendig and Chernick's Disorders of the Respiratory Tract in Children*. 8th ed. Philadelphia: Elsevier; 2012:976-994.
3. Sharma GD. Pleural effusion (nonbacterial). In: Light ML, Blaisdell CJ, Homnick DN, Schechter MS, Wienberger MM, eds. *Pediatric Pulmonology*. 1st ed. Elk Grove Village, IL: American Academy of Pediatrics; 2011:559-570.
4. Tutor JD. Chylothorax in infants and children. *Pediatrics*. 2014;133:722-733.
5. Calder A, Owens CM. Imaging of parapneumonic pleural effusions and empyema in children. *Pediatr Radiol*. 2009;39:527.
6. Light RW. Clinical practice. Pleural effusion. *N Engl J Med*. 2002;346:1971.
7. Walker W, Wheeler R, Legg J. Update on the causes, investigation and management of empyema in childhood. *Arch Dis Child*. 2011;96:482.
8. Kira S. Reexpansion pulmonary edema: review of pediatric cases. *Paediatr Anaesth*. 2014;24(3):249-256.
9. Hendaus MA, Janahi IA. Parapneumonic effusion in children: an up-to-date review. *Clin Pediatr (Phila)*. 2016;55(1):10-18.
10. Krenke K, Urbankowska E, Urbankowski T, Lange J, Kulus M. Clinical characteristics of 323 children with parapneumonic pleural effusion and pleural empyema due to community acquired pneumonia. *J Infect Chemother*. 2016;22:292-297.
11. Carter E, Waldhausen J, Zhang W, Hoffman L, Redding G. Management of children with empyema: pleural drainage is not always necessary. *Pediatr Pulmonol*. 2010;45:475.
12. Kontouli K, Hatziagorou E, Kyrvasilis F, Roilides E, Emporiadou M, Tsanakas J. Long-term outcome of parapneumonic effusions in children: lung function and exercise tolerance. *Pediatr Pulmonol*. 2015;50:615-620.
13. Marhuenda C, Barceló C, Fuentes I, et al. Urokinase versus VATS for treatment of empyema: a randomized multicenter clinical trial. *Pediatrics*. 2014;134:e1301-e1307.
14. Sonnappa S, Cohen G, Owens CM, et al. Comparison of urokinase and video-assisted thoracoscopic surgery for treatment of childhood empyema. *Am J Respir Crit Care Med*. 2006; 174:221.
15. Rahman NM, Maskell NA, West A, et al. Intrapleural use of tissue plasminogen activator and DNase in pleural infection. *N Engl J Med*. 2011;365:518.
16. Tauber D. Pneumothorax and pneumomediastinum. In: Light ML, Blaisdell CJ, Homnick DN, Schechter MS, Wienberger MM, eds. *Pediatric Pulmonology*. Elk Grove Village, IL: American Academy of Pediatrics; 2011:571-581.
17. Johnson NN, Toledo A, Endom EE. Pneumothorax, pneumomediastinum, and pulmonary embolism. *Pediatr Clin North Am*. 2010;57:1357.
18. Sahn SA, Heffner JE. Spontaneous pneumothorax. *N Engl J Med*. 2000;342:868.
19. Robinson PD, Cooper P, Ranganathan SC. Evidence-based management of paediatric primary spontaneous pneumothorax. *Paediat Respir Rev*. 2009;10:110.
20. Miller KS, Sahn SA. Chest tubes: indications, technique, management, and complications. *Chest*. 1987;91:258.
21. Durai R, Hoque H, Davies TW. Managing a chest tube and drainage system. *AORN J*. 2010;91:275.
22. Baumann MH, Sahn SA. Medical management and therapy of bronchopleural fistulas in mechanically ventilated patients. *Chest*. 1990;97:721.
23. Lillegard JB, Kennedy RD, Ishitani MB, Zarroug AE, Feltis B. Autologous blood patch for persistent air leak in children. *J Pediatr Surg*. 2013;48(9):1862-1866.
24. Caceres M, Ali SZ, Braud R, Weiman D, Garrett Jr HE. Spontaneous pneumomediastinum: a comparative study and review of the literature. *Ann Thorac Surg*. 2008;86:962.
25. Kokoska ER, Chen MK, New Technology Committee. Position paper on video-assisted thoracoscopic surgery as treatment of pediatric empyema. *J Pediatr Surg*. 2009;44:289.
26. Karpelowsky J. Paediatric thorascopic surgery. *Paediatr Respir Rev*. 2012;13:244.
27. Rolla M, D'Andrilli A, Rendina EA, Diso D, Venuta F. Cystic fibrosis and the thoracic surgeon. *Eur J Cardiothorac Surg*. 2011;39:716.
28. Erlichman I, Breuer O, Shoseyov D, Cohen-Cymberknoh M, et al. Complicated community acquired pneumonia in childhood: different types, clinical course and outcome. *Pediatr Pulmonol*. 2017;52(2):247-254.

33 Neurologic and Neuromuscular Disorders

Brian K. Walsh

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. Discuss the components of the central and peripheral nervous systems controlling normal respiration.
2. Explain how the nervous system interacts with the muscles of respiration during normal and pathologic breathing.
3. Identify which muscle groups are enervated by the brainstem and how bulbar weakness interferes with protecting the airway and clearing secretions.
4. Identify the most common central nervous system conditions affecting respiratory pattern and neuromuscular impairment.
5. Identify the most common peripheral nervous system conditions causing neuromuscular and respiratory impairment.
6. Describe important features of the respiratory physical examination for children with neuromuscular weakness.
7. Describe tests available to quantify respiratory compromise for children with neuromuscular weakness.
8. Describe the respiratory aids available to support respiration for children with neuromuscular weakness.
9. Explain the indications and proper use of respiratory aids for children with neuromuscular weakness.
10. Identify the multisystem and nonrespiratory complications related to neuromuscular disease.

Key Terms

bulbar muscles
disorders of the motor nerves
disorders of the neuromuscular junction
diurnal ventilation
myopathies
neuromuscular control of respiration
neuromuscular disease
poliomyelitis
respiratory control
spinal muscular atrophy

Although there are many congenital and acquired neuromuscular conditions presenting in childhood, the uniting feature of all these disorders is their effect on the respiratory system. The primary cause of morbidity and mortality for children with neuromuscular disease is respiratory compromise. As such, health care providers should have a comprehensive understanding of the physiology of normal breathing, its derangements in neuromuscular disorders, the evaluation of patients with weakness, and specific aspects of their care.

NEUROMUSCULAR CONTROL OF RESPIRATION

Advances over the previous century provided detailed understanding of the control of respiration and the various components involved in breathing, but there remain significant gaps in our comprehension of the overall system. The presence of a "neuromuscular respiratory system" was first recognized by the second-century anatomist and physician Galen.[1] Central and reflex control of breathing has been subsequently described by investigators, including

Hering, Breuer, and Head, with significant contributions in the early twentieth century by Haldane and Priestley on the role of carbon dioxide in chemical respiratory control.[2] This chapter focuses on the present state of understanding of the **neuromuscular control of respiration.**

CENTRAL NERVOUS SYSTEM

The respiratory system brings oxygen into the body to fuel energy production and removes carbon dioxide, a metabolic waste product. Central nervous system (CNS) control occurs in the cerebral cortex, which supports voluntary breathing actions, and incorporates input from the brainstem, which is involved with automatic breathing actions. CNS signals are transmitted to the anterior horn cells of the spinal cord and then to the motor neurons supplying the respiratory muscles. Separate pathways in the spinal cord support both voluntary (corticospinal) and involuntary (reticulospinal) ventilation and transmit signals through descending pathways to motor neurons in the cervicothoracic portion of the spinal cord. These motor neurons transmit signals through peripheral nerves and across the neuromuscular junction to the muscles of respiration. Dysfunction in any part of this control system, from brainstem to respiratory muscles, can result in respiratory failure.

PERIPHERAL NERVOUS SYSTEM

Each lower motor neuron arises from the cell body in the spinal cord (anterior horn cell) to supply the respiratory muscles. The efferent nerves extend to the diaphragm and intercostal muscles and to the accessory muscles of the neck. The diaphragm is supplied by the phrenic nerve, the intercostal muscles by the intercostal nerves, the accessory muscles of the neck from the cervical plexus, and the abdominal muscles from the lumbar nerve roots.

The nerves divide into branches when reaching the muscle fiber and apply themselves to the muscle membrane at the motor endplates. At these junctions, the chemical transmitter acetylcholine is released to depolarize the muscle membrane and causes intracellular calcium release, which in turn serves to initiate contraction of the muscle fiber.

RESPIRATORY MUSCLES

The muscles of respiration are divided into three groups: inspiratory muscles, expiratory muscles, and accessory muscles. Although not formally classified as accessory muscles of respiration, the muscles of the upper airway are also important in maintaining airway patency and may lose function with certain neuromuscular disorders.

The main inspiratory muscle is the diaphragm, which contributes almost three quarters of the inspiratory capacity. Cervical nerves III to V contribute to form the phrenic nerve, which drives the diaphragm. Additional inspiratory force is provided by the external intercostal muscles, which contract to expand the rib cage during inspiration. The innervation of the intercostal muscles is via the intercostal nerves, which come off the thoracic spinal nerve roots.

The expiratory muscles include the internal intercostals, which help to reduce the thoracic volume, as well as the accessory abdominal muscles. These include the internal and external obliques and the transversus abdominus, which contract to displace the diaphragm into the thoracic cavity, and the rectus abdominus, which also contributes to increasing pleural pressure during exhalation.

The accessory muscles of respiration include the sternocleidomastoid, scalenes, trapezii, latissimus dorsi, and platysma and pectoralis groups. These groups are active predominantly with increased respiratory work, such as exercise, or loss of functional residual capacity, which occurs with infection or neuromuscular weakness. By contributing to rib cage expansion, these muscles support inspiration during active ventilation, although function during quiet breathing also exists.

Respiratory Control System

Respiratory control is divided into both voluntary and metabolic control systems. Voluntary control originates in the cerebral cortex and is mediated by tracts in the dorsolateral spinal cord; voluntary control regulates ventilation affected by sleep, pain, or anxiety. Metabolic control, mediated by the ventrolateral pathways, incorporates inputs from central chemoreceptors within the medulla. Peripheral receptors in the carotid and aortic bodies respond to fluctuations in arterial oxygen pressure (Pao_2), arterial carbon dioxide pressure ($Paco_2$), and pH. These various receptors operate via feedback loops that help to contribute to respiratory drive and regulate the ventilatory pattern in most normal physiologic states.

In addition, mechanical receptors in the lung and airways provide feedback to the respiratory centers and stimulate spinal reflexes that further regulate the breathing pattern. Examples of mechanical receptor control include the Hering-Breuer reflex, which prevents overinflation, coughing, bronchoconstriction, and the recruitment of accessory muscles during respiratory distress. Related mechanical receptors in the upper airway also induce coughing, glottic closure, vagal stimulation, and singultus (hiccups).

Bulbar Muscles

The **bulbar muscles** are not related to ventilation but are important in protecting the airway and secretion clearance. The bulbar muscles are enervated by the motor neurons emanating from the brainstem. This muscle group controls the epiglottis and other glottic structures, tongue, mouth, larynx, and throat. Bulbar

muscle weakness impairs swallowing, coughing, speech, and other throat and pharyngeal activities. Bulbar muscle weakness also leads to severe fixed and variable extrathoracic upper airway obstruction on forced inspiratory and expiratory respiratory efforts. Examples of forced respiratory efforts include coughing, sneezing, respiratory distress, and pulmonary function testing.

NEUROMUSCULAR DISEASES AFFECTING THE RESPIRATORY SYSTEM

Neuromuscular disease is a broad term that encompasses many diseases that affect muscle function either directly, via muscle pathology, or indirectly, via nerve pathology. The diseases themselves are associated with a diverse range of muscle impairment from increased muscle tone with rigidity and spasticity to muscle weakness and flaccidity. This chapter covers primarily those affecting infants and children with muscle weakness or paralysis, because these conditions affect the respiratory system by impairing ventilation and airway clearance. Children with progressive neuromuscular weakness undergo a typical progression of respiratory insufficiency or failure. Figure 33-1 represents the typical evolution, relationships, and proposed therapies.

CENTRAL NERVOUS SYSTEM

Conditions in the CNS that affect respiration include either those that affect the brainstem respiratory centers or the pathways connecting these centers to the motor neurons in the spinal cord.

Disorders of the Brain

One of the best examples of a CNS disorder that affects breathing is congenital central hypoventilation syndrome (CCHS). Also known as "Ondine's curse," this represents a condition of hypoventilation associated with sleep. The name refers to the mythical character Ondine, who after professing his love "with every waking breath" was cursed by the water nymph he betrayed to stop breathing on falling asleep. Although almost all cases of CCHS are congenital, affecting approximately 1 in 200,000 live births, it can also be acquired through spinal cord or other CNS injury. CCHS, manifested by nocturnal hypoventilation and respiratory arrest, is diagnosed by polysomnography and treated with lifetime nocturnal mechanical ventilation or phrenic nerve pacing.

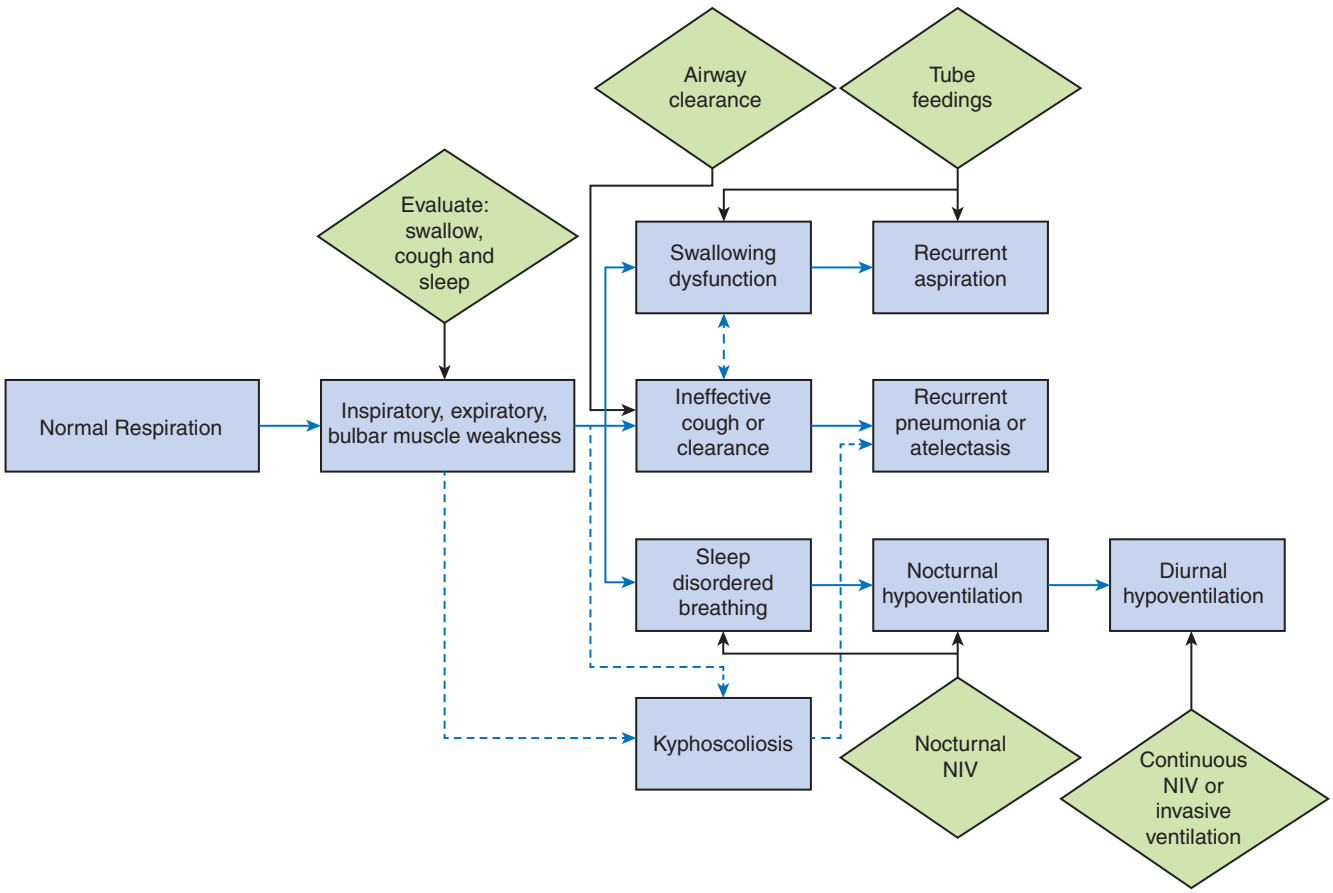


FIGURE 33-1 Typical evaluation of neuromuscular disease *(gray boxes)* and assessments and interventions *(green diamonds)*. *Solid lines* represent known progression, and *dotted lines* represent associations or complicating factors.

Case Study

You are called to evaluate an otherwise healthy full-term neonate in the newborn nursery who appears to turn blue when sleeping. What steps would you take in evaluating this patient for a neuromuscular disease?

See Evolve Resources for answers.

Other cranial conditions affecting respiration in infants and children include congenital disorders such as hydrocephalus and anencephaly, along with genetic neurodegenerative disorders such as Tay-Sachs disease and Friedreich ataxia. Acquired CNS disorders include neoplasms, infarction, hemorrhage, and anoxic injury.[3] All these conditions are associated with multiple organ system symptomatology, resulting from diffuse neurologic injury and loss of autonomic control. Respiratory symptoms of these conditions include changes in respiratory drive or pattern, respiratory and upper airway muscle weakness with loss of airway clearance ability, and chronic aspiration.

Disorders Affecting the Spinal Cord

Trauma. Almost 11,000 Americans sustain a spinal cord injury every year, costing an approximated 9.7 billion dollars in health care expenditure.[3] The spinal cord nerve roots that control diaphragm function exit the spine at the level of the cervical vertebrae. Spinal cord injury above cervical vertebra III will require tracheostomy and mechanical ventilation or phrenic nerve pacing.[4] Spinal cord injuries between vertebrae III and V will have variable amounts of respiratory impairment, and those below the fifth vertebra almost always allow independent breathing. However, the abdominal and intercostal rib muscles involved in cough function exit the spinal cord lower in the thoracic spine. Therefore lower spine injuries may permit spontaneous respiration but have significant impact on airway clearance mechanisms.

Chiari malformations. Chiari malformations are congenital malformations characterized by a small or misshapen skull, causing the cerebellum to protrude through the bottom of the skull into the spinal canal. Under these circumstances, the brainstem, spinal cord, cranial nerves, or the cerebellum may be stretched or compressed. In addition, the flow of cerebrospinal fluid around the brain and spinal cord can be obstructed, causing hydrocephalus or a cyst to form within the spinal cord, known as *syringomyelia*.[5] Estimates indicate that between 0.5% and 1% of live births in the United States may be affected by a Chiari malformation.[5] Symptoms of Chiari malformations are variable and related to the affected areas. Many patients with Chiari malformations report no symptoms, but those who do complain of headaches, dizziness, vision changes, muscle weakness, or balance problems.[6] Younger children may present with difficulty swallowing, choking, irregular breathing patterns, or apnea. Chiari malformations can be easily diagnosed by magnetic resonance imaging and are treated by surgical decompression.

Other conditions. Less common causes of spinal cord impairment include spinal tumors, infections, and birth injury. Spinal tumors either originate locally in the CNS or are metastatic. Meningiomas are primary CNS tumors that develop from the meninges, the membrane that surrounds the brain and spinal cord. They are rare in children, with pediatric cases accounting for only 1.5% of all cases.[7] Metastatic spinal tumors are also rare in children but may be seen with invasive lymphomas and have been reported in other childhood cancers.[8] CNS infections, such as epidural abscesses, can have both local inflammatory and mass effect on the spinal cord, causing neuromuscular symptoms to develop. Finally, spinal cord injury may be a rare complication of the birthing process. In this situation, traction applied to the infant's head while assisting delivery may result in nervous system trauma. These injuries include cervical spinal cord hematomas as well as direct nerve and nerve root stretch injury.

PERIPHERAL NERVOUS SYSTEM

Disorders of the Motor Nerves

Acute paralytic **poliomyelitis** was once the most common neuronopathy in the United States.[9] However, massive immunization campaigns have been effectively instituted and all but eliminated community-acquired poliovirus infections in the United States. As a result, the spinal muscular atrophies are now the most common cause of degenerative nerve cell disease in children.

Spinal muscular atrophy. The **spinal muscular atrophies** (SMAs) include a number of different disorders that clinically manifest as muscle weakness as a result of progressive destruction of the motor neurons of the spinal cord and brainstem. The SMAs are hereditary disorders transmitted by autosomal recessive inheritance, with three recognized forms categorized by severity and age of onset. All types are caused by defects at the same site on chromosome 5, and the overlap in clinical features is considerable.[10] SMA type I, also called Werdnig-Hoffmann disease, is the acute infantile form, which usually presents within the first 6 months of life. In these children, limb weakness develops rapidly, whereas the facial muscles are slower to fail and the extraocular muscles are essentially spared. The result is a child who appears alert and responsive but cannot move. The respiratory effects of SMA type I include weakness of the bulbar, abdominal, and intercostal muscles, which makes feeding difficult and leads to aspiration and a weak, ineffective

cough. A weak cough results in recurrent pneumonias and poor airway clearance. Even relatively minor viral infections result in severe airway and ventilator compromise. Without intervention, most infants will die of respiratory insufficiency and infection before reaching 1 year of age.[10]

SMA type II, the chronic childhood form, has a later onset and often more insidious course. Some affected children may be able to sit unsupported, but usually proximal muscle weakness prevents these children from standing or walking independently and leads to scoliosis; these children eventually become wheelchair dependent.[11] The course of SMA type II is unpredictable; long intervals without progression of weakness are expected, and survival into adulthood is common. SMA type III (Kugelberg-Welander disease) is the mildest form; affected patients are able to stand and walk independently and have much slower progression of muscle weakness compared with the other two forms.

Poliomyelitis. Poliomyelitis is an infection caused by the polio virus and was one of the most dreaded childhood diseases of the twentieth century in the United States.[9] Most infected individuals are asymptomatic or experience only mild, nonspecific viral symptoms. However, in a small proportion of patients, the virus enters the CNS, where it infects and destroys motor neurons in the spinal cord, leading to muscle wasting and weakness. Most commonly, this causes a self-limited case of nonparalytic viral meningitis, but in a small proportion of patients the infection causes permanent wasting and paralysis. Depending on the site of paralysis, paralytic polio is classified as spinal, affecting the nerves of the trunk and extremities; bulbar, affecting the nerves that control breathing, speaking, and swallowing; or bulbospinal, representing a combination of these two forms. Bulbospinal polio is particularly problematic because it affects the nerves in the cervical spine region that control diaphragm function. Destruction of these nerves makes independent respiration, swallowing, and effective coughing impossible. Lifelong ventilator support and airway clearance is essential for the survival of these patients.

Guillain-Barré syndrome. Guillain-Barré syndrome (GBS), or acute inflammatory demyelinating polyradiculoneuropathy, is an acute, autoimmune process that affects the peripheral nervous system. Guillain-Barré syndrome is not hereditary, affects persons of all ages, and has an approximate population incidence that ranges from 1 to 3 per 100,000 population.[12] Although its cause is not completely understood, GBS is probably triggered by an acute infectious process, which leads to antibody-mediated destruction of the myelin sheaths that coat peripheral nerves. This demyelination leads to nerve conduction block, which causes weakness and often sensory and autonomic changes as well.[13] Guillain-Barré syndrome usually presents as an ascending weakness or paralysis that starts in the legs and spreads to the upper limbs and the face. The weakness is often preceded by sensory symptoms such as "pins and needles" and muscle tenderness, followed by a complete loss of deep tendon reflexes. Patients often experience rapid progression of symptoms; more than three quarters of patients reach a nadir in strength within 3 weeks of symptom onset. Autonomic dysfunction, characterized by arrhythmias, blood pressure lability, and gastrointestinal dysfunction, may also be present.[14] Respiratory paralysis occurs in roughly 14% to 18% of children with GBS, and approximately 20% of all patients with GBS require intensive care during the acute phase of illness. Treatment is mainly supportive, although corticosteroids, plasmapheresis, and intravenous immunoglobulin have all been used with variable success. Although plasmapheresis is considered the treatment of choice in adults, certain technical factors may limit its usefulness in children. Careful monitoring of patients' respiratory status, accompanied by intubation and mechanical ventilation when required, constitutes the mainstay of acute supportive care. If the child is well ventilated during the critical time of profound paralysis, complete recovery can be expected.[12] Most children fully recover within 6 months, and fewer than 10% have symptom recurrence.[12,13]

Disorders of the Neuromuscular Junction

Infantile botulism. Human botulism results from eating food contaminated with the organism *Clostridium botulinum* or the toxin it produces.[15] The clinical spectrum of infantile botulism ranges from asymptomatic carrier states, mild hypotonia, and failure to thrive to severe with progressive, life-threatening paralysis or sudden death. Most infants experience a prodromal syndrome of constipation and poor feeding, followed by progressive bulbar and skeletal muscle weakness and loss of tendon reflexes. Typical features on examination include diffuse hypotonia, ptosis, dysphagia, and a weak cry. Respiratory history and examination are often notable for respiratory insufficiency and apnea. Diagnosis is confirmed by the isolation of *C. botulinum* organisms from the stool. In general, botulism is a self-limited disease lasting 2 to 6 weeks, and even with the use of immunoglobulin therapy the infant requires meticulous supportive respiratory care. In severe cases, this support is lifesaving. Recovery is often complete, but relapse can occur in as many as 5% of affected infants.

Myasthenia gravis. Myasthenia gravis is an autoimmune disorder characterized by fluctuating muscle weakness and easy fatigability.[16] The pathophysiology of the disorder occurs at the neuromuscular junction,

where circulating antibodies block synaptic receptors, inhibiting the effect of neurotransmitter chemicals, most notably acetylcholine; this prevents muscle contraction. The current prevalence of myasthenia gravis in the United States is estimated to be about 20 per 100,000 population, although frequent misdiagnosis means that the true prevalence is likely higher.[17] Juvenile myasthenia describes the immune-mediated form of myasthenia gravis that occurs in late infancy through adult life. Two forms are recognized:

- *Ocular myasthenia,* in which the eye muscles are primarily or exclusively affected
- *Generalized myasthenia,* in which moderate to severe weakness occurs in bulbar, limb, trunk, and even respiratory muscles

The initial features of both the ocular and generalized forms are usually ptosis, diplopia, or both.[17] Prepubertal onset is associated with a slight male bias and ocular symptoms only, whereas postpubertal onset is associated with a strong female bias and generalized myasthenia. Patients with myasthenia gravis often have little chronic respiratory compromise and are symptomatic only during periods of myasthenia crisis, when symptoms, particularly bulbar symptoms, suddenly escalate. During a crisis, patients may have sudden paralysis of the respiratory muscles, temporarily requiring assisted ventilation. Treatment also includes using cholinesterase inhibitors to help transmission of acetylcholine and immune suppressants such as corticosteroids and cyclosporine. Exchange transfusions and intravenous immunoglobulin therapy rapidly restore function but are temporary measures.[17]

Congenital myasthenia and *familial infantile myasthenia* are terms used to describe clinical syndromes that are caused by several different genetic defects and are generally rare. Respiratory insufficiency and feeding difficulty may be present at birth or develop during infancy. Usually, ptosis and generalized weakness are present at birth. Many affected newborns require mechanical ventilation, but over a course of weeks most infants become stronger and no longer need ventilator support.

A transitory myasthenic syndrome is observed in 10% to 15% of offspring of myasthenic mothers. The syndrome is believed to be caused by the transfer of antibody from the myasthenic mother to her normal fetus. Symptoms are generally observed within hours of birth. The severity of newborn symptoms correlates with the newborn's antibody concentration and not the severity of weakness in the mother, which is generally exacerbated during pregnancy. Difficulty feeding and generalized hypotonia are the major clinical features; they are eager to feed, but suckling quickly causes fatigue. Respiratory insufficiency is uncommon, and weakness becomes progressively worse in the first few days of life and then improves. Recovery is complete, and transitory neonatal myasthenia does not develop into myasthenia later in life.

Other conditions affecting the neuromuscular junction. In the medical setting, there are a number of other causes of incomplete or failed transmission at the neuromuscular junction related to drug exposure. These medications include antibiotics, corticosteroids, antirheumatics, lidocaine, lithium, and anesthetic agents.

MYOPATHIES

Myopathies are diseases of the skeletal musculature causing muscle weakness and degeneration. Myopathies are caused by inherited genetic defects and by inflammatory, endocrine, and metabolic disorders.

Duchenne and Becker Muscular Dystrophy

The muscular dystrophies are a group of genetic disorders with multisystem symptoms involving the cardiac, respiratory, gastrointestinal, endocrine, and nervous systems. Although there are more than 100 diseases that have similarities to muscular dystrophy, the two most common muscular dystrophies that present in childhood are Duchenne and Becker muscular dystrophy. Duchenne muscular dystrophy (DMD) is the most common childhood form of muscular dystrophy, occurring in roughly 1 in 3500 live male births.[18] The male preponderance is related to its inheritance pattern: DMD is an X-linked genetic disorder, resulting in female carriers and affected males. DMD presents in early childhood with proximal muscle weakness, which manifests as difficulty in running, climbing stairs, and standing. The muscle weakness is progressive and eventually leads to profound skeletal and respiratory muscle weakness in all cases. By adolescence, all patients with DMD are wheelchair bound and require assistance with ventilation. Becker muscular dystrophy is also an X-linked inherited muscular dystrophy, with a distribution of muscle wasting and weakness similar to that of DMD. However, Becker muscular dystrophy typically has a milder course, with symptom onset in the second decade or later.

There is no cure for any of the muscular dystrophies, and current therapy is supportive. Treatment goals are to maintain function, prevent contractures, and provide psychological support for the child and family. Traditional estimates suggest that up to 90% of patients with DMD die of respiratory failure before reaching 20 years of age.[19] Muscular dystrophy affects the heart as well, and the second leading cause of death in DMD is cardiomyopathy and cardiac failure, or arrhythmia.[18] However, aggressive intervention with noninvasive ventilation, airway clearance techniques, and surgical correction of spine deformation to improve lung volumes at the onset of respiratory symptoms has been demonstrated to

significantly reduce morbidity and prolong life for patients with muscular dystrophy.[19]

Myotonic Dystrophies

Myotonic dystrophy is a highly variable inherited disease characterized by chronic, slowly progressive muscle wasting and weakness, cataracts, heart conduction defects, and endocrine disorders.[20] The muscles most commonly affected are the voluntary muscles in the face, neck, and lower arms and legs and, in more severe cases, the intercostal muscles and the diaphragm.[20] Myotonic dystrophy most commonly presents in adolescence or adulthood, but a severe congenital form exists and is associated with mental retardation, orthopedic problems, and other developmental delays. Affected infants are extremely hypotonic and may have difficulty feeding. They often require ventilatory support, at least temporarily, because of muscle weakness and decreased central ventilatory drive. Similar to the muscular dystrophies, the overwhelming majority of affected children die in infancy. However, supported ventilation, corrective surgery, and tube feeding have all extended the life span of patients and dramatically improved quality of life for these children and their families. Chapter 12 discusses airway clearance techniques related to this patient population.

Glycogen Storage Diseases

The glycogen storage diseases are a family of 12 inherited errors of metabolism that result in enzyme defects in glycogen synthesis or breakdown. In general, clinical classifications can be made on the basis of whether affected organs include the liver only, or additionally the muscles, blood cells, connective tissue, heart, brain, and kidneys. In terms of respiratory involvement, glycogen storage disease type II (also called *Pompe disease* or *acid maltase deficiency*) has the most severe symptoms. Pompe disease is a rare, autosomal recessive disorder occurring in roughly 1 in 40,000 to 100,000 live births.[21] It is caused by a deficiency in the enzyme α-1,4-glucosidase, which causes glycogen accumulation in cellular lysosomes and leads to progressive weakness in all muscles.[21] Like all the congenital disorders, the severity of symptoms of Pompe disease are related to age at onset. Infantile onset is the most severe form and is characterized by the development of marked hypotonia, hepatomegaly, and severe cardiomegaly within several months of birth. Mental development is usually normal, although most children die of respiratory or cardiac complications before 2 years of age. Late-onset Pompe disease occurs in patients with minimal—as opposed to absent—levels of the acid maltase enzyme.[21] Symptoms in these affected individuals present in adolescence or adulthood, tend to progress somewhat more slowly, and include primarily weakness of muscles in the trunk, lower limbs, and the diaphragm. A small number of adult patients live relatively normal lives without major limitations.

Electrolyte Abnormalities

Less common causes of muscle weakness in the outpatient setting include electrolyte abnormalities—most commonly caused by insufficient dietary intake. Potassium is essential for many body functions, including muscle and nerve activity. Maintenance of the electrochemical gradient of potassium between the intracellular and extracellular space is essential for normal nerve function. Mild hypokalemia is often asymptomatic; however, moderate hypokalemia may cause diffuse muscular weakness, myalgias, and arrhythmias. This is particularly important when attempting to liberate a patient from mechanical ventilation, because the respiratory muscles could be in a weakened state (atrophy vs. fatigue), and electrolyte abnormalities will only add to this impairment. Severe hypokalemia has been associated with respiratory depression from severe impairment of skeletal muscle function. Similarly, hypomagnesemia can cause weakness and muscle cramps and may contribute to impairments in respiratory muscle function. Hypomagnesemia, which can be seen in the presence of hypokalemia, hypocalcemia, and hypophosphatemia, should prompt the evaluation of other electrolyte disturbances that can further exacerbate these clinical symptoms.[22]

RESPIRATORY EVALUATION OF CHILDREN WITH NEUROMUSCULAR DISEASE

PULMONARY FUNCTION TESTING

Neuromuscular weakness affecting the respiratory system initially develops as impaired cough and airway clearance, with gradual progression to nocturnal and eventually daytime hypoventilation. Monitoring the respiratory status of a patient with neuromuscular weakness depends on the underlying disease, its rate of progression, and extent of involvement. Because most conditions involve weakness of the inspiratory and expiratory muscles, pulmonary function testing including muscle strength assessment is the main mode of testing, with polysomnography and noninvasive measures of hypoventilation as the disease progresses in severity.

The use of pulmonary function tests in diagnosing and monitoring the progression of the neuromuscular disease has been well established in adults, but pediatric testing remains a challenge. Although newer techniques in respiratory muscle strength testing are being introduced, most school-age children and adolescents are best monitored by standard spirometry with maximal inspiratory and expiratory pressure monitoring (Figure 33-1).[23] Additional testing includes assessment of cough flows, because it is the main determinant of respiratory compromise. However, because peak

cough flows have been well correlated with forced vital capacity (FVC) and forced expiratory volume at 1 second (FEV_1), these tests remain the mainstay of pulmonary function testing in this population.[24]

Standard spirometry is performed according to the standards of the American Thoracic Society (New York, NY). Measurements include FVC, FEV_1, and forced inspiratory volume displayed primarily as a flow–volume loop. Including forced inspiratory volume allows for separate evaluation of extrathoracic and upper airway obstruction in children with bulbar weakness. Measuring maximal expiratory pressure and maximal inspiratory pressure and, in some instances, static mouth pressures allows monitoring of diaphragm and other cough-related strength.[25] For patients with Duchenne muscular dystrophy, a decline in FVC has been demonstrated to be a useful predictor of worsening respiratory muscle weakness and death, so that interventions such as pulmonary clinical monitoring, secretion clearance, and ventilatory assistance devices can be recommended to be initiated at specific rates of decline. An FVC less than 20% of predicted, or 1 L, is associated with significant carbon dioxide retention and a limited survival rate past 3 years.[18] Last, static lung volume measurements in this population usually reveal restriction, which may be the result of multiple factors, including diminished chest wall compliance, reduced inspiratory muscle strength, and kyphoscoliosis if present (Figure 33-2).

Measuring carbon dioxide tension and oxygen analysis are useful adjuncts when determining whether an assisted ventilation device may be required. Noninvasive capnography and pulse oximetry are easily applied in the clinic, but arterial gas analysis should be performed if these are not available. In addition, noninvasive monitoring of cardiac output, using capnometry and a modified Fick equation, may be done to determine the cardiac function

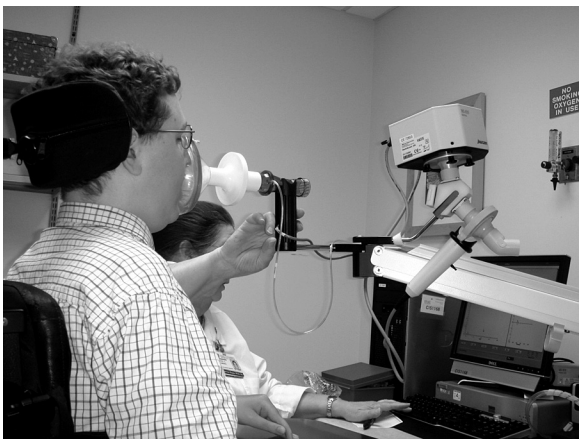


FIGURE 33-2 Spirometry. Most school-age children and adolescents are best monitored by standard spirometry with maximal inspiratory and expiratory pressure monitoring. In this image a mask has been substituted for a mouthpiece because of bulbar weakness and inability to use or create a seal around a standard mouthpiece.

Case Study

You have just completed pulmonary function testing on a 5-year-old boy who has Duchenne muscular dystrophy and appears to be following the usual disease course. Although he has difficulty running and climbing stairs, he has not progressed to need respiratory support at this time. Mom seeks your advice about when to have her son "trached" (a tracheostomy performed). What would you advise?

See Evolve Resources for answers.

of patients with cardiac involvement but should not replace echocardiography for definitive analysis. Daytime monitoring should be performed every 3 months, or more frequently with diminished mucus mobilization, decline in lung function, and reduced peak cough flows.[18] With further progression of carbon dioxide retention and muscle weakness and advancing concerns regarding nighttime hypoventilation, home overnight oximetry or polysomnography may be useful in determining the early need for assisted respiratory support.

Measurement of cough effectiveness and lung volume, combined with monitoring for hypoventilation, may provide an assessment of trends that could facilitate the timeliness of initiating airway clearance and ventilatory support. With patient and caregiver education, these studies may help patients sustain more normal daily activities and direct the care needed to minimize the complications associated with respiratory muscle weakness.

SLEEP STUDIES

Polysomnography must be performed and sleep-disordered breathing monitored in all patients with neuromuscular weakness. Nighttime sleep–disordered breathing often precedes diurnal respiratory failure in affected patients. Polysomnography is the most complete diagnostic test available to assess for the nature and severity of the sleep disturbance.[26] Sleep assessment allows for anticipatory evaluation and more timely recognition and management with assisted ventilation. Full polysomnography should include sleep stage recording, arousal documentation, and monitoring of oxygen saturation, hypoventilation, and hypercapnia.[27] Together, this testing allows for monitoring of sleep complaints and treatable conditions in an otherwise progressive disease process. See Chapter 25 for more details.

RESPIRATORY CARE OF CHILDREN WITH NEUROMUSCULAR DISEASE

GENERAL CONSIDERATIONS

The onset of pulmonary symptoms of children with neuromuscular disease largely depends on the underlying disease.[24] For example, a boy with Becker

muscular dystrophy is likely to have few respiratory symptoms until late adolescence or adulthood, whereas an infant with SMA type I will almost certainly develop symptoms in the first few months of life. In either case, however, a predictable sequence of events will occur, leading each child to experience progressive respiratory insufficiency and eventually respiratory failure. Initially, respiratory muscle weakness is manifested as a weak cough and impaired airway clearance, which leads to recurrent atelectasis and chest infections.[24] As respiratory muscle weakness progresses, patients experience nocturnal hypoventilation and symptoms related to hypercapnia. These symptoms include nightmares, frequent wakening, early morning headaches, and daytime sleepiness. At this point, most patients maintain relatively normal daytime respiration and are eucapnic while awake. However, further deterioration in respiratory muscle strength eventually leads to daytime respiratory insufficiency and daytime hypercapnia.[24] Complete respiratory failure follows shortly thereafter; the trajectory of this decline, however, is unique to each patient and disease and is usually hastened by serious illness or concomitant conditions such as scoliosis. With early and proactive institution of cough-assist devices or mechanical ventilatory support, this trajectory may be effectively slowed.

Many of the interventions used to support airway clearance and ventilation in adults have also been used to assist children; however, limitations in size and the inability of young children to cooperate with or comprehend respiratory therapies can present unique challenges. Although respiratory insufficiency or some form of cardiopulmonary disease is the most common cause of death among children with almost any congenital or acquired neuromuscular disorders, innovations in pediatric ventilatory assistance have considerably extended survival and improved quality of life for affected children.[18] Although it may be difficult to find the appropriate-sized equipment and implementation, it does exist. The industry of pediatric assisted ventilation and airway clearance is growing year by year.

AIRWAY CLEARANCE MECHANISMS

Airway clearance is achieved in a healthy individual via two mechanisms: mucociliary transport and cough clearance. The mucociliary escalator lining the bronchial tree moves a thin layer of mucus upward toward the proximal airway, where the mucus and entrapped particles are sensed and expelled via cough clearance. Normal coughing is a highly controlled reflex with defined phases. The initial phase is inspiration, when a maximal inspiration is performed to get air behind the mucus or debris that needs to be cleared. The next phase is the compressive phase, during which the glottis is closed and the abdominal muscles contract. This allows intrathoracic pressure to rise and narrows the central airways, making the velocity of the airflow higher. The last phase of coughing is expulsion, during which the glottis is opened and air is released at a high velocity, carrying with it collected mucus and debris.

Children with neuromuscular weakness may have trouble with each phase of coughing; inspiratory muscle weakness reduces vital capacity and maximal inhaled volume, bulbar muscle weakness can lead to impaired glottic closure, and expiratory muscle weakness reduces the maximal intrathoracic pressure and expulsive force.[28] The significance of this cannot be overstated: In patients with neuromuscular disease, most episodes of acute respiratory failure result from the inability to eliminate airway secretions and mucus during otherwise benign chest infections. A peak cough flow less than 160 L/minute in adults is associated with impaired secretion clearance, but early intervention at 250 to 270 L/minute is recommended for beginning cough assistance.

Facilitating Clearance of Mucus

Mucus mobilization can be facilitated by good enteral hydration, use of humidity and medications that reduce mucus viscosity, and assisted maneuvers to clear secretions from the airways. These maneuvers include manual physiotherapy, mechanical or vibratory chest percussion, and postural drainage. The goal of these therapies is to transport secretions in the peripheral airways centrally to larger airways, where assisted coughing can more easily expel them from the respiratory tract. Commercially available mucolytics commonly used for this purpose include dornase alfa, bicarbonate (HCO_3^-), and *N*-acetylcysteine (NAC). Dornase alfa (Pulmozyme) is an aerosolized enzyme that hydrolyzes the extracellular DNA in infected or colonized sputum, reducing sputum viscoelasticity. If proper airway clearance is provided and pulmonary infections avoided, dornase alfa may not be helpful. Dornase alfa is only approved by the Food and Drug Administration (FDA) for cystic fibrosis. Similarly, NAC cleaves the disulfide bonds in mucoproteins, reducing their chain lengths and thinning lung mucus. All mucus has disulfide bonds. NAC has been known to cause bronchospasm, therefore limiting its success if pretreatment with a bronchodilator is not provided. The least used mucolytic is the oldest, and that is 2% to 4% bicarbonate. HCO_3^- has been instilled into the airway of intubated patients or aerosolize to reduce viscosity of mucus. The reduction in viscosity is created by the elevation in mucus pH. These medications can be used as daily maintenance therapy or on an as-needed basis during infections. If necessary, NAC can be used up to six times a day to facilitate mucus clearance.

Chest percussion is the manual clapping performed by a caregiver to the patient's thorax, alternating from the ventral, lateral, and dorsal aspects of the chest for

periods usually lasting 10 to 20 minutes at a time. Chest vibration is similar in application, but instead of manual clapping the thorax is vibrated via a handheld device or a circumferential chest vest. A third option is intrapulmonary percussive ventilation (IPV), in which high-frequency percussive ventilation is delivered through an IPV device used either alone or in conjunction with aerosol therapy.[28] Percussion and vibration maneuvers are often repeated several times every day, depending on the quantity of mucus, its viscosity, and its adhesiveness to the airway and the patient's health status. In particular, more frequent use of percussion or vibration is an important component of therapy during respiratory tract infections, when mucus production can often overwhelm a weak child's clearance mechanisms. See Chapter 12 for more details on airway clearance or Chapter 20 for more details of inhaled medications.

Assisted Coughing

For effective coughing, sufficient strength is needed in bulbar, inspiratory, and expiratory muscles. For patients with generalized weakness, manually assisted coughing (MAC) can permit successful long-term use of noninvasive ventilatory support.[28] For effective MAC, the patient inspires maximally, augmented by either breath stacking or assisted insufflation, and an abdominal thrust or thoracic squeeze, timed to glottic opening, is applied by an assistant or caregiver.[28] For those using abdominal thrusts, a one-handed technique with counterpressure applied to the thorax with the other hand can further increase cough strength. If upper limb weakness is not involved, a patient can use either maximal insufflation or abdominal thrust in isolation and augment cough peak flow. There are some limitations to assisted cough, however; MAC requires a cooperative patient willing and able to provide adequate physical effort and a committed caregiver able to assist multiple times a day.

Mechanical in-exsufflators are cough-assist devices that attach to the patient via an oronasal interface. These work by helping to deliver deep insufflations until the lungs are fully expanded, followed by an immediate negative pressure exsufflation that helps to facilitate mucus mobilization (Figure 33-3). Settings usually range from positive 20 to 30 cm H_2O followed by a negative 20 to 30 cm H_2O. When mechanical cough-assist devices are used for secretion clearance, multiple cycles are given in one sitting, until no further secretions are induced. Some patients with severe bulbar weakness may not tolerate mechanical assistance and require manual cough assistance.

Glossopharyngeal Breathing

Glossopharyngeal breathing (GPB), sometimes called "frog breathing," can be used to provide brief periods of normal alveolar ventilation for a patient with neuromuscular weakness who spends periods off a ventilator, or during times of unexpected ventilator failure. The technique of GPB is to augment insufflation by "gulping" air in a series of breaths, closing the glottis between "gulps" to entrap air in the lungs. Using this method, one glossopharyngeal "breath" often consists of six to nine gulps of air. Although severe bulbar muscle weakness can limit the effectiveness of GPB, previous reports of its use in patients with almost no independent breathing and no vital capacity have been published. This technique has been used to facilitate independent breathing for periods ranging from minutes to all day.

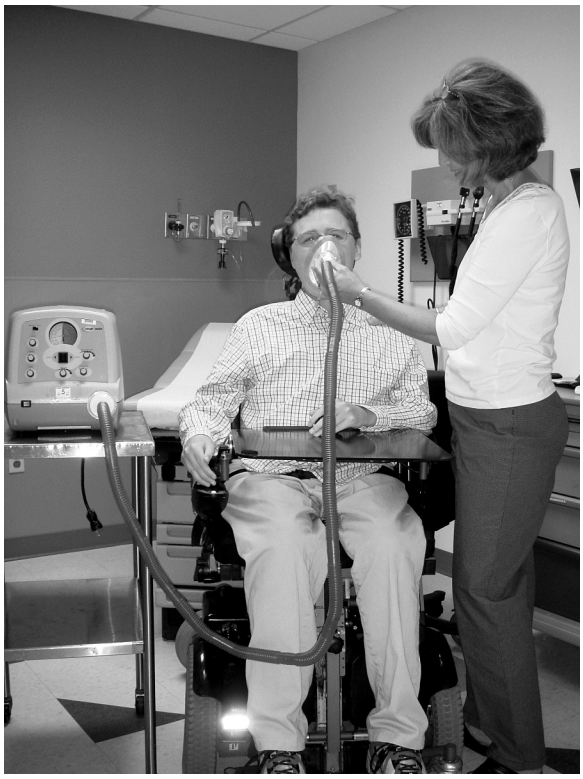


FIGURE 33-3 Mechanical cough assist. Mechanical cough-assist devices attach to the patient via an oronasal interface and deliver deep insufflations until the lungs are fully expanded, followed by an immediate negative pressure exsufflation until the lungs are fully deflated.

MECHANICAL VENTILATORY SUPPORT

Noninvasive Ventilation

In the early 1980s, noninvasive ventilation was pioneered first by Rideau and colleagues in France and subsequently by Bach and colleagues in the United States.[29] Since that time, several large studies have shown that noninvasive ventilation is not only effective and well tolerated but is a preferred method of respiratory support for patients with progressive neuromuscular disease.[29] Indeed, work has demonstrated that chronic noninvasive ventilation can extend the average life expectancy for patients with DMD by an average of 6 years and even restore normal life

expectancy for older patients with static weakness, such as long-term polio survivors.[29] Noninvasive ventilation appears to succeed because it allows fatigued respiratory muscles to rest, improves pulmonary mechanics, and restores normal ventilatory sensitivity to carbon dioxide levels.

The goals of assisted ventilation in children are to maintain pulmonary compliance and normal lung and thoracic growth and to maintain normal alveolar ventilation. (See Chapter 16 for more details on noninvasive ventilation.) Lung and thorax growth is particularly important when the onset of weakness is in infancy, as is the case with patients with SMA type I. In these cases the lungs and chest wall do not grow normally because of the inability to take deep breaths. It is important for the caregivers of these children to move their thoracic cavity with large tidal volumes (mimic a sigh) several times a day to prevent abnormal growth and reduce atelectasis. Currently there are no ventilators on the market that offer a sigh, so this will need to be manually done. As children age and hypoventilation develops, assessment of pulmonary function determines when assisted ventilation support is indicated, usually with progression from nocturnal-only ventilation to around-the-clock assistance as muscle weakness progresses.

Nocturnal Ventilation

Generally accepted indications for initiating nocturnal ventilation include rapid progression of weakness, hypercapnia or end-tidal carbon dioxide levels exceeding 45 to 50 mm Hg during or at the end of sleep, arterial desaturation below 95% during sleep, and symptoms of respiratory insufficiency.[30] The level of nocturnal support is adjusted until there is satisfactory resolution of symptoms and saturations consistently remain greater than 95%. Because of the thoracic deformities that are commonly present, tidal volume or pressure calculation may be inaccurate. In these cases auscultating the basilar lung regions provides a baseline for initial pressure or volume settings.

Initial means of respiratory support include a variety of noninvasive methods. In children, choice of assist device or ventilator mode and patient interface is likely to be dictated by patient age and size. Although the mouthpiece intermittent positive pressure ventilation (IPPV) with lip seal to minimize leak may be preferred in certain instances, these are available only in adolescent and adult sizes. Therefore nasal ventilation is the most practical means of noninvasive ventilatory support for small children. Younger children and infants can often be easily fitted with nasal interfaces such as adapted continuous positive airway pressure circuits or nasal pillows, nasal masks, or full-face masks, although custom headgear might be necessary (Figure 33-4). With any of these designs, the clinician must ensure that a proper fit not only minimizes leaks

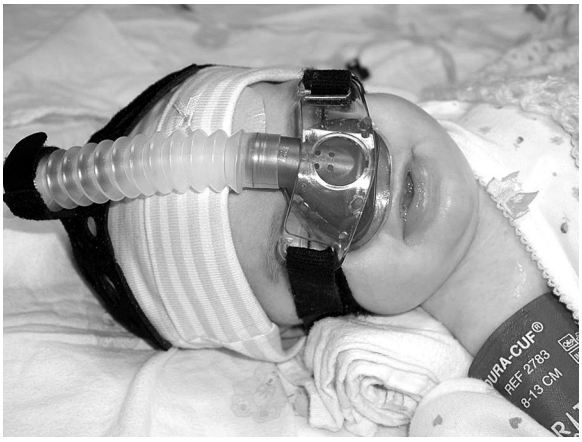


FIGURE 33-4 Infant nasal bilevel positive airway pressure. Nasal ventilation is the most practical means of noninvasive ventilatory support for small children. Although fittings for custom headgear may be necessary, younger children and infants can often be easily fitted with nasal interfaces such as adapted continuous positive airway pressure circuits or nasal pillows, nasal masks, or full-face masks. (Reprint permission from Dr. Howard Panitch, Children's Hospital of Philadelphia.)

but avoids pressure on the bridge of the nose and prevents future face deformity. Nocturnal ventilation is often best instituted via a portable volume ventilator. Ventilator settings should be adjusted to mimic age- and weight-based norms for tidal volume and respiratory rate. In older children, bilevel respiratory assist devices may be used, but because pressure levels are set, they do not accommodate progressive changes in muscle weakness. However, new volume-targeted pressure devices offer a suitable, more compact alternative that can automatically accommodate increasing muscle weakness.

Often, nocturnal ventilatory assistance improves both nocturnal and **diurnal ventilation,** and the overnight rest allows the respiratory muscles to improve daytime stamina. In fact, most patients use diurnal ventilation for the first time during chest infections, weaning off and returning to isolated nocturnal use, for periods lasting up to several years.[31]

Diurnal Ventilation

Daytime use of ventilatory assistance becomes necessary when patients develop end-diurnal hypoventilation.[31] Again, the goal of ventilatory assistance is normalization of arterial blood gas and elimination of respiratory symptoms.[31] Ample evidence exists that children, adolescents, and adults who are able to cooperate overwhelmingly prefer noninvasive ventilation.

Mouthpiece positive pressure ventilation has now been studied in several cohorts of end-stage patients and has been demonstrated to be a safe and effective means of chronic ventilation, even in patients with respiratory failure and no reserve (Figure 33-5).[31] It is extremely well tolerated by patients, even in sleep; is a user-friendly system during eating and social activities; and is also relatively inexpensive.[31]

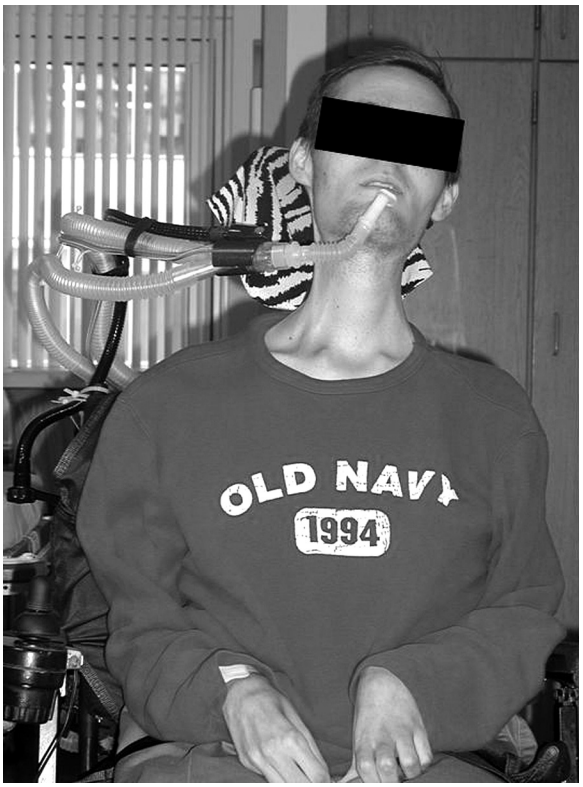


FIGURE 33-5 Mouthpiece ventilation. Mouthpiece intermittent positive pressure ventilation is a safe and effective means of chronic ventilation, even in patients with respiratory failure and no reserve. This mode of support is often preferred by adolescents and adults because it both provides adequate respiratory support and permits normal social interaction

Tracheostomy

Tracheostomy has long been a part of traditional management for patients with progressive neuromuscular weakness.[32] Often, tracheostomy tubes are placed during times of respiratory crisis, during or after bouts of respiratory failure triggered by chest infections. Newer therapeutic approaches to patients with neuromuscular weakness discourage tracheostomy, not only because it is often unnecessary but also because noninvasive support is overwhelmingly preferred by patients. Tracheostomy tubes present numerous disadvantages by impeding normal swallowing and phonation and limiting social interactions; in addition, more advanced in-home health care assistance and intensive follow-up is required. Hygiene issues are also a concern when considering a tracheostomy tube. Tube and stoma care can be uncomfortable, skin breakdown at the stoma site leads to cutaneous infections, and tracheostomy tubes risk sudden plugging with mucus, which can be life threatening.

Although adolescents and adults prefer noninvasive ventilatory aids for all the reasons given previously, it is important to mention that tracheostomy has also been favorably viewed by many patients. In general, we recommend that as patients demonstrate a need for ventilatory assistance, noninvasive ventilation be pursued first. Tracheostomy is probably best reserved for those patients with severe bulbar weakness and chronic aspiration, if arterial blood gas tensions can no longer be controlled, if there are patient–interface difficulties, or if there is failure to thrive. It is also important to remember that a subpopulation of patients—those with spinal cord injury and Guillain-Barré in particular—may benefit from temporary tracheostomies to facilitate hospital discharge and entry into a rehabilitation program. The long-term goal in these cases is to improve respiratory muscle strength, permitting successful decannulation.

Although more and more centers are developing expertise with chronic noninvasive ventilation, it is estimated that a minority use mouthpiece positive pressure ventilation. The reasons for this are explained by a combination of family and practitioner unfamiliarity with noninvasive methods and poor availability or uncertainty about how to use home cough-assist devices. This underscores the importance of connecting patients and their families early in the course of the disease with an accredited center caring for a high volume of patients with neuromuscular disease.

NONRESPIRATORY CARE

General medical concerns will cross all stages of growth and development for children with neuromuscular weakness, and attention must be paid to nutritional and cardiac status, extent of scoliosis and restrictive respiratory disease, the contribution of weakness to other organ system functioning, the need for communication assistance, and mental health care. Some of these concerns, such as cardiomyopathy and arrhythmias, relate to the multisystem effects of the neuromuscular conditions. Others, such as surgical correction of contractures and scoliosis, can be an important strategy in maintaining mobility and preserving lung function.

End-of-life care issues are inevitable in the course of progressive neuromuscular disease. In the discussion of these events it is important to provide the facts and answer every question fully and in terms the parents or patient can understand, without frightening technical language. This communication is one of the most difficult tasks in providing care to these patients. It requires tact, skill, empathy, and complete support of any decisions made by the parents or patient. The three primary goals include deciding on end-stage pain and dyspnea control, providing spiritual and psychiatric support, and respecting choices concerning tests and treatments.[18]

TRANSITION TO ADULTHOOD

Improved technology and advances in respiratory care have significantly increased the life expectancy of

children with neuromuscular weakness. Transition to adulthood requires increasing reliance on ventilator assistance, nursing support, and assistive technologies to help achieve independent living.[24] Another issue that persists across all childhood chronic illnesses is the need for age-appropriate caregivers, so that older adolescents and adults can begin to receive care in an adult health care environment.[33]

Children with neuromuscular weakness require more life-sustaining equipment and assistance in achieving independence. More personal assistance, either from family or skilled nursing, is required in providing basic care needs. Increased support has been associated not only with extended life expectancy but improved quality of life as well.[34] Unfortunately, the timing of instituting these assistive technologies and skilled nursing care remains dependent on the individual patient and clinical scenario.

Successful transition requires attention to the challenges associated with providing ventilatory assistance to the young adult with neuromuscular weakness. Additional issues during the transition process include facilitating coordination of care among multiple subspecialists, establishing a cadre of skilled caregivers, and arranging support for maintaining activities of daily living. If successful, the transition is likely to result in continued maintenance of a high quality of life despite the physical limitations associated with the underlying condition.[34]

Key Points

- Understanding neuromuscular control of respiration and airway clearance is important in avoiding associated complications and developing the best plan of therapy.
- Being proactive with assisted ventilation in a progressive neuromuscular disease can help avoid pulmonary infections and sequelae.
- Early monitoring of disease progression with pulmonary function testing can assist with proactive therapy before signs and symptoms of hypoventilation or ineffective airway clearance occur.
- Newer therapeutic approaches to patients with neuromuscular weakness discourage tracheostomy.
- Communication is one of the most difficult tasks in providing care to progressive neuromuscular disease patients. It requires tact, skill, empathy, and complete support of any decision made by the parents or patients.

Assessment Questions

See Evolve Resources for answers.

1. Which of the following are muscles of inspiration?
   - I. Diaphragm
   - II. Internal intercostals
   - III. External intercostals
   - IV. External oblique muscles
   - V. Rectus abdominus

   A. I and II
   B. I and III
   C. I, III, and V
   D. II and IV
   E. I, IV, and V
2. Which condition(s) of the central nervous system affect(s) respiration?
   A. Tay-Sachs disease
   B. Congenital hydrocephalus
   C. Congenital central hypoventilation syndrome
   D. A, B, and C
   E. B and C
3. Which condition is the most common myopathy affecting respiratory muscle function in childhood?
   A. Spinal muscular atrophy
   B. Myasthenia gravis
   C. Muscular dystrophy
   D. Guillain-Barré
   E. Scoliosis
4. Guillain-Barré is an acute, autoimmune process that affects the peripheral nervous system and causes:
   A. Inevitable respiratory failure, tracheostomy, and mechanical ventilation
   B. Hereditary weakness that progresses from the legs to the arms
   C. Mild hydrocephalus and confusion along with chest wall weakness
   D. Demyelination of the peripheral nerve sheaths, leading to conduction abnormalities
   E. Pain, starting in the arms and chest and leading to arm and chest weakness
5. Which of the following is an autoimmune disorder of infancy and childhood that occurs when antibodies block synaptic receptors at the neuromuscular junction?
   A. Myotonic dystrophy
   B. Pediatric botulism toxicity
   C. Infantile spinal muscular atrophy
   D. Juvenile myasthenia gravis
   E. Infantile transitional myasthenia gravis
6. A neuromuscular disease evaluation of the respiratory system of a child with neuromuscular weakness might include which of the following?
   - I. Spirometry with a flow–volume loop
   - II. Polysomnography
   - III. Electroencephalogram
   - IV. Mixed venous blood gases
   - V. Maximal inspiratory and expiratory pressures

   A. I and V
   B. I, II, and V
   C. III and V
   D. II, III, and V
   E. II, III, and IV

7. There are several phases of a normal cough to create sufficient cough flow for effective pulmonary clearance. The patient with neuromuscular weakness:
   - **A.** Is unable to produce peak cough flows
   - **B.** May have difficulty with any of the phases of an effective cough
   - **C.** Is able to produce high expiratory flows but does not generate enough volume for an effective cough
   - **D.** Has impaired glottic closure and diaphragmatic force for an effective cough
   - **E.** Does not have true impairment of cough flows, because it is relative to the reduced vital capacity
8. Glossopharyngeal breathing:
   - **A.** Is known as "frog breathing," which inflates the lungs by gulping air
   - **B.** Has limited effectiveness in patients with bulbar weakness
   - **C.** May provide normal alveolar ventilation in the case of a malfunctioning mechanical ventilator
   - **D.** A and B only
   - **E.** All of the above
9. Select the two indications for initiating nocturnal ventilatory assistance for a pediatric patient with neuromuscular weakness:
   - **I.** Supine negative inspiratory force of 60 to 90 cm H_2O
   - **II.** Hypercapnia during sleep with end-tidal carbon dioxide levels in excess of 50 mm Hg
   - **III.** Documented evidence of right-sided heart failure with peaked P waves on electrocardiogram (ECG)
   - **IV.** Arterial oxygen tension less than 88 mm Hg during 20% of the sleep study
   - **V.** Oxygen desaturation to less than 95% during sleep and symptoms of respiratory insufficiency
     - **A.** I and III
     - **B.** I and V
     - **C.** II and IV
     - **D.** II and V
     - **E.** III and IV
10. Placing a tracheostomy tube to facilitate mechanical ventilation for progressive neuromuscular weakness:
    - **A.** Is reserved only for patients with severe bulbar weakness, chronic aspiration, and inability to maintain acceptable blood gas values
    - **B.** May be temporary in children with spinal cord injury or Guillain-Barré
    - **C.** May be temporary to provide rest of the respiratory muscles and aggressive pulmonary hygiene
    - **D.** A and B
    - **E.** B and C

REFERENCES

1. Derenne JP, Debru A, Grassino AE, Whitelaw WA. History of diaphragm physiology: the achievements of Galen. *Eur Respir J*. 1995;8:154.
2. Remmers JE. A century of control of breathing. *Am J Respir Crit Care Med*. 2005;172:6.
3. National Center for Injury Prevention and Control, Centers for Disease Control and Prevention. *Spinal Cord Injury (SCI): Fact Sheet*. Bethesda, MD: Centers for Disease Control and Prevention; 2008. Available at: www.cdc.gov/ncipc/factsheets/scifacts.htm. Accessed October 2008.
4. Hirschfeld S, Exner G, Luukkaala T, Baer GA. Mechanical ventilation or phrenic nerve stimulation for treatment of spinal cord injury-induced respiratory insufficiency. *Spinal Cord*. 2008;46:738.
5. Fenoy AJ, Menezes AH, Fenoy KA. Craniocervical junction fusions in patients with hindbrain herniation and syringohydromyelia. *J Neurosurg Spine*. 2008;9:1.
6. Halawa A, Krishnaswamy G. Tussive headache with weakness and atrophy of the right hand. *Rev Neurol Dis*. 2007;4:224.
7. Kumar V, Abbas AK, Fauto N. *Robbins and Cotran Pathologic Basis of Disease*. 7th ed. Philadelphia: WB Saunders; 2004.
8. Laningham FH, Kun LE, Reddick WE, Ogg RJ, Morris EB, Pui CH. Childhood central nervous system leukemia: historical perspectives, current therapy, and acute neurological sequelae. *Neuroradiology*. 2007;49:873.
9. De Jesus NH. Epidemics to eradication: the modern history of poliomyelitis. *Virol J*. 2007;4:70.
10. Kaindl AM, Guenther UP, Rudnik-Schöneborn S, et al. Spinal muscular atrophy with respiratory distress type 1 (SMARD1). *J Child Neurol*. 2008;23:199.
11. Lunn MR, Wang CH. Spinal muscular atrophy. *Lancet*. 2008;371:2120.
12. Hauck LJ, White C, Feasby TE, Zochodne DW, Svenson LW, Hill MD. Incidence of Guillain-Barré syndrome in Alberta, Canada: an administrative data study. *J Neurol Neurosurg Psychiatry*. 2008;79:318.
13. Sarnat H. *Guillain-Barré Syndrome*. Philadelphia: Elsevier Saunders; 2007.
14. Finkelstein JS, Melek BH. Guillain-Barré syndrome as a cause of reversible cardiomyopathy. *Tex Heart Inst J*. 2006; 33:57.
15. Tseng-Ong L, Mitchell WG. Infant botulism: 20 years' experience at a single institution. *J Child Neurol*. 2007;22: 1333.
16. Conti-Fine BM, Milani M, Kaminski HJ. Myasthenia gravis: past, present, and future. *J Clin Invest*. 2006;116:2843.
17. Juel VC, Massey JM. Myasthenia gravis. *Orphanet J Rare Dis*. 2007;2:44.
18. Birnkrant DJ, Panitch HB, Benditt JO, et al. American College of Chest Physicians consensus statement on the respiratory and related management of patients with Duchenne muscular dystrophy undergoing anesthesia or sedation. *Chest*. 2007;132:1977.
19. Bach JR, Ishikawa Y, Kim H. Prevention of pulmonary morbidity for patients with Duchenne muscular dystrophy. *Chest*. 1997;112:1024.
20. Cardamone M, Darras BT, Ryan MM. Inherited myopathies and muscular dystrophies. *Semin Neurol*. 2008;28:250.
21. Katzin LW, Amato AA. Pompe disease: a review of the current diagnosis and treatment recommendations in the era of enzyme replacement therapy. *J Clin Neuromuscul Dis*. 2008;9:421.

22. Pathare N, Stevens JE, Walter GA, et al. Deficit in human muscle strength with cast immobilization: contribution of inorganic phosphate. *Eur J Appl Physiol*. 2006;98:71.
23. Nicot F, Hart N, Forin V, et al. Respiratory muscle testing: a valuable tool for children with neuromuscular disorders. *Am J Respir Crit Care Med*. 2006;174:67.
24. Panitch HB. Respiratory issues in the management of children with neuromuscular disease. *Respir Care*. 2006;51:885, discussion 894.
25. Steier J, Kaul S, Seymour J, et al. The values of multiple tests of respiratory muscle strength. *Thorax*. 2007;62:975.
26. Dhand UK, Dhand R. Sleep disorders in neuromuscular diseases. *Curr Opin Pulm Med*. 2006;12:402.
27. Toussaint M, Chatwin M, Soudon P. Mechanical ventilation in Duchenne patients with chronic respiratory insufficiency: clinical implications of 20 years published experience. *Chron Respir Dis*. 2007;4:167.
28. Panitch, HB. Respiratory Implications of Pediatric Neuromuscular Disease. *Respir Care*. 2017;62:826.
29. Rideau Y, Gatin G, Bach J, Gines G. Prolongation of life in Duchenne's muscular dystrophy. *Acta Neurol (Napoli)*. 1983;5:118. and Bach JR, Alba AS, Saporito LR. Intermittent positive pressure ventilation via the mouth as an alternative to tracheostomy for 257 ventilator users. *Chest*. 1993;103:174. As cited in Simonds AK, Muntoni F, Heather S, Fielding S. Impact of nasal ventilation on survival in hypercapnic Duchenne muscular dystrophy. *Thorax*. 1998; 53:949.
30. Laub M, Berg S, Midgren B. Symptoms, clinical and physiological findings motivating home mechanical ventilation in patients with neuromuscular diseases. *J Rehabil Med*. 2006; 38:250.
31. Toussaint M, Steens M, Wasteels G, Soudon P. Diurnal ventilation via mouthpiece: survival in end-stage Duchenne patients. *Eur Respir J*. 2006;28:549.
32. Bach JR. Medical considerations of long-term survival of Werdnig-Hoffman disease. *Am J Phys Med Rehabil*. 2007; 86:349.
33. Denboba D, McPherson MG, Kenney MK, Strickland B, Newacheck PW. Achieving family and provider partnerships with children with special health care needs. *Pediatrics*. 2006;118:1607.
34. Kohler M, Clarenbach CF, Böni L, Brack T, Russi EW, Bloch KE. Quality of life, physical disability, and respiratory impairment in Duchenne muscular dystrophy. *Am J Respir Crit Care Med*. 2005;172:1032.

34 Transport of Infants and Children

Leslie M. Gonzalez

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. Discuss and recognize the importance of team composition, roles, and education.
2. Review and compare the caveats of each mode of transport.
3. Explain the role of communication during a medical transport.
4. List the specific equipment needed for pediatric transport.
5. Demonstrate how to provide a patient assessment in a nontraditional environment.
6. Review safety and accreditation requirements for pediatric transport agencies.

Key Terms

dedicated transport teams **UHF/AM transceiver** **unit-based transport teams**

Since the late 1980s the care of critically ill pediatric patients has experienced rapid development in technology and improvement in patient outcomes. Today many infants and children who previously would have died are surviving because of the evolution of critical care and effective transport systems. The cost of such care has also been known to be expensive and has necessitated regionalization of intensive care centers to larger tertiary care centers. This regionalization has led to the need for safe and effective patient transport systems. For neonatal transport, antenatal transport of a mother and high-risk fetus to a tertiary center is preferred so the baby can be delivered in a facility with the specialized staff members of a tertiary care facility already in house, with the proper training and skill practice to perform advanced care for specialized needs. However, this is not always possible because of maternal complicating factors.[1,2] In these cases the critically ill neonate must often be transported after birth. In most states the operation of a neonatal and pediatric transport team is based at neonatal and pediatric tertiary centers. Each state typically has its own specific rules and regulations for staffing, training, equipment, and safety. There are few things more challenging and yet rewarding to clinicians than transporting critically ill infants and children from a local hospital to a tertiary care medical center. Respiratory therapists must adjust their focus to monitoring the status of patients and performing procedures while operating in a dynamic environment, such as a moving ambulance or aircraft.

The ages, sizes, and diagnoses of transported neonatal and pediatric patients encompass virtually the entire scope of the critically ill population, from a 500-g infant to a 100-kg adolescent. Transporting neonatal and pediatric patients with serious illness or trauma to facilities specializing in the care of these patients has resulted in significantly improved outcomes.[3-4] The skilled transport of critically ill patients is an intervention of the highest value and an activity in which respiratory therapists should be proud, enthusiastic, and encouraged to participate.

TEAM COMPOSITION

STAFFING

Critical care transport requires experienced personnel with advanced clinical skills, additional training, and education. If the team is to function autonomously, they must work together with others involved in the transport process. Personnel are the single most valuable asset of any transport system. Because the stabilization and critical care skills required for critically ill pediatric patients are specialized, the composition of the team is important. Team composition varies among different health care institutions across the country. More important than the exact credentialing of the transport personnel is the training and skills of the team. A qualified transport team should consist of individuals who have typically 2 years of pediatric and neonatal critical care experience and training in the special needs of children during transport and who have participated in the transport of these patients with the frequency to maintain their expertise.[5] Transport team members must often function with a high workload of critical tasks that are frequently evolving, and thus the team must adapt dynamically to achieve its goals.[6]

Most transport teams are composed of one or more of the following health care team members:

- A registered nurse
- A respiratory therapist
- An emergency medical technician
- A neonatal nurse practitioner
- A staff physician, resident, or fellow

Data show that most pediatric transport teams in the United States are led by a nurse and accompanied by a respiratory therapist. The use of a specialized pediatric transport team (registered nurse and respiratory therapist) has been shown to result in lower morbidity than the traditional emergency medical services (EMS) helicopter staffed with a flight/trauma nurse and a paramedic.[3,7] The bulk of the research on prehospital care has focused on the adult population. Consequently, little of the care provided by EMS to pediatric patients is based on evidence from prehospital care research.[8,9] However, studies have been problem solving EMS training on pediatric care and are implementing strategies to help better prepare EMS personnel for more pediatric cases.[10] A respiratory therapist is at an advantage because of the large number of transported pediatric patients who require respiratory support. The background and training of nurses and respiratory therapists are so different that such a team creates a broader scope of knowledge and experience when both are used. This combination works successfully in most critical care and even routine transports.[11] A recent national survey showed that neonatal transport teams primarily are composed of registered nurses and respiratory therapists.[12]

Although many nonneonatal pediatric teams may include a resident or attending physician, there is little published evidence that this team model offers improved outcomes compared with non–physician-based teams. All pediatric transport teams should have a mechanism to identify critical patient transports that may require the addition of a physician to the transport team. All team members should be cross-trained so that each member of the team can function at the others' skill level. The medical director of the pediatric transport program should be a critical care intensivist, anesthesiologist, or neonatologist with an interest in transport medicine.[13]

Though most exclusive neonatal and pediatric transport teams are affiliated with children's hospitals, the administrative home of the transport team varies with each institution. **Unit-based transport teams** are staffed and scheduled within the intensive care unit (ICU) or, in the case of respiratory therapists, within the respiratory care department. The transport staff are generally given a patient care assignment and then "pulled" from that assignment when a transport call is received. This patient assignment is then back filled by the department staff, or an on-call person is used to fill the assignment until the transport is completed. From an administrative standpoint this is the most cost-effective use of personnel resources.

Dedicated transport teams are scheduled and staffed separately from the ICU personnel. These staff members generally "float" throughout the hospital without a patient assignment when they are not on transport. They are there to assist other hospital personnel but can leave immediately when a transport call is received. A large volume of transports is necessary to justify a dedicated transport team. Most transport programs have found that once volumes exceed 1000 to 1200 transports per year, it is fiscally advantageous to allocate the resources for a dedicated transport team. Personnel accustomed to managing transport coordination are the best suited for accomplishing the relatively complex logistics of transporting critically ill patients.

The objective of adequate staffing is to ensure that each member of the transport team has the opportunity to participate in enough transports per month (15 to 20 per month) to maintain a high level of competency while at the same time making sure not to overwork the staff and create "burnout." Transport team professionals have unique responsibilities and are exposed to powerful demands. They cannot avoid incidents that pose personal threats to their own emotional well-being. Contact with dead or severely ill or injured children, for example, can be detrimental to the caregiver.[14]

TRAINING

The neonatal and pediatric transport team plays a vital role in the transport of critically ill children to tertiary pediatric facilities. Pediatric transport practitioners are experienced personnel must have a wide range of high-level clinical competence dealing with many

Box 34-1 Minimal Requirements for Transport Team Members

TRANSPORT NURSE

- Licensed by the state
- Two years of experience as a registered nurse, including 12 months of neonatal intensive care unit or pediatric intensive care unit (NICU/PICU) experience
- Current basic cardiac life support (BCLS) certification
- Current neonatal resuscitation program (NRP) certification
- Current pediatric advanced life support (PALS) certification
- Current advanced cardiac life support (ACLS) certification
- Certificate of added qualification in neonatal pediatric transport (C-NPT)—National Certification Corporation (NCC)
- Has participated in a pediatric transport course and has demonstrated a working knowledge of transport equipment and transport supplies
- Has observed a program-specified number of transports and been checked off by a preceptor and medical control physician before being released for transport duty

TRANSPORT RESPIRATORY THERAPIST

- Registered respiratory therapist (RRT) by the National Board for Respiratory Care (NBRC)
- Neonatal and pediatric specialty credentialed (RRT-NPS) by the National Board for Respiratory Care
- Licensed by the state
- Two years of NICU/PICU experience
- Current BCLS certification
- Current NRP certification
- Current PALS certification
- Current ACLS certification
- NCC C-NPT
- Has participated in a pediatric transport course and has demonstrated a working knowledge of transport equipment and transport supplies
- Has observed a program-specified number of transports and been checked off by a preceptor and medical control physician before being released for transport duty

diseases affecting children. The team must be comfortable caring for critically ill patients, whether at small referral hospitals or during the transport process itself by ground ambulance or air. The transport team is a vital component of successful patient care during transport to a tertiary care center. This highly specialized team brings the basic services of the neonatal intensive care unit (NICU) or pediatric intensive care unit (PICU) to the patient's bedside. The transport team is also the first to assess the patient from this advanced care facility and initiate the care they require to be able to be transported as stable as possible to their tertiary care facility.

The qualities of the team members are as important as the team composition. The selection process should include interviews not only with the nursing and respiratory leadership but with the medical director of the transport team under whose license the person will operate. Ideal candidates should have exemplary clinical skills, leadership and decision-making abilities, flexibility, compassion, and assertiveness, all while working in a high-stress transport service.

See Box 34-1 for a list of minimal requirements for transport team members.

Inadequate training of pediatric caregivers has been correlated with increased morbidity.[5,6] Several different professional organizations have developed training and educational requirements for pediatric transport teams. The Air & Surface Transport Nurses Association (ASTNA, Greenwood Village, CO), American Association for Respiratory Care (AARC, Irving, TX), Commission on Accreditation of Medical Transport Systems (CAMTS, Anderson, SC), American Academy of Pediatrics (AAP, Elk Grove Village, IL), and National Certification Corporation (NCC, Chicago, IL) are commonly recognized. In general, they recommend that transport nurses and respiratory therapists have at least 2 years of pediatric critical care experience. Annual recurrent training should include didactic material and hands-on training in procedures that are used during transport (Box 34-2). The use of high-fidelity patient simulation has also grown in acceptance of neonatal and pediatric transport team members.

Additional courses such as Pediatric Fundamental Critical Care offered by the Society of Critical Care Medicine and the neonatal-focused S.T.A.B.L.E. program also offer didactic training options.

Simulation-Based Medical Education

Simulation-based medical education (SBME) is believed to be superior to the traditional style of medical education from the viewpoint of the active and adult learning theories. SBME can provide a learning cycle of debriefing and feedback for learners and evaluation of procedures and competency. SBME offers both

Box 34-2 Annual Recurrent Training Topics*

- Advanced airway management
- Central line/umbilical artery line insertion
- Peripheral intravenous catheters/interosseous (IO) placement
- Thermoregulation
- Identification and treatment of pneumothorax
- Stabilization of critically ill pediatric patients
- Acid-base balance
- High-altitude physiology (for air transport)
- Stress factors in transport (e.g., noise, vibration)
- Transport equipment operation
- Transport-based simulation scenarios
- Aircraft and ambulance safety procedures
- Aircraft evacuation drills
- Community relations

*Not exclusive.

learners and patients a safe environment for practice and error. Effective team performance in complex environments requires that team members hold a shared understanding of the task, their equipment, and their teammates. Therefore many of the simulation-based training (SBT) systems and programs have been designed (partly) to enhance shared, team cognition.[15,16]

MODES OF TRANSPORTATION

The single largest expense of a transport program is in the operation and maintenance of its transport vehicles. The selection of specific vehicles is an important decision that must include many different factors. The vehicles must be safe and have the operational characteristics appropriate for the program requirements. All vehicles used to transport patients must comply with local, state, and federal guidelines for both air and ground ambulances. The vehicles must have 110-volt AC electrical power available for the medical equipment used during transport. There should be sufficient medical gas (medical air and oxygen) capacity for all transport operations plus reserve capacity for use in the event of mechanical breakdown. The vehicles must also have provisions for suction equipment. The medical equipment used in transport, as well as the stretcher or incubator, must be safely secured within the vehicle during transport. The vehicle must have interior room that will allow the transport team to treat and assess the patient and, on occasion, perform procedures safely during transport.[17] All transport vehicles must have two-way communication capability, using radios or cellular phones. Each mode of transport—ground, rotor wing (helicopter), and fixed wing (airplane)—has advantages and disadvantages. The vehicle chosen should be appropriate for the patient population and geographic area served.

GROUND TRANSPORT

Ground transport should be considered when distances are 30 miles or less one way for critical patients and less than 80 miles one way for stable patients. The ground transport vehicle should be an ambulance equipped with the special equipment needed for intensive care transport. The ambulance should have a hydraulic or electrical lift for loading the heavy transport incubators used in neonatal transport (Figure 34-1). The incubator should be secured by a designed floor-securing system or at minimum with four-point restraint straps.[18] The ambulance interior should be large enough to secure two transport incubators for transport of twins and room to seat the transport team members required for the care of two patients.

Advantages and disadvantages of ground transportation are listed in Box 34-3.

AIR TRANSPORT

Rotor Wing

Helicopters are effective for rapid transport of critical patients within a 30- to 150-mile radius.[19] The size of the helicopter and the corresponding size of the cabin within the helicopter must be adequate to handle the equipment and transport team members. The transport team must be able to access and treat the patient during flight should an emergency arise. A neonatal transport team with a transport incubator will typically require a midsized twin-engine aircraft to have enough room for proper patient care (Figure 34-2).

FIGURE 34-1 An ambulance with a stretcher-mounted neonatal transport incubator. (Courtesy Children's Medical Center, Dallas.)

Box 34-3 Advantages and Disadvantages of Ground Transportation

ADVANTAGES
- Lowest operating cost
- Ability to go directly from hospital to hospital
- Ability to carry a large number of staff and equipment
- Ability to transport in poor weather

DISADVANTAGES
- Slower response time over greater distances
- Can be slowed or stopped by traffic congestion
- Road noise and vibration

Box 34-4 Advantages and Disadvantages of Rotor Wing Transportation

ADVANTAGES
- Rapid response time within a 30- to 150-mile radius
- Ability to fly directly from hospital to hospital

DISADVANTAGES
- High operating and capital expenses
- Small operating radius without refueling
- Small cabin area allows limited medical procedures (no cabin pressurization)
- Limited payload for personnel and equipment
- Inability to fly in inclement weather

FIGURE 34-2 Memorial Hermann Life Flight operates a midsized twin-engine helicopter that has the capacity to transport a neonatal transport team with a transport incubator. (Courtesy Memorial Hermann Hospital, Houston, Texas.)

Advantages and disadvantages of helicopters are listed in Box 34-4.

Fixed-Wing Aircraft

Airplanes are effective for long-distance patient transport. Because airplanes fly from airport to airport, the increased coordination of ground ambulances for two airports, the time required to load and unload at both airports, and the additional ground transport time must be balanced against the time required to drive from hospital to hospital. Under normal circumstances the time needed to drive 120 miles is greater than the fixed-wing aircraft transport time for the same distance. All airplanes used for critical patient transport should have the ability to control the cabin altitude (pressurization), which makes the transport of critically ill patients with marginal arterial oxygenation possible (Figure 34-3).

Advantages and disadvantages of airplanes are listed in Box 34-5.

EQUIPMENT

The equipment, both communication and medical, carried on board an ambulance, helicopter, or airplane will need to meet various standards. In general, the equipment should be as lightweight as possible, be both electrical and battery operated, and should not interfere electromagnetically with aircraft navigation or communication equipment.[20] It should be as ruggedly constructed as possible. All equipment should be well secured for the duration of transport.[18]

FIGURE 34-3 A jet-engine aircraft that has the ability to transport two patients and five medical crew members within a pressurized cabin. (Courtesy of Children's Medical Center, Dallas.)

Box 34-5 Advantages and Disadvantages of Airplanes

ADVANTAGES
- Rapid response time for distances greater than 120 miles
- Ability to fly long distances
- Larger cabin area to allow for more medical procedures
- Ability to control cabin altitude (pressurization)
- Larger payload for equipment and personnel including family members
- Ability to fly in inclement weather

DISADVANTAGES
- Moderate operating and capital expenses
- Requires an airport to land, and thus an ambulance transfer at both ends of the flight

COMMUNICATIONS

The transport team should always have the ability to communicate with the online medical control physician who is supervising the transport. This communication has traditionally been accomplished via radio for both ground and air transport. However, the use of cellular phones in ground ambulances has steadily increased, especially with more cellular companies offering a "walkie-talkie"–type option. Both helicopters and airplanes are equipped with VHF radios for communicating with air traffic control. EMS helicopters are generally equipped with another type of radio, called a **UHF/AM transceiver.** This additional radio allows communication with ground support agencies (fire, police, etc.) and their dispatch centers. The transport teams on the helicopter can contact their online medical control via this UHF radio. Because of the short-range limitations of UHF radios, fixed-wing air ambulances should be equipped with a satellite-type cell phone for air-to-hospital communication. This will allow communication from almost any location around the world.

MEDICAL

Monitoring Equipment

Electrocardiogram monitoring, pulse oximetry monitoring (Sao_2), and blood pressure monitoring are standard practice during the transport of critically ill patients. Most modern transport monitors incorporate the following:
- Electrocardiogram (ECG)
- Sao_2 (pulse oximeter)
- Noninvasive blood pressure monitoring (blood pressure cuff)
- Invasive blood pressure monitoring (pressure transducers)
- Patient temperature monitoring (skin probes)

End-tidal carbon dioxide ($ETco_2$) monitoring is a valuable option on most transport monitors; monitoring $ETco_2$ provides the transport team with a visual method to ensure effective ventilation in the intubated patient during transport. Alarm limits should be set for each transport. Because of the high noise levels found in the transport environment, visual alarm indicators are usually more helpful than audible alarms.[21-23] Visual alarms have also been shown to help alleviate stress in patients and help them to remain stable throughout the transport.[24] Earmuffs like the ones used for magnetic resonance imaging and computed tomography are now being carried and used by transport teams to help neonates with the noise levels. Monitors with interchangeable battery packs allow for quicker turnaround times as an alternative to waiting for batteries to recharge.

Ventilator

Use of a transport ventilator will allow the transport team to provide the same level of care given or already established in an ICU. Transport ventilators are now available with most of the intensive care parameters (i.e., positive end-expiratory pressure, synchronized intermittent mandatory ventilation, noninvasive ventilation, adjustable fraction of inspired oxygen, and pressure support) in small, portable, lightweight cases. Ventilators with external battery packs allow for quicker turnaround times compared with waiting for an internal battery to recharge. Many newer models now have "hot swappable" batteries that allow the operator to change out batteries while the ventilator continues to function. The decision to use a volume-limited or a pressure-limited ventilator should be based on the patient's size and ventilatory requirements. A manual resuscitation bag should always be carried on transport in the event of ventilator malfunction. Transport team members should be reminded that studies have shown there are tendencies to hyperventilate the patient while using a manual resuscitator.[25-27]

Transport Incubator

The ability to transport an infant with a body weight of 5 kg or less in a neutral thermal environment requires the use of a transport incubator. There are several commercially available transport incubators. They are modular units that allow customers to select among different models of heart monitors, ventilators, infusion pumps, and oxygen and air sources. When considering the purchase of a transport incubator, the first concern should be the type of vehicle in which the incubator will be transported. For example, the primary factor if planning to use the incubator in an aircraft (especially a helicopter) would be the weight and size of the incubator. Other factors to consider include battery power, which should be able to power the incubator for 2 to 3 hours; easy access to the infant without excessive heat loss; ability to visually monitor the infant at all times; and adequate lighting of the patient in dark areas.

Infusion Pumps

The syringe pump–type infusion pump is popular with transport teams because it requires no special tubing or cassette. A standard syringe (between 1 and 60 mL) is loaded onto the pump. The pump applies constant pressure to the plunger of the syringe and can be programmed for infusion rates from 0.1 to 999 mL/hr. These pumps are lightweight and battery powered, capable of running for 3 to 4 hours between charges. There are now also small portable infusion pumps that can use premixed bags of medication or fluid for larger volume infusions. These infusion pumps may even have built-in drug libraries in them.

Point-of-Care Testing

Pediatric transport teams are gradually moving to the use of a commercially available portable blood gas analyzer. Studies have shown that point-of-care testing reduces stabilization times and can have the potential to improve the quality of care during transport.[28-30] Most analyzers have a small, battery-powered, handheld unit and a variable set of testing cartridges. Transport teams are able to do blood analysis either during transport or at small outlying hospitals that do not have the ability to analyze small blood samples. The following parameters can be determined with three or four drops of blood: pH, carbon dioxide pressure (Pco_2), oxygen pressure (Po_2), sodium (Na), potassium (K), ionized calcium (iCa), glucose (Glu), hematocrit (Hct), and hemoglobin (Hb).

Medications

The type and quantity of medications carried by the transport team should meet the requirements for care of the various patients transported. If the team operates under medical protocols, each medication carried should have its own protocol for use. Proper attention should be given to the storage of medication and for a system to check for expiration of stored medications. Medications should be stored to prevent exposure of extreme temperatures of heat or cold. A process must also be developed to handle drugs requiring refrigeration, such as surfactant.

Medical Gas Supply

Pediatric transport teams who transport low-birth-weight infants will need to have both medical oxygen and medical air available while on transport. This will allow for the use of a blender to titrate the inspired oxygen of low-birth-weight infants. It is critical that the amounts of gas needed be calculated on the basis of projected use. The amount of gas taken should be approximately double that required. This allows for emergency usage in the event of mechanical breakdown of a vehicle. In ground ambulances, where weight is less of a consideration, additional medical gas supplies are usually provided by size H cylinders. This additional gas source allows the team to conserve the gas supply on the incubator. In aircraft, where weight is a significant consideration, the use of aluminum and Kevlar cylinders has become the standard because of their low weight. Most fixed-wing aircraft have electrical air compressors to provide medical air and liquid oxygen systems for medical oxygen, thus providing gases over a long duration. A small portable oxygen supply such as a D-sized cylinder should also be available for emergency use or equipment failure.

Supplies

The type and quantity of disposable supplies carried by the transport team should be sufficient for the proper care of the various patients transported. Weight and portability of the system to carry the needed supplies should be assessed.

PATIENT ASSESSMENT AND STABILIZATION

Assessment of the patient begins with the first phone call from the referring hospital. The basic information required to initiate a transport should include the following[31]:

- Name
- Weight
- General description of the patient's condition
- Any relevant medical history
- Current vital signs, including oxygen saturation, heart rate, respiratory rate, and blood pressure
- Any current major clinical problems
- Status of current lines, fluids, medications, treatments, etc.

The referring hospital should be given any recommendations for changes in medical management and the estimated time of arrival of the transport team. The referring hospital should also be given phone numbers and instructions to call back with any questions or significant changes in the patient condition before the transport team's arrival.

On arrival, assessment of the patient by the transport team should be thorough yet rapid. Stabilization at the referring hospital has become a much-discussed topic. The question of "stay and play" or "scoop and run" is debated in transport conferences across the country. The goal of the transport team should be to transport the patient in the most stable condition possible. Proper stabilization should be designed to minimize the number of adverse incidents (e.g., hypoxic or hypotensive events) that may occur during the transport. At the same time, the team should avoid the temptation to perform time-consuming therapeutic testing procedures while on transport. Before departure it is very helpful to briefly discuss with the family what has been done to stabilize their child and where the child will be admitted once the transport is completed. Directions

and contact information for the receiving facility is also helpful for the family of the patient.

ADVANCED TRANSPORT

HIGH-ALTITUDE PHYSIOLOGY

A complete understanding of flight physiology is essential to provide optimal patient care in the air–medical environment.[32,33] Normal physiologic responses to changing altitude are further complicated when transporting an already compromised patient.

Boyle's law states that at constant temperature, volume is inversely proportional to pressure. As the aircraft and patient rise in altitude, the volume of contained gases expands. This expansion has the following clinical implications for patient care:

- Increased respiratory rate and depth
- Changes in intravenous flow rates
- Nausea and vomiting
- Increased need to urinate
- Increased pain
- Endotracheal tube cuff expansion (prevented by filling the cuff with normal saline)
- Increased sinus pressure in the case of those with head colds or blocked sinuses
- Further expansion of pneumothorax

Dalton's law of partial pressure states that the pressure of a gas mixture equals the sum of the partial pressures of gases making up the mixture. As the aircraft climbs to altitude, the barometric pressure within the aircraft drops; the fraction of inspired oxygen remains the same (21%), but the delivery of oxygen to the patient is reduced because of decreased partial pressure.

Cabin pressurization allows the transport team to compensate for the decreased barometric pressure at flight altitude. Each aircraft manufacturer designs a maximal pressurization limit for their aircraft. This limit is based on the maximal pressure differential between cabin pressure and actual barometric pressure at flight altitude, which is expressed as a ratio of flight altitude to cabin pressure, each given as pounds per square inch (psi). Cabin pressurization creates an artificial atmospheric pressure inside the aircraft, known as *cabin altitude*. The cabin altitude can be adjusted from sea level to a maximal differential (usually 5000 to 6000 feet) depending on patient requirements and aircraft operations. An aircraft flown with a sea-level cabin altitude will not experience any of the effects of high altitude, but this could have a negative effect on the operation of the aircraft. Because of the pressure differential, the aircraft might need to be flown at a lower flight altitude to allow for the sea-level cabin pressurization. This lower flight altitude might increase the fuel burn (possibly requiring a fuel stop), slow the aircraft and thus increase transport time, and expose the aircraft to more severe weather concerns. Documentation of the cabin altitude during the patient transport should be included in the patient transport record. If for any reason flight cabin altitude may compromise the patient's condition, medical control should be contacted.

Most large twin-engine airplanes have pressurization systems. There are no helicopters with pressurization systems. It is imperative that the transport team be aware of an aircraft's abilities and limitations before using the vehicle in patient care.

NITRIC OXIDE

The use of nitric oxide for the treatment of some congenital cardiac diseases and pulmonary hypertension in the neonatal and pediatric population is well established in the literature.[34,35] At many community hospitals, nitric oxide may also be administered to some very-low-birth-weight premature infants to potentially lower the risk of lung and brain damage. Therefore it is likely that the number of requests to transport a patient already receiving nitric oxide will continue to increase. Furthermore, the beneficial effects of nitric oxide in the stabilization and transport of critically ill neonatal and pediatric patients may require transport teams to initiate the use of nitric oxide before transport.[36] The transport respiratory therapist must be able to integrate the nitric oxide delivery device with the patient's ventilator and monitor the various gas levels. As with all transport equipment, the nitric oxide delivery device should be as lightweight as possible, should be both electrically and battery operated, should not interfere electromagnetically with aircraft navigation or communication equipment, and should be ruggedly constructed.[32] The nitric oxide delivery device and the cylinder should be well secured for the duration of transport. A considerable amount of study has been focused on the exposure of the transport team to exhaled nitric oxide and on the scenario of a catastrophic release of gas from a nitric oxide cylinder within the small working area of an ambulance or aircraft. The results have shown that the high air exchange rates within ambulances and aircraft and the low doses of nitric oxide used make environmental nitric oxide toxicity unlikely.[37]

SAFETY OF TRANSPORT

Every transport program (air or ground) must provide a safe work environment. There should be a structured safety program in place to protect both the patient and the transport team members.[13] This program should include the following:

- A safety officer
- An incident reporting process
- Strict safety policies that are enforced
- Annual safety training
- Regularly scheduled transport safety committee meetings
- Regular safety assessments

Recommendations and actions from the transport safety committee must be linked to the transport program's performance improvement program. Safe performance in the transport environment starts with properly trained and educated personnel.[38] Didactic education should include the following:

- Disease physiology and how it relates to transport
- Safety
- Communications
- Stress management
- Survival training
- Legal aspects of transport

Whenever possible, opportunities to practice classroom instruction in the back of an aircraft or ambulance during actual operations are invaluable. Many programs now have mockups of vehicles in which to practice patient care in a transport environment.

The use of red lights and sirens (RLS) should be monitored and addressed, because overuse has been shown to increase risk to the patient, public, and caregivers.[39-42] Every transport program should have a post-accident/incident action plan (PAIP).[13] The plan should include the process for notification of the following in the event of an accident involving the transport team:

- Transport team management
- Hospital administration
- Physicians
- Risk management
- Transport team members
- Transport team families
- Public affairs
- Media

ACCREDITATION

The transport program must be in compliance with local, state, and federal regulations related to the transport of neonatal and pediatric patients. Regulations that involve the following all have an effect on the transport of patients, documentation requirements, team composition, equipment and supplies, and transfer or transport consent forms.

- Certificates of need
- City/county/state/federal licensure
- Emergency medical services state health departments
- Consolidated Omnibus Budget Reconciliation Act (COBRA)
- Emergency Medical Treatment and Active Labor Act (EMTALA)
- Centers for Medicare and Medicaid Services (CMS)
- Federal aviation regulations (FARs)
- Federal Aviation Administration (FAA)

The program director must be knowledgeable about all these regulations and requirements. The transport staff must also be aware of and understand the regulations that influence the day-to-day operations of the program.

The Commission on Accreditation of Medical Transport Systems (CAMTS) is a peer-review organization comprising 21 transport-related organizations that offer a program of voluntary evaluation of compliance with a set of accreditation standards. The core elements of the standards include aircraft and ambulance configuration, communications, legal requirements, maintenance, management, pilots and drivers, medical direction, scope of care, safety program, scheduling, and training and education of personnel. By participating in the voluntary accreditation process, transport teams can verify their adherence to quality standards to themselves, their peers, medical professionals, insurance companies, and the general public. At present several different states and counties require the CAMTS standards as the minimal standards required of transport teams for state and county licensing.

Case Study

You are called for a 29-week imminent delivery at an outside facility 1 hour away from your tertiary care facility. The MOC is in preterm labor and estimated birth weight is 1800 grams. Prepare for transport.

DISCUSS:

1. Team preparation, communication en route, and roles assigned.
2. What you anticipate and the equipment and materials would you plan to take.
3. Identify risks of 29 week gestational age baby.

AIRWAY PREPARATION

- Bag and mask
- Endotracheal tube, size 3.0 (consider having a 2.5 ready for back up)
- Blade size 0 (consider having a 00 ready as back up)
- Carbon dioxide detector
- Tape or securement device
- Surfactant

KEY POINT

SURFACTANT	INITIAL DOSE
Poractant alfa	2.5 mL/kg
Calfactant	3 mL/kg
Beractant	4 mL/kg

PIV PREPARATION

- PIV supplies
- UAC/UVC supplies

MEDICATIONS

- Fluids: normal saline, dextrose
- Sedation

ADDITIONAL EQUIPMENT

- Portable blood gas equipment
- Equipment to ensure thermoregulation.

You arrive at the hospital and MOC is being rushed to the operating room (OR) after experiencing extreme abdominal pain and bright red vaginal bleeding. In the OR, fetal heart tones are 50 beats/minute.

DISCUSS:

- Think about delivery preparation.
- Gather supplies needed, including checking the warmer temperature.
- Include PPV initial settings and Fio_2.
- Discuss preparation for code and resuscitation skills with neonatal resuscitation program guidelines related to a low fetal heart rate.
- Consider placement of an orogastric tube as well as UVC/PIV.
- Discuss code medications to have ready such as epinephrine and NS bolus.
- Discuss when to know to stop with code and administration of PRBCs once the patient has stabilized as well as obtaining a blood gas.

The baby is handed over to your team, and upon quick assessment the baby is blue, with no respiratory effort or tone, and the initial heart rate is 40 beats/minute despite bulb suctioning with drying and vigorous stimulation. What actions should be taken next?

DISCUSS:

- Pulse oximeter should be placed on the baby's right wrist.
- PPV should be started (pressures roughly around 20/5 with an Fio_2 of 30%).
- Prepare for intubation.

You are now at 2 minutes of life and the baby's heart rate slowly improves with your PPV and is now at 50 beats/minute; color has not improved much, and there is still no visible respiratory effort or tone, and the Spo_2 is reading 33%. What will you do next?

- Begin compressions.
- Increase Fio_2.
- Intubate and verify proper placement
  - Co_2 detector color change
  - Bilateral and equal breath sounds
  - Mist in the endotracheal tube
  - Secure airway
- Reassess heart rate

You reassess the heart rate, and it is now above 60 beats/minute and continues to rapidly increase. What actions would you like to take next?

DISCUSS:

- Stop chest compressions.
- Prepare for stabilization.
- Administer fluids and medication.
- Obtain blood gas.
- Prepare for blood transfusion.
- Obtain a chest radiograph.
- Call attending to update.
- Pack up and prepare for transport back to the tertiary care facility.

Case Study

You are in the emergency room and are called for an 8-year-old with asthma who has been wheezing for 2 days with an upper respiratory infection but worsened this afternoon; his mom stated he had been giving himself puffs of his inhaler every half hour most of the day. Upon arrival the patient complains of shortness of breath and is kneeling on the floor in a tripod position, is anxious, and has audible wheezing, and intercostal retractions are present.

DISCUSS:

- Identify patient severity.
- Call for help right away.
- Have delegation of roles assigned.
- Request equipment:
  - Oxygen
  - Albuterol
  - Monitors

The patient is placed on the monitor, and vital signs are heart rate, 130 beats/minute; respirations, 37 breaths/minute; blood pressure, 100/60 mm Hg; Spo_2, 85% on room air. The patient is diaphoretic, has a racing pulse, and has red cheeks. What do you do next?

- Student should initiate the use of oxygen (applying a nonrebreather if one is not already on).
- Albuterol should be started (continuous use is recommended).
- Monitor the patient and vital signs.
- Obtain blood gases.
- Start intravenous access.

Spo_2 increases to 90% with interventions. However, the patient has diminished breath sounds bilaterally, increased work of breathing, and severe intercostal retractions. What do you suggest next?

- Start magnesium.
- Continue continuous albuterol.
- Call the pediatric intensive care unit and prepare to transport.
- Have bilevel positive airway pressure on standby.

Key Points

- The transport of critically ill neonates and pediatric patients is a very specialized level of care requiring extensive training and clinical experience of the staff. Team composition may vary, but typically specially trained registered nurses and respiratory therapists staff these teams. Each team member brings a needed level of critical care found in neonatal and pediatric intensive care units to the patient. Discuss and recognize the importance of team composition, roles, and education.

- The transport of critically ill neonates and pediatric patients can occur via ground or air depending on the distance needed to be traveled. Ground ambulances are common transport vehicles, because they are the least expensive to operate versus any aircraft. They offer the advantage of direct hospital-to-hospital transfer and large space for transport staff and equipment. Disadvantages included road noise and vibration and potential slow response because of road conditions including traffic and weather. Rotor wing aircraft offer fast transport in distances less than 150 miles and often can provide hospital-to-hospital transfer. Disadvantages of rotor wing aircraft include high cost of operation and limited cabin space for medical team and patients. Fixed wing aircraft are typically less expensive to operate than rotor wing aircraft. Fixed wing aircraft are typically used for distances more than 120 miles and can fly long distances. Disadvantages of fixed wing aircraft include the need for an airport to land, and thus an ambulance transfer at both ends of the flight. Review and compare the caveats of each mode of transport.
- Communication is extremely important during medical transport. As technology has improved, the ability to contact medical control in any mode of transport has become easier. The use of cell phones, radios, and even Internet-capable tablet devices offer multiple advantages. Explain the role of communication during a medical transport.
- The equipment needed for the transport of critically ill neonates and pediatric patients needs to provide the critical care found in ICUs but must be portable and lightweight. Equipment should have a long battery life or have the capability to interchange batteries while the equipment is in operation. List the specific equipment needed for pediatric transport.
- Patient assessment in the transport environment can be a challenge versus hospital-based care assessments. Use of monitors, alarm conditions, and visual assessment of the patient is very important. Demonstrate how to provide a patient assessment in a nontraditional environment.
- Safety during medical transport of neonate and pediatric patients is imperative not only for the patient but also for the medical crew. Use of red lights and siren during ground ambulance transport needs to be evaluated, because this can significantly increase the danger to the public as well as the patient and medical crew. Safe operations also must be conducted around aircraft.
- The Commission on Accreditation of Medical Transport Services (CAMTS) primarily provides accreditation of transport program services. This organization offers peer-reviewed standards vetted by multiple specialists involved in medical transport. Review safety and accreditation requirements for pediatric transport agencies.

Assessment Questions

See Evolve Resources for answers.

1. Rapid transport of a neonate or a pediatric patient with a serious illness or trauma to a specialty facility can result in which of the following?
   - **A.** Improved outcomes
   - **B.** No difference
   - **C.** Worse outcomes
   - **D.** Unknown
2. Which of the following is the single most important asset in transport?
   - **A.** Aircraft
   - **B.** Lifesaving equipment
   - **C.** Ambulance
   - **D.** Personnel
3. How many transports are typically required to justify a dedicated team?
   - **A.** 300 to 500
   - **B.** 500 to 700
   - **C.** 700 to 900
   - **D.** 1000 to 1200
4. What is the single largest expense of a transport team?
   - **A.** Personnel
   - **B.** Transport vehicles
   - **C.** Transport ventilators
   - **D.** Cardiopulmonary monitors
5. What types of alarms are preferred in transport?
   - **A.** Audible
   - **B.** Visual
   - **C.** Both audible and visual
   - **D.** None
6. Why should mechanical ventilators be used during transport?
   - **A.** Many of them offer the same level of support as intensive care unit (ICU) ventilation.
   - **B.** They help prevent hyperventilation associated with manual ventilation.
   - **C.** Monitoring of pressure, tidal volume, and minute ventilation can be achieved with appropriate alarm functions.
   - **D.** All of the above
7. Many transport teams are offering point-of-care testing with a portable blood gas analyzer for what reason(s)?
   - **A.** It reduces stabilization times and improves quality of care.
   - **B.** Many blood gas analyzers are small and battery powered.
   - **C.** It compensates for clinical assessment skills.
   - **D.** A and B
8. The simple goal of the transport team is to:
   - **A.** Transfer the patient in the most stable condition possible
   - **B.** Transfer the patient within the “golden hour”
   - **C.** Scoop and run
   - **D.** None of the above
9. According to Boyle’s law, what will the endotracheal tube (ETT) cuff pressure do when the aircraft climbs in altitude?
   - **A.** Remain the same
   - **B.** Increase in pressure
   - **C.** Decrease in pressure
   - **D.** The pilot balloon pressure will increase, but the ETT cuff pressure will remain constant
10. Every transport program should have a:
    - **A.** Rescue plan
    - **B.** Backup plan
    - **C.** Postaccident/incident action plan
    - **D.** Media coverage plan

REFERENCES

1. Martin SR. *Inter-facility Maternal Transports*. Jan. 2017/Oct. 27, 2015. https://www.uptodate.com.
2. Scott, J. Obstetric Transport. *Obstet Gynecol Clin North Am*. 2016;43(4):821-840.
3. Orr RA, Felmet KA, Han Y, et al. Pediatric specialized transport teams are associated with improved outcomes. *Pediatrics*. 2009;124(1):40-48.
4. McNamara PJ, Mak W, Whyte HE. Dedicated neonatal retrieval teams improve delivery room resuscitation of outborn premature infants. *J Perinatol*. 2005;25(5):309-314.
5. Kronick JB, Frewen TC, Kissoon N, et al. Pediatric and neonatal critical care transport: a comparison of therapeutic interventions. *Pediatr Emerg Care*. 1996;12:23.
6. Eppich WJ, Brannen M, Hunt EA. Team training: implications for emergency and critical care pediatrics. *Curr Opin Pediatr*. 2008;20:255.
7. Stroud MH, Prodhan P, Moss MM, Anand KJ. Redefining the golden hour in pediatric transport. *Pediatr Crit Care Med*. 2008;9:435.
8. National Research Council. *Emergency Medical Services: at the Crossroads*. Washington, DC: The National Academies Press; 2007.
9. Sayre MR, White LJ, Brown LH, McHenry SD. The National EMS Research strategic plan. *Prehosp Emerg Care*. 2005;9:255.
10. Brown SA, Hayden TC, Randell KA, Rappaport L, Stevenson MD, Kim IK. Improving pediatric education for emergency medical services providers: a qualitative study. *Prehosp Disaster Med*. 2017;32(1):20-26.
11. Blakeman, TC, Branson, RD. Inter- and Intra-hospital transport of the critically Ill. *Respir Care*. 2013;58(6):1008-1023.
12. Karlsen KA, Trautman M, Price-Douglas W, Smith S. National survey of neonatal transport teams in the United States. *Pediatrics*. 2011;128:685.
13. Commission on Accreditation of Medical Transport Systems. *Accreditation Standards of the Commission on Accreditation of Medical Transport System*. 9th ed. Anderson, SC: CAMTS; 2012:20.
14. Freehill KM. Critical incident stress debriefing in health care. *Crit Care Clin*. 1992;8:491.
15. Murphy M, Curtis K, McCloughen A. What is the impact of multidisciplinary team simulation training on team performance and efficiency of patient care? An integrative review. *Australas Emerg Nurs J*. 2016;19(1):44-53.
16. Akaike M, Fukutomi M, Nagamune M, et al. Simulation-based medical education in clinical skills laboratory. *J Med Invest*. 2012;59:28.
17. Scott S, Smith C, O'Connor T. A multidisciplinary approach to neonatal ambulance design. *Neonatal Netw*. 1994;13:13.
18. Kempley ST, Ratnavel N, Fellows T. Vehicles and equipment for land-based neonatal transport. *Early Hum Dev*. 2009;85:491.
19. Brink LW, Neuman B, Wynn J. Air transport. *Pediatr Clin North Am*. 1993;40:439.
20. Nish WA, Walsh WF, Land P, Swedenburg M. Effect of electromagnetic interference by neonatal transport equipment on aircraft operation. *Aviat Space Environ Med*. 1989;60:599.
21. Macnab A, Chen Y, Gagnon F, Bora B, Laszlo C. Vibration and noise in pediatric emergency transport vehicles: a potential cause of morbidity? *Aviat Space Environ Med*. 1995;66:212.
22. Sittig SE, Nesbitt JC, Krageschmidt DA, Sobczak SC, Johnson RV. Noise levels in a neonatal transport incubator in medically configured aircraft. *Int J Pediatr Otorhinolaryngol*. 2011; 75:74.
23. Korniewicz DM, Clark T, David Y. A national online survey on the effectiveness of clinical alarms. *Am J Crit Care*. 2008;17:36.
24. Bouchut, JC, Van Lancker E, Chritin V, Gueugniaud PY. Physical stressors during neonatal transport: helicopter compared with ground ambulance. *Air Med J*. 2011;30(3):134-139.
25. Donoghue, AA, Hsieh TC, Myers S, Mak A, Sutton R, Nadkarni V. Videographic assessment of cardiopulmonary resuscitation quality in the pediatric emergency department. *Resuscitation*. 2015;91:19-25.
26. Niebauer JM, White ML, Zinkan JL, Youngblood AQ, Tofil NM. Hyperventilation in pediatric resuscitation: performance in simulated pediatric medical emergencies. *Pediatrics*. 2011;128(5):e1195-e1200.
27. O'Neill JF, Deakin CD. Do we hyperventilate cardiac arrest patients? *Resuscitation*. 2007;73:82.
28. Di Serio F, Petronelli MA, Sammartino E. Laboratory testing during critical care transport: point-of-care testing in air ambulances. *Clin Chem Lab Med*. 2010;48(7):955-961.
29. Macnab AJ, Grant G, Stevens K, Gagnon F, Noble R, Sun C. Cost benefit of point of care blood gas analysis vs. laboratory measurement during stabilization prior to transport. *Prehosp Disaster Med*. 2003;18:24-28.
30. Kost GJ, Sakaguchi A, Curtis C, Tran NK, Katip P, Louie RF. Enhancing crisis standards of care using innovative point-of-care testing. *Am J Disaster Med*. 2011;6:351.
31. Reimer-Brady JM. Legal issues related to stabilization and transport of the critically ill neonate. *J Perinat Neonatal Nurs*. 1996;10:59.
32. Raszynski A. Aviation physiology and international transport of infants and children. *Int Pediatr*. 1999;14:99.
33. McAdams RM, Dotzler SA, Pole GL, Kerecman JD. Long-distance air medical transport of extremely low birth weight infants with pneumoperitoneum. *J Perinatol*. 2008;28(5):330-334.
34. Steinhorn RH. Therapeutic approaches using nitric oxide in infants and children. *Free Radic Biol Med*. 2011;51(5):1027-1034.
35. Hill KD, Lim DS, Everett AD, Ivy DD, Moore JD. Assessment of pulmonary hypertension in the pediatric catheterization laboratory: current insights from the Magic registry. *Cathet Cardiovasc Interv*. 2010;76(6):865-873.
36. Lowe CG, Trautwein JG. Inhaled nitric oxide therapy during the transport of neonates with persistent pulmonary hypertension or severe hypoxic respiratory failure. *Eur J Pediatr*. 2007;166(10):1025-1031.
37. Kinsella JP, Griebel J, Schmidt JM, Abman SH. Use of inhaled nitric oxide during interhospital transport of newborns with hypoxemic respiratory failure. *Pediatrics*. 2002;109:158.
38. Ratnavel N. Safety and governance issues for neonatal transport services. *Early Hum Dev*. 2009;85(8):483-486.
39. O'Brien DJ, Price TG, Adams P. The effectiveness of lights and siren use during ambulance transport by paramedics. *Prehosp Emerg Care*. 1999;3:127.
40. Bigham BL, Buick JE, Brooks SC, Morrison M, Shojania KG, Morrison LJ. Patient safety in emergency medical services: a systematic review of the literature. *Prehosp Emerg Care*. 2012;(16):20-35.
41. King BR, Woodward GA. Pediatric critical care transport—the safety of the journey: a five-year review of vehicular collisions involving pediatric and neonatal transport teams. *Prehosp Emerg Care*. 2002;6:449.
42. Marques-Baptista A, Ohman-Strickland P, Baldino KT, Prasto M, Merlin MA. Utilization of warning lights and siren based on hospital time-critical interventions. *Prehosp Disaster Med*. 2010;25(4):335-339.

Home Care

35

Lauren Perlman

Outline

Learning Objectives

After reading this chapter the reader will be able to:

1. Discuss the critical components of a discharge plan for the child who is respiratory technology dependent.
2. Recognize barriers that may delay the hospital discharge of a child who is respiratory technology dependent.
3. Compare the three types of oxygen systems available for use in the home.
4. Describe the procedure used to attach the apnea–bradycardia monitor and the scenarios in which a monitor is indicated.
5. List the essential components of a trach-to-go bag.
6. Recognize the need for decannulation and changing the tracheostomy tube.
7. Discuss how caregivers are best prepared in caring for a ventilator-dependent child at home.
8. Discuss the considerations needed in selecting the home ventilator and the home medical equipment provider.

Key Terms

decannulation
discharge planner
durable medical equipment (DME)
home assessment
Medicaid
plan of care

Advances in pharmaceuticals and medical devices have made it possible for parents and health care professionals to care for infant and pediatric patients who are technology dependent. Today an unprecedented amount of that medical care is being provided in the child's home. The reasons are many for this shift toward care at home. Medical equipment is now more portable and better able to accommodate home care needs. There is also the ever-increasing pressure to reduce health care costs and shorten hospital stays by expediting the transition from hospital to home. Perhaps most important is the growing belief that prolonged hospitalizations have a negative impact on the development of infants and children, and therefore the home is the optimal setting for a medically stable, technology-dependent patient.[1]

In 1981 the move toward caring for technology-dependent children at home caught national attention when, during a press conference, President Ronald Reagan cited the case of 3-year-old Katie Beckett. Katie

had been hospitalized since she was admitted at 3 months old with viral encephalitis. Regulations at that time mandated that she remain in the hospital for **Medicaid** to cover her medical bills. Two days after that press conference, the Secretary of Health and Human Services waived the rules that were preventing Katie from being discharged to her home, where she could be treated far less expensively. Only a few months after that, a waiver program was established that enables a child living at home to receive Medicaid-funded long-term care services. That program remains in place today and is often referred to as the *Katie Beckett waiver.*[2]

DISCHARGE PLANNING: THE DECISION TO GO HOME

Discharge planning is defined as a plan for a patient's continuum of care during transition to home or another facility. Upon arrival, neonatal and pediatric intensive care facilities are moving toward planning for discharge to an alternative site of care.

Alternative sites may include the child's home, foster care, long-term care facilities, and hospice care. The intent for discharge planning is to reduce the hospital stay, which minimizes medical costs and risk of additional infection. These infections could include ventilator-associated pneumonia (VAP), methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant enterococci (VRE).

Central to the discharge planning process is a multidisciplinary team of health care professionals who work together to establish an appropriate discharge plan (Box 35-1). Extensive collaboration between the team and the parents is necessary to ensure that discharge planning is achieved properly.[3] This team of health care professionals may include a medical staff member designated to assist in the discharge planning, social worker, physician on-service in unit, and postdischarge physician, as well as private duty nursing (PDN) services and, if applicable, insurance case management. Another important role is provided by the **durable medical equipment (DME)** provider. Durable medical equipment is the medical equipment used by patients in the home or in a facility to aid in providing a better quality of living. Additional team members may also include the occupational therapist, physical therapist, respiratory therapist, and speech therapist. All these members are integral parts of the team and are helpful in establishing the home plan of care.

Box 35-1 Multidisciplinary Health Care Professional Team Members Involved in a Discharge

1. Discharge planner
2. Social worker
3. Physician (on-service in unit)
4. Postdischarge physician
5. DME provider
6. PDN services
7. Insurance case management
8. Occupational therapist
9. Physical therapist
10. Respiratory therapist
11. Speech therapist

DME, Durable medical equipment; *PDN*, private duty nursing.

Before making the decision to provide home care for a child dependent on technology, a discharge plan is developed.[4] This plan is often referred to as a **plan of care,** which is defined as a written and detailed plan implemented to meet the medical needs of the patient. Critical components of this plan of care include the following:

- Social: Assessment of patient and family needs as well as identification and education of in-home caregivers.
- Financial responsibility: Assessment of available financial resources, such as private insurance versus state Medicaid programs. A Medicaid program is a health insurance plan provided by the state and federal government for qualifying low-income individuals and families.
- **Home assessment:** An evaluation of the home environment in which a ventilator-dependent child is to reside.
- Providers in home: Identification and availability of medical equipment and health care resources.
- Communication: Open communication between the parent and caregivers and the discharge planning team.
- Barriers: Recognition of barriers that may delay the discharge home.

PATIENT AND FAMILY ASSESSMENT

The entire discharge planning team should meet and assess the needs of both the child and family. Before the discharge home, the child must be medically stable and receiving optimal ventilatory, nutritional, and developmental support.[5] Assessment includes evaluation of the family's ability, availability, and commitment to care for their child as well as a psychosocial assessment for parenting risk factors that could potentially result in adverse outcomes.[6] Limitations, including language, physical, and cognitive, may delay discharge until appropriate support can be provided to the family to help overcome these barriers.

The family's involvement is critical to the health and well-being of the child.[7] Involvement of bedside care is critical for the parent or caregiver so that a "norm" can be established. Involvement may include tracheostomy changes, following established feeding regimens, and evaluation of alarms that may occur. Additional time is required for the DME provider to conduct caregiver training regarding equipment and supplies needed in the home. After training is

complete, the parent or caregiver should be able to return demonstration of the equipment by explaining usage and cleaning procedures. All progress on training must be reported back to the discharge planning team. The private duty nursing agency must also meet with the family to familiarize himself or herself with the caregiver, patient, and plan of care.

Checklists have been found to be a useful tool so that all discharge planning team members may see the status of the parent or caregiver skill base. Some facilities use contracts with caregivers to outline expectations in the home.

IDENTIFICATION AND EDUCATION OF IN-HOME CAREGIVERS

In most situations at least two people, usually the parents, are identified as the primary caregivers. These caregivers must have the ability and commitment to learn and actively participate in the child's care at home. The educational component of the discharge plan includes training not only the primary caregivers but also any other individuals who identify themselves as a support person for the child (i.e., grandparents, extended family, and close friends) and even the child to the greatest extent possible. Because there are many aspects to consider as part of the discharge planning process, the DME provider begins the training of home care equipment and supply at the time the referral is made. This is done to ensure that all necessary paperwork, insurance verifications, and home assessments are completed. Also, a planned emergency escape route from the home will need to be discussed with the caregiver.

All education, whether knowledge or skill based, must be consistent and at the level of understanding of each participant.[9] The level of care that parents of technology-dependent children are expected to provide is far beyond that normally expected of parents. Mastery of the skills requires both material knowledge and practical experience. Training should be provided by an experienced professional who can also recognize unvoiced needs of the primary caregivers. A training manual that includes a detailed checklist is a useful tool to organize the required skills and help avoid missing any essential steps. It also assists in providing consistent education while serving as a resource for the caregivers (Box 35-2). Because most individuals obtain more information by actually performing procedures, it is imperative that the caregivers be given the opportunity to perform hands-on care with the child in a controlled hospital environment. With the hospital staff assuming a supportive role, the caregivers should provide as much hands-on care of the child as possible. Participating in mock scenarios also provides opportunities to problem solve and practice skills and emergency techniques.[10]

Box 35-2 Essentials of a Home Care Training Manual

- Basics of anatomy and physiology
- Orientation checklist
- Supply list of equipment and supplies
- Special care procedures (tracheostomy care cleaning, emergency procedures)
- Equipment manuals

Caregivers, especially those with children who require a tracheostomy or ventilator, are required to participate in an in-hospital trial or rooming-in period in which they are responsible for the total care of their child. The goal of this period is to build confidence in their ability to care for their child while also offering an opportunity for backup assistance and coaching. While rooming-in, the caregivers are responsible for all routine care (i.e., feeding, bathing, dressing), respiratory care (i.e., treatments, ventilator checks, suctioning), medication delivery, equipment cleaning and troubleshooting, and arranging for relief periods with cocaregivers. Before discharge, they must have demonstrated knowledge and competency as well as be independent in successfully handling all aspects of their child's care.[11-13]

FINANCIAL RESOURCES

In today's managed care arena, high cost and inadequate funding of care are usually the major obstacles to providing quality care at home. Funding necessary to provide long-term care to the technology-dependent child varies, depending on the complexity of care required, the level of parental capability, and responsibilities the parents may have (e.g., other children, work outside the home). Although home care costs are usually less than the cost for care in the hospital, parents often find that their insurance does not cover 100% of the cost at home as it did in the hospital. These nonreimbursable costs may be for home equipment and supplies, transportation to and from the hospital and clinics, and even changes made to the home to accommodate the child and equipment. Inadequate reimbursement creates a financial hardship for families and may be cause for DME providers and nursing agencies to refrain from providing services to the child. Limited payment for home care equipment and personnel has in many cases limited the scope and practice of mechanical ventilation in the home and delayed discharge for months. This has led professional societies to work together to create expert guidelines for mechanical ventilation outside the intensive care unit.[14]

Because professional care can be costly, it is essential to establish a solid financial plan to fund this care long before discharge. It should be determined early whether the insurance policy has a limit on medical equipment, supplies, and home care resources. The funding source must cover the cost of equipment,

supplies, and professional services, such as skilled nursing and physical, occupational, and speech therapies. In most cases, insurance will fund these needs as long as the patient meets the criteria of medical stability and the physician certifies a plan of care and completes a certificate of medical necessity. There should be continued communication with the child's insurers. A case manager is usually assigned by the payer to monitor care and ensure it is cost effective. Notifying the case manager early in the discharge process is essential to maximize the available dollars. In many cases, the home medical equipment provider is the expert on reimbursement for home medical supplies.[15,16]

HOME ASSESSMENT

Depending on the home equipment needed, an on-site evaluation of the patient's home may be required before discharge to address any concerns or problems in the home environment. The evaluation includes assessment of the physical space, electrical capabilities, heating and cooling system, in-house water supply, availability of 24-hour telephone access, and geographic location of the home (Box 35-3). With many modern families only having cellular phones and financial limitations restricting some families' access to landlines, the DME and PDN companies meet many limitations regarding communication with caregivers. It is best to address these issues early in the discharge planning process so that adequate time is available to make any necessary changes.

It is essential that the house be fully accessible for the child and the home care staff. There must be enough room for the child and equipment to be easily moved in and out of the home. Children who are ventilator dependent ideally need a bedroom of their own so that family members are not disturbed by the care needed during sleep or the nursing staff. The bedroom must be large enough to accommodate the medical equipment as well as a comfortable chair for the nurse to use. An area for supplies and equipment storage should be designated and counter space made available for cleaning small equipment and reusable items. The room must be climate controlled, with proper ventilation, and free of drafts. The amount of medical equipment in the room can cause a small room to heat up quickly, and some mechanical ventilators will shut down if the temperature exceeds a certain level.

The electrical circuitry of the home must be evaluated to determine whether there are a sufficient number of grounded electrical outlets to provide safe operation of the equipment. Because multiple pieces of equipment may be running simultaneously, the household circuitry must support the total amperage of the equipment to be supplied. If not, another circuit breaker must be installed.

Box 35-3 Checklist for Home Assessment

- Adequate electrical power and wiring
- Appropriate heating and cooling system
- Working smoke detectors
- Satisfactory lighting
- Sufficient space in bedroom for equipment
- Counter space to clean equipment
- Storage space for equipment
- Ample physical space for nurse or caregiver to work
- Door sizes to accommodate child and equipment entry
- Steps or wheelchair ramps to access home
- Telephone service to initiate 911 service
- Emergency escape route planned
- Fuse/breaker box labeled

DURABLE MEDICAL EQUIPMENT AND SUPPLY

Durable medical equipment includes any product or device (Box 35-4) that is used by patients in the home or in a facility to aid in providing a better quality of living. The equipment required depends on the child's medical condition. The company that supplies this equipment is referred to as the *DME provider.* Additional equipment may be needed at each site that the child attends (i.e., daycare, school). Equipment that will be used at home should be used in the hospital first so that caregivers can become familiar and proficient with its use. Any differences in its use at home should be addressed before discharge.[8]

When selecting a DME provider, the following must be considered:

1. *Does the provider supply all the equipment needed?* Many providers are no longer supplying apnea monitors. It may also prove difficult to find one that provides tracheostomy and ventilator supplies.
2. *Does the provider have a contract with the child's health care insurer, or is it considered out-of-network?* Caregivers are required to pay much less for the equipment and supplies when an in-network provider is selected.
3. *Does it employ respiratory therapists who are trained to provide the patient or caregiver with education, psychosocial support, and physical assessment needed for children who require specialized respiratory equipment and supplies?*

Box 35-4 Examples of Durable Medical Equipment

1. Air compressor
2. Oxygen concentrator
3. Mechanical ventilator
4. Continuous positive airway pressure systems
5. Bilevel positive airway pressure systems
6. Wheelchairs
7. Infusion pumps
8. Suction machines
9. Pulse oximeter
10. Apnea bradycardia monitor

4. *Does it provide service to the area in which the child lives?* It is essential that the selected DME provider have a pediatric staff that is available for consultation and emergency coverage 24 hours a day, 7 days a week.

HOME CARE PERSONNEL AND COMMUNITY RESOURCES

Home care involves cooperation and collaboration between the hospital and the home nursing and community services. The visiting nurse or home care agency that will be supporting the child at home is contacted before discharge and given therapy and medication regimens, a follow-up appointment schedule, and instructions on general care of the child. These instructions include recognizing signs that would indicate the child is becoming ill and how to seek medical help. Acknowledgment of the parents as experts in the care of the child is an essential point during the education of the nursing and DME providers. Some caregivers may even choose to assist in teaching the home care staff about the needs of their child. Home care nurses must be educated on use of the medical equipment that will be in the home. This training is most often made available by the DME provider. If the child is of school age, the teachers and school nurse also need to understand any special needs and limitations the child may have. Respite services and emergency staffing in case the caregiver is ill should also be included in the discharge plan.[8]

Before discharge, a primary care provider is identified and an initial appointment scheduled. It is imperative that the designated primary care provider be one who is agreeable to caring for a technology-dependent child. Not every physician is willing to assume responsibility for a medically fragile child who is moving into the home environment. Unfortunately, failure to obtain a primary care provider can delay discharge home. Appointments for follow-up care with each physician specialist (e.g., surgery, pulmonary, otolaryngology) should also be arranged before discharge, with every effort made to schedule the appointments together on the same day. This not only decreases the burden on the family but has also proven to improve compliance. Each family is given a telephone list that includes the office and emergency phone numbers of the child's physicians and community resources (Box 35-5).

Public awareness is a vital part of the technology-dependent child's acceptance back into the community. The local utility company must be informed that for medical reasons the child is dependent on electricity. This information is provided through a letter signed by the physician. Having the letter on file allows the company to make it a high priority to restore electricity to the home in the event of a power outage and may even qualify the family for a discounted rate. A similar letter stating that the child needs a functioning communication system is sent to the telephone company. The water and sewage company as well as the local emergency medical service providers are also contacted and provided with information concerning the child's medical condition. Some emergency medical service or volunteer departments have little or no experience in caring for a child with a tracheostomy or who is ventilator dependent. In that case special training should be arranged and a plan developed for the child's needs before discharge. Such community awareness allows for a smooth transition from the hospital to the home and to the school environment.

Box 35-5 Health Care and Community Resources Telephone List

The resource telephone list should include phone numbers for the following:

- Listing of physicians involved in care, including specialties
- Hospital to which patient would be transported in case of emergency
- Pharmacy
- Durable medical equipment provider
- Private duty nursing agency
- Therapies: occupational, physical, speech
- School and daycare
- Insurance contact
- Utility companies

COMMUNICATION WITH THE DISCHARGE PLANNING TEAM

When parents are overwhelmed by the uncertainty of their child's condition and future, they often develop unrealistic expectations of outcomes, time frames, and discharge dates. Open communication with the discharge planning team is key to providing a successful discharge home and preventing readmission to the hospital. The purpose of the initial meeting is often simply to determine whether home care is suitable and manageable for the child. Patient care conferences in which the family and the discharge planning team candidly discuss the needs of the child and what they will face at home should continue at strategic points during the discharge process. These conferences provide an opportunity for the family to meet the home health providers, including nurses and respiratory therapists, and to voice any questions or concerns they may have. The meetings should focus on establishing the needs of the family and the child as well as providing a detailed plan for discharge and discussing any problems that may affect its success. It is during these meetings that the home care therapist clarifies the time frame in which training and equipment setup must be completed. Because the child's and family's needs often change over time, this also provides an opportunity to review the family's needs, how they are managing, and progress toward the home care goals.[8]

BARRIERS THAT DELAY DISCHARGE

Many technology-dependent children remain hospitalized for extended periods even though they are considered medically stable. Unfortunately, it is often a nonmedical reason that delays the discharge. These barriers may include the inability to obtain a safe home environment or alternative care site, lack of financial resources, or uncooperativeness within the family. Diverse sociocultural backgrounds, including problems stemming from language, can impact communication and the learning needs of the caregivers. Delays in obtaining medical equipment or a provider for the equipment will in turn delay beginning the education for the caregivers. Other barriers to discharge include the inability to provide home nursing or community resources as well as failing to identify all pertinent problems or needs.[4,17-19]

OXYGEN THERAPY AT HOME

Unlike adults, in whom measurement of the arterial partial pressure of oxygen is considered critical, the need for home oxygen therapy for infants and children is established on the basis of oxygen saturation as measured by pulse oximetry.[1,20] Although some children will require oxygen for many years, the majority who are discharged home with oxygen need it for a limited period. Eventually they will require it only at night, and then wean off completely.

The three types of oxygen systems available for the home environment are liquid oxygen, oxygen concentrators, and compressed oxygen cylinders. Selection of the system is commonly the responsibility of the DME provider. Regardless of the type of oxygen system provided, it is essential that the DME provider be advised of the specific flow rate the child requires. This will determine which flow meter to use with the system. Although there are flow meters available that provide "microflows" with readings as low as 0.025 L/minute, some clinicians do not advocate using them. When weaning from oxygen begins, most infants are decreased to 0.1 L/minute and do not require lower flows before going to room air. There is also some concern that a caregiver could become confused by the decimal points and inadvertently administer the incorrect flow.[20]

Before discharge home, the child's caregivers must receive the oxygen equipment and successfully complete training in its use. If the child attends daycare or school, then arrangements should also be made to instruct responsible staff and teachers in use of the equipment.

LIQUID OXYGEN SYSTEM

The liquid oxygen system consists of a base unit reservoir and a small, portable canister used for patient transport (Figure 35-1). The canister weighs 8 to 10 lb and is carried with a shoulder strap or rolling cart. When the canister becomes empty it is refilled from the base unit. The base unit has a flow meter that can deliver oxygen at low to high flow rates.

FIGURE 35-1 Stationary liquid oxygen (LOX) system with a portable system capable of being refilled by the patient or family. (Image used by permission from Nellcor Puritan Bennett, LCC, Boulder, CO, part of Covidien and Paul Bowen Photography.)

Advantages to this system are that no electricity is required and little noise is produced. Also, some caregivers prefer to use the canister for transport rather than an oxygen cylinder. A disadvantage to using this system is that the base unit requires regular refilling by the DME provider. Frequency depends on both the oxygen flow rate and the size of the reservoir and can be as often as once a week to every other month. Another disadvantage to the liquid oxygen system is that it vents continually to prevent pressure from building within the reservoir, resulting in a loss of oxygen regardless of whether the flow is on or off. Caregivers must therefore be reminded that liquid oxygen will evaporate and portable units should be checked for contents and filled just before use. Many insurers will no longer afford the patient liquid oxygen because of the cost to maintain it in the home setting.

OXYGEN CONCENTRATORS

First produced in the 1960s, the oxygen concentrator is an electrical device capable of separating oxygen from nitrogen in room air, collecting the oxygen, and then dispensing it through a flow meter (Figure 35-2).[21,22] Most concentrators provide greater than 90% oxygen. On some concentrators the flow meters can be changed to provide low flow rates (Figure 35-3), whereas others

FIGURE 35-2 Oxygen concentrator. (Courtesy AirSep, Buffalo, NY.)

FIGURE 35-3 Close-up view of the low-range flow meter on an oxygen concentrator. (Courtesy AirSep, Buffalo, NY.)

have dual flow meters to accommodate the varied needs of the patient (Figure 35-4). The DME provider needs to evaluate each concentrator's specifications before use with pediatric patients to ensure it can be used with low flows. When using concentrators, oxygen cylinders are provided for the patient to use for transport and for backup in the case of an electrical power outage.

FIGURE 35-4 Oxygen concentrator with dual flow meters set at different flow rates. (Courtesy AirSep, Buffalo, NY.)

As long as there is an electrical source, an oxygen concentrator provides an unlimited supply of oxygen and does not need to be refilled. It can be easily moved from room to room and requires minimal maintenance. However, the concentrator's motor may produce additional heat and noise. Caregivers may notice that use has resulted in an increase in their monthly electrical bill. Portable oxygen concentrators (POCs) are available both for land use and for flight. Currently the maximum flow rate for continuous oxygen delivery from a POC is 3 L/minute. Continuous oxygen flow is required for administration of oxygen into a ventilator system as well as to younger infants and children who cannot initiate oxygen flow from a pulse-flow type of device.[54]

OXYGEN CYLINDERS

A compressed gas cylinder is usually made of seamless aluminum or fiberglass so that it can be as lightweight as possible. Oxygen cylinders are considered a cost-effective method of providing oxygen because they do not require electricity and can be stored for a long period without leakage. The major disadvantages of cylinders are the storage space required and the potential safety hazards as a result of the gas being contained under high pressure. Although the cylinders are smaller, they may still seem a bit more bulky than the liquid oxygen canister.

Portable cylinders are available in a variety of sizes and are identified by letter designations. At one time the E cylinder was the smallest available in portable

cylinders, making liquid oxygen the number one choice for pediatric patients. Today, however, compressed gas cylinders are gaining in popularity thanks to the availability of smaller cylinders with custom carrying cases and regulators that allow flows as low at 1/32 L/minute. This is ideal for patients who are graduates of the neonatal intensive care unit (NICU) and need the smallest amount of flow.

APNEA–BRADYCARDIA MONITORS

An apnea–bradycardia monitor, more commonly referred to as an *apnea monitor,* is a portable machine that noninvasively monitors an infant's respiratory rate and heart rate. When there is apnea beyond a preset time limit, or when the infant's heart rate falls below or exceeds preset limits, an alarm will sound to notify the caregivers. Rather than being purchased by the caregiver, an apnea monitor is usually rented from a DME provider, because they are usually only needed for a short time. There are various apnea–bradycardia monitors that also incorporate a pulse oximeter.

For effective monitoring, monitors should be equipped with an event recorder that is able to capture and store cardiopulmonary events. The events are provided in a printout, commonly known as a *download.* Downloading is the process by which the information stored in the monitor is retrieved. At one time, the DME provider could perform a download for the information over the phone. This would require a hard-wired phone line or landline to download the appropriate software via a modem from the DME provider. With most people using cellular phones and no longer having a hard-wired phone, the option of downloading via modem is obsolete. This requires the DME provider to go to the patient's home or physician's office and complete the download with a direct connection. A laptop is used to store the information, which is then sent on to the physician. The download contains a printout of waveforms; a log of the events, including the frequency of alarms and how low the heart rate dropped; and the frequency of monitor use. The information obtained can be used to distinguish the type of apnea, decide the type of medical treatment needed, and determine compliance and when to discontinue the monitor. If a child lives a long distance from the DME provider, a second monitor may be placed in the home for convenience of the DME provider and is not usually covered by the insurance. To have consistent, consecutive data when downloading the memory, it is recommended that only one monitor be used and the other kept solely for backup in case of monitor malfunction.

MONITOR PLACEMENT

An apnea monitor may be considered medically necessary for infants who meet the following conditions:

- Have apnea of prematurity, which is defined as documented episodes of periodic breathing that result in prolonged apnea (20 seconds or greater) or bradycardia (heart rate less than 80 beats/minute). Because the neurologic breathing control mechanisms may not have matured by the time a newborn is ready for discharge home, an apnea monitor may be required to monitor the infant when a caregiver is not in constant attendance. It is up to the physician to decide when the monitor is no longer needed.
- After receiving caffeine for treatment of apnea or bradycardia. The monitor is considered medically necessary until the infant is event free for 2 weeks after the medication is discontinued.[53]
- Have experienced an apparent life-threatening event (ALTE), which is defined as an episode characterized by a combination of apnea, color change, choking, gagging, or muscle tone change that required mouth-to-mouth resuscitation or vigorous stimulation. The monitor is used until the infant is event free for 2 to 3 months.
- Have pertussis with positive cultures. The monitor is used for 1 month after the diagnosis.
- Are diagnosed with gastroesophageal reflux disease accompanied by apnea, bradycardia, or oxygen desaturation. The monitor is indicated until the infant is event free for 6 weeks.
- Have neurologic or metabolic disorders affecting respiratory control.
- Have chronic lung disease and require noninvasive or invasive ventilatory support.
- Have two siblings who died of sudden infant death syndrome (SIDS). These infants may be monitored until they have remained event free and are 1 month older than the age at which their siblings died. Because there is no proof that apneic episodes are related to SIDS, the American Academy of Pediatrics (Elk Grove Village, IL) released a policy statement in 2003 that does not recommend apnea monitoring in infants with only one SIDS sibling.[23] However, this diagnosis is not usually covered by insurance.

Although an apnea–bradycardia monitor may be a helpful adjunct to monitoring an infant requiring mechanical ventilation, use of this monitor is redundant, and caution should be advised when interpreting alarm conditions. The reverse is also true: As long as heart rate is maintained and minimal chest excursion occurs, the alarm on the monitor will not be activated. However, this does not necessarily indicate that the ventilator is functioning properly. An infant with a tracheostomy is often prone to mucous plugging or **decannulation.** During these potentially life-threatening events, the apnea alarm will not be activated as long as the infant can struggle against an occlusion in the tracheostomy tube or breathe through an open stoma after accidental decannulation. Likewise, the bradycardia alarm usually becomes activated late during this type of event. When monitoring an infant with a tracheostomy, the clinician and parents must be aware

of the potential hazards and the limitations of the monitor.

CAREGIVER EDUCATION

The DME provider usually trains the parents in the use and care of the monitor. Parents are instructed to use the monitor whenever the infant is sleeping (naps and at night), when riding in the car, and anytime the infant is not being held or closely watched. To monitor the infant, electrodes are either stuck on the infant's chest or held in place with a soft belt and the heart rate and respiratory pattern are measured by means of a method known as *impedance pneumography* (Box 35-6). The monitor should be placed on a table near the infant, not on the floor, and at least 1 foot away from electrical devices such as televisions, air conditioners, telephones, electric water bed heaters, nursery monitor intercoms, oscillating fans, and humidifiers. Interference from these devices, although uncommon, may affect the monitor's performance. If items (e.g., diapers, toys) are near the monitor, they should be placed so that they do not block the displays or muffle the alarms. Caregivers should be advised not to allow the infant to sleep with adults, children, or pets at any time while being monitored, because their movement may prevent the monitor from working properly. Parents should check daily that the monitor's alarms sound by disconnecting the leads from the infant. They should also perform a daily inspection of the electrodes, lead wires, and power cords as well as a cleaning procedure. A logbook should be provided for parents to record the date and time of all events, unique observations about the monitor, and any intervention required (i.e., stimulation, resuscitation). The hook-and-loop belt can be washed by hand in soapy water, rinsed well, and hung to air dry. Moving the patches just slightly can help minimize skin irritation. The belt should be tight enough to fit only one finger between the belt and the infant's chest. If the belt is too loose, signals for breathing and heart rate will not be picked up and may result in frequent loose lead or false alarms. If the belt is too tight, it may interfere with the infant's breathing. Powder, oil, and lotion can disrupt the monitor's conduction and result in false alarms. If skin irritation becomes an issue, the parent should contact the referring physician for directives. Unless traveling outside the home, the apnea monitor should be plugged into an electrical outlet so that the batteries can remain fully charged.

Education for parents also includes infant cardiopulmonary resuscitation (CPR) and recognizing the signs of apnea. Parents should be instructed to respond to alarms by turning on the light if the room is dark and immediately checking the infant for signs of breathing. If the infant is breathing and skin color is good, parents should check the electrode placement, lead wires, and cable. If the infant is pale, cyanotic, or not breathing, stimulation is immediately required. It is essential that parents be taught not to shake their infant as a form of stimulation, because vigorous shaking may result in severe head and neck injury and even death. If the infant does not respond, then cardiopulmonary resuscitation (CPR) is indicated immediately. Any time CPR is performed, the infant should be seen immediately by a physician.

Most monitors have built-in algorithms that differentiate precordial movement from chest wall movement, but false alarm conditions are common. The most common reason for a false alarm is shallow breathing. An infant may be having abdominal breathing, and the chest wall is not moving enough to be recognized as a breath. Lead wires that connect the electrodes to the monitor can become loose during vigorous infant activity, often resulting in false alarms. There is an increased chance of obtaining false alarms when the infant is playing, burping, being fed, and moving. Other causes of false alarms are crying, the Valsalva maneuver, incorrect lead or belt placement, poor skin contact, broken lead wires, and a low battery. Although there is no way for a parent to distinguish between a real and a false alarm when it initially sounds, especially if the infant is breathing by the time the parent arrives, information obtained from a download will include the amount of time the infant did not breathe and what the heart rate was at that time. The download can allow for differentiation between real apneas and loose lead wires, because there is an abrupt drop in the heart rate with a loose lead wire instead of the gradual drop that occurs with a true apneic event.

Changes in heart rate may be the source of annoying intermittent alarms for which a cause is difficult to find. Usually this is from an apneic episode that may not be long enough to alert the parents of apnea but

Box 35-6 Lead Placement for Apnea Monitors

1. Wash and dry infant's chest. Do *not* use lotions, oil, or powders.
2. Connect electrodes to lead wires, making sure metal tips of lead wires are pushed all the way in.
3. Place foam belt on a flat surface, then place infant's back on the belt. Line the belt up with infant's nipples.
4. Position electrodes on belt (smooth side up) with each electrode under an armpit lined up with infant's nipples. White lead is on the infant's right side, *not* the caregiver's right (hint: "White is Right") and black is on the infant's left side, *not* the caregiver's left.
5. Wrap belt around infant's chest and fasten with the hook-and-loop tab. Check belt to make sure it is tight, so caregiver can fit only one finger between belt and infant's chest wall. Belt may be shortened by cutting it.
6. Connect lead wires to patient cable. White lead goes to cable for right arm (marked *RA*). Black lead goes to cable for left arm (marked *LA*).
7. Turn monitor to "ON."

that causes the heart rate to decelerate and briefly activate the bradycardia alarm. A rare cardiac arrhythmia may also cause a similar situation. Proper settings to minimize false alarms are important, because parents become conditioned to most alarms being false. They must be constantly reminded of this phenomenon and encouraged not to delay in responding to the monitor when it alerts them.

PULSE OXIMETERS

The pulse oximeter is used for continuous monitoring as well as "spot checks." Its use in the home is indicated for infants and children who require continuous oxygen therapy and whose oxygen need varies from day to day or with activities, including feeding, sleeping, and playing. By monitoring the oxygen saturation, the caregiver has the ability to increase or decrease the oxygen flow rate to maintain a specific oxygen saturation range.[1] Use of a pulse oximeter may also be indicated during the process of weaning from oxygen therapy and to monitor infants and children who have a tracheostomy or are using mechanical ventilation at home. Both the variation in oxygen saturation and heart rate may alert the caregiver of the patient's need for attention. Alarm parameters should be discussed with the patient's caregivers with implications of each. The oximeter probe placement should be assessed on a regular basis to protect the patient from skin irritation. Potential inaccuracies associated with oximeter readings may result from poor perfusion and excessive movement of the child.[24]

A CHILD WITH A TRACHEOSTOMY

Although children receive a tracheostomy for a variety of medical conditions, there are three primary indications for placement: to provide a stable airway for children with upper airway obstruction, to provide an interface for long-term invasive mechanical ventilation, and to allow for more effective pulmonary toilet in children with excessive secretions or aspiration. Placement of a tracheostomy in a child may be a lifesaving maneuver, but it has a significant impact on the family as well as on socialization and health of the child. Parents are concerned that they will never hear their baby cry or their child speak. Because of the small diameter of the infant and pediatric tracheostomy tube, there remains the potential hazard of airway obstruction, and the child requires constant observation. To minimize this risk, adequate humidification, effective suctioning, CPR, tracheostomy care with regular tube changes, and decannulation are essential components of home care management. Because there is little research to guide the care of a child at home with a tracheostomy, in the absence of scientific data many recommendations are based on consensus, the care performed in the hospital, and local clinical practice.[25] Unfortunately, many times procedures are determined by insurance coverage policies when payment limits the type and amount of supplies that will be reimbursed.[26]

At least two family members—usually the parents—must be identified as primary caregivers, and education should begin as early as possible. Caregivers must understand basic airway anatomy, recognize the signs of respiratory distress, and demonstrate how to respond to an emergency. They must also be able to demonstrate proper use of the home medical equipment (Box 35-7), suctioning technique, how to clean and change out the tracheostomy tube, and proper placement and care of the speaking valve. The DME provider will educate the caregivers on the respiratory and tracheostomy equipment. The hospital staff will provide the remaining education. Caregivers are encouraged to frequently visit the hospital and to participate in as much of their child's bedside care as possible. A child with a tracheostomy must have emergency supplies readily available at all times. An emergency bag, or trach-to-go bag, should accompany the child at all times (Box 35-8). The contents of this bag should not be used at the bedside but instead used only when the child is away from the home. Caregivers must attend a CPR class that includes training with an emphasis on emergency management of the airway and tracheostomy tube. They must be able to

Box 35-7 Home Medical Equipment and Supplies Needed for a Child With a Tracheostomy

- Self-inflating manual resuscitation bag
- Oxygen supplies
  - Stationary and portable oxygen supply systems
  - Oxygen tubing and bleed-in adapters
- Heated humidifier with a tracheostomy collar (to use at night)
- Air compressor or high-pressure concentrator to power humidifier
- Heat and moisture exchangers (to use during day)
- Suction supplies
  - Portable and stationary suction machines
  - Suction collection canister and connecting tubing
  - Suction catheter kits
  - Single-dose normal saline units
  - Sterile water
  - Gloves
- Tracheostomy supplies
  - Tracheostomy tubes: current size
  - Tracheostomy tubes: next smaller size
  - Tracheostomy ties: hook-and-loop or twill tape
  - Cotton-tipped applicators or gauze
  - Tracheostomy cleaning kits
  - Water-soluble lubricant
- Disinfectant solution
- Monitoring systems
  - Pulse oximeter (optional)
  - Apnea monitor (optional)

Box 35-8 Contents of a "Trach-to-Go" Bag

- DeLee suction trap to use if suction machine fails
- Suction catheters and gloves
- Small bottle of sterile water for cleaning suction catheter
- Single-dose normal saline units for irrigation
- Lubricant for tracheostomy tube insertion
- Two tracheostomy tubes (current size, one size smaller)
- Extra obturator
- Tracheostomy ties (hook-and-loop or twill tape)
- Blunt-nosed scissors for cutting tracheostomy ties
- Self-inflating resuscitation bag with mask
- Heat and moisture exchangers
- Stethoscope

recognize respiratory distress, such as accidental decannulation and a plugged tube, and respond to emergency situations quickly, including changing the tube.[27]

AIRWAY SUCTIONING

Simplicity is an essential component of successful home medical management, especially with suctioning. Home suctioning differs from the aseptic, sterile technique used in the hospital, where a sterile glove and a sterile catheter are used for each suctioning procedure. Two methods are used at home: the *modified clean technique*, defined as using a sterile catheter with clean, nonsterile, disposable gloves, and the *clean technique*, defined as the use of a clean but nonsterile catheter with clean, nonsterile gloves or freshly washed, clean hands.[28] When performing suctioning by the clean technique, the hands are washed thoroughly before beginning the procedure. The suction catheter begins as a sterile catheter, but instead of being discarded, it is washed, disinfected, and reused (Box 35-9). There is some variation among caregivers regarding how long a catheter is used before it is cleaned. Some clean the catheter after every suctioning procedure, whereas others change the catheter every 8 to 24 hours. Should the catheter be contaminated (i.e., dropped on the floor), it should be cleaned at that point.[28] If other individuals in the home are ill, the modified clean technique, using a sterile catheter and clean glove, should be used temporarily. Some professional clinicians may choose to use sterile technique in the home while the child is ill.

Box 35-9 Cleaning Suction Catheters in the Home

1. Using a 20-mL syringe, flush the catheter clean with either sterile or boiled water or 3% hydrogen peroxide.
2. Soak in one (not all) of the following to disinfect:
   A. 1:50 dilution of bleach for 3 minutes (1 teaspoon of bleach to 1 cup of water)
   B. 70% isopropyl alcohol for 5 minutes
   C. 3% hydrogen peroxide for 30 minutes
   D. Commercial disinfectant, such as Control III, for 15 to 20 minutes
3. Rinse the inside and outside of catheter with sterile or boiled water.
4. Place on a clean paper towel to air dry and then store in a clean, sealed plastic bag.

In addition to learning the suctioning techniques, caregivers must be able to recognize the need for suctioning. Suctioning is based on clinical assessment and should be performed on an as-needed basis rather than scheduled. Typically caregivers are taught to suction when the child wakes up in the morning or after a nap, because secretions accumulate in the airway during sleep. They should suction after chest physiotherapy and respiratory treatments when indicated and when secretions can be heard in the tube. Suctioning should be performed if the child seems restless or uncomfortable or exhibits signs and symptoms of respiratory distress. If the child has an effective cough, suctioning is performed infrequently. If the child exhibits copious amounts of secretions or is ill, more frequent suctioning may be required, as often as every 2 to 4 hours.

Caregivers should be taught to note the amount, color, and consistency of the secretions and to report significant changes to their physician. To prevent injury to the tracheal mucosa, the suction catheter is inserted in the tracheostomy to only ¼ to ½ inch beyond the tip of the tube.[29] A suction catheter should be premeasured and marked and then set aside for caregivers to use as a measuring guide. Routine use of normal saline for lavage is not recommended.[28] Caregivers must demonstrate proficiency at suctioning when the child is in the hospital, before the rooming-in period.

All children with a tracheostomy should have a stationary and portable suction machine (Figure 35-5). In addition to an internal battery that can be charged from AC power, the portable suction unit must have a cigarette lighter adapter to charge off of the car battery. The caregiver is advised to take the trach-to-go bag with the patient whenever leaving the house. A DeLee suction trap should be kept in the bag for use in case the suction unit fails. Suction catheters, oral suction

FIGURE 35-5 Battery-powered portable suction machine. (Courtesy Drive DeVilbiss Healthcare LLC. Vacu-Aide® is a registered trademark of Drive DeVilbiss Healthcare.)

tubes, and suction canisters are supplied by the DME provider. A manual self-inflating resuscitation bag with external peak end-expiratory pressure (PEEP) valve, appropriate-size mask, oxygen, and extra suction canisters should be kept in the home and readily available in case of an emergency (Box 35-10).

DECANNULATION AND TUBE CHANGES

The purpose of changing the tracheostomy tube in the home is to minimize infection and the formation of granulation tissue.[30] As a general rule for children, the tube is changed once a week or as needed should it become obstructed. All caregivers must be taught to change the tube routinely and during an emergency if the child suddenly experiences signs and symptoms of respiratory distress (Box 35-11).[31] Before the rooming-in period and before a child can be discharged home, both primary caregivers are required to demonstrate that they can correctly and independently change the tracheostomy tube. Caregivers are strongly encouraged to be available to change the tracheostomy tube as often as possible while the child is in the hospital.

If possible, tube changes should be performed in the early morning before the child eats (Box 35-12). It is best for two caregivers to be present when changing the tracheostomy tube: one to remove the tube and the other to insert the clean one. All equipment, including the emergency supplies, should be gathered and readily available at the bedside. To change the tube, a blanket or towel roll is placed under the child's shoulders to extend the neck. While one caregiver holds the tube in place, loosens the ties, and then removes the tube, the other caregiver inserts the clean tube. The clean tracheostomy ties are attached, the child's work of breathing is assessed, and assurance is made that the airway is intact.

Box 35-10 Emergency Tracheostomy Supplies Kept at the Bedside

- Extra tube, same size currently using
- Extra tube, one size smaller
- Obturator
- Tracheostomy tube ties
- Scissors
- Manual resuscitator bag, external PEEP valve, and appropriate-size mask
- Standby oxygen, if ordered

PEEP, Peak end-expiratory pressure.

Box 35-11 Indications for Changing a Tracheostomy Tube

- Scheduled change is due
- Suction catheter does not pass freely (plugging)
- Respiratory distress is unresolved by suctioning or other interventions
- Oxygen desaturation is unresolved by suctioning or other interventions
- Accidental decannulation

Box 35-12 Steps in Performing Tracheostomy Change

1. Wash hands.
2. Gather equipment.
3. Suction patient, then wash hands again.
4. Arrange workspace with adequate lighting.
5. Place obturator in the extra identical tracheostomy tube; thread ties or collar through one side of tube.
6. Lightly coat tip of tube with water-soluble lubricant.
7. Place child on back with a rolled towel under the shoulders.
8. Cut and remove old ties and pull tube out with a curved, downward motion.
9. Gently insert tube into the stoma, using a downward and forward motion that follows the curve of the tube.
10. Remove the obturator immediately after inserting the tube.
11. Using a syringe with sterile water, inflate the pilot balloon to the prescribed amount.
12. Secure the ties.
13. Suction as needed.
14. Assess the child's respiratory status.

Two tracheostomy tubes should always be available at the bedside and in the trach-to-go bag. One tube should be the size the child is currently using and the other tube should be one size smaller. The smaller tube is available in case a situation exists in which the current size cannot be reinserted. If resistance is met when attempting to replace the current tube, then the smaller tube is placed until further medical assistance can be obtained. A child's stoma can close quickly, so placement of a smaller tube will preserve the opening. Cuffless tubes are preferred in children; however, a cuffed tube may be required if the child is being mechanically ventilated.

HUMIDIFICATION SYSTEMS

Several types of humidification systems can be used in the home care environment. Humidification during mechanical ventilation is necessary to prevent destruction of airway epithelium, hypothermia, atelectasis, and thickening of secretions. The humidification system chosen should provide a minimum of 30 mg of H_2O/L of delivered gas at 30° C (86° F) and meet specifications of the American National Standards Institute (Washington, DC). These are especially important in the pediatric population requiring continuous mechanical ventilatory support that uses high peak inspiratory flow rates.[32]

A portable, 50-psig air compressor or a 20-psig high-flow, high-pressure oxygen concentrator with a heated humidifier and tracheostomy collar is an excellent humidification system. The humidifier should be stabilized near the child's bed, either attached to the bed or to a table located nearby. Parents may be

instructed in the preparation of sterile water and normal saline at home (Box 35-13). The tracheostomy collar is often bulky and limits the child's mobility. Therefore it is suggested that unless the child is being mechanically ventilated, the collar and heated humidity should be used during sleep at night and a heat and moisture exchanger (HME) be used during transport and daytime hours. The first attempt at using the HME should take place in a controlled setting several days before the child is discharged home. The caregivers should be taught to observe for signs and symptoms of respiratory distress associated with the lack of humidification. The HME should never be used with another humidification system. The added moisture will wet the exchanger and increase the child's work of breathing through the exchanger. The caregiver should understand that airway obstruction may occur if secretions are trapped in the HME. If the child requires oxygen, the addition of a T-ring adapter, side ring adapter, or HME with oxygen port placed around the tracheostomy tube can reduce the amount of oxygen flow necessary to maintain the child's oxygen saturation levels. These adapters can be used with the HME and with the tracheostomy collar.

COMMUNICATION AND SPEAKING VALVES

Children begin to communicate from the moment they are born. Communication is an innate component of every human who interacts with the environment and is part of the bonding process for parents and caregivers. Research also shows that speech and language development is interdependent on and interactive with motor and cognitive development. A child with a tracheostomy may be limited in his or her ability to vocalize, and speech therapy becomes an essential part of the home care plan. The goal of speech therapy is to improve deficits in speech and language development. Therapy assists in developing oral motor skills, maximizing language, and encouraging nonvocal behavior. Many forms of communication are used with pediatric tracheostomy patients, including computers, sign language, leak speech, and speaking valves. The benefits of combining all forms of effective communication are critical to the child's development.[33,34]

Leak speech may be used while a child is on mechanical ventilation by reducing the tracheostomy tube cuff inflation if present or increasing ventilator support to raise airflow through the vocal cords, nose, and mouth when an uncuffed tracheostomy tube is in use.

Restoration of airflow through the upper airway also restores sensation to the oropharynx as well as the sense of smell and taste. In turn this improves appetite, overall nutritional intake, and swallowing efficiency.[35]

The speaking valve allows a child to speak without occluding the tracheostomy stoma manually. Opening only during inspiration, the speaking valve allows air to enter the airway. On expiration the valve closes, which results in air being forced out of the airway through the larynx, nose, and mouth (Figure 35-6). The

Box 35-13 Preparing Sterile Distilled Water and Normal Saline at Home

1. Buy distilled water from a local store.
2. Obtain clean glass jars with lids. Baby food jars work well for saline.
3. Boil the distilled water for 15 minutes.
4. For normal saline, add 1 tablespoon of noniodized salt to 1 quart of distilled water (or ¼ teaspoon of salt to 1 cup of distilled water) and boil for 15 minutes.
5. Sterilize the jars by completely immersing them in water and boiling for 15 minutes.
6. Sterilization must be done on a stove. Do not use a dishwasher or a microwave.
7. Pour the water out of the pan and allow the jars and lids to cool in the pan.
8. Remove the jars and lids from the pan without touching the inside of the jars or lids.
9. Place the jars and lids upright on a clean towel.
10. Pour the boiled distilled water into the jars and place the lids on tightly.
11. Do not pour any used solution back into the jar.
12. After 3 days, discard any leftover solution and resterilize the jar and lid.

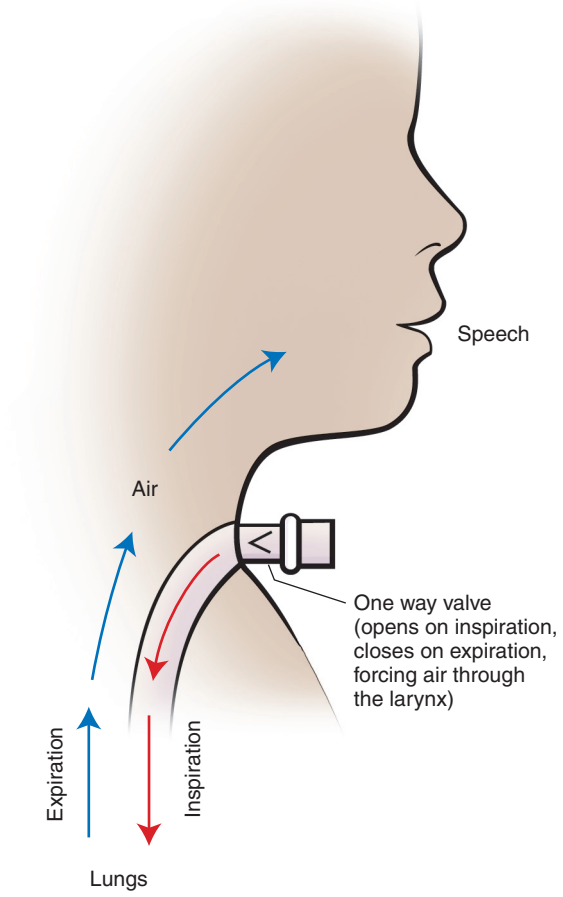


FIGURE 35-6 Tracheostomy speaking valve enables speech by redirecting exhaled air around the tracheostomy tube and through the larynx and upper airway.

patient can resume speaking, which enhances social interaction and decreases frustration by making it easier to vocalize spontaneously. Ideally, leak speech or a speaking valve should be considered as soon as possible after tracheostomy tube placement when the medical condition allows. Successful transitioning techniques used when placing the valve include play therapy and distractions such as coloring books, whistles, and toys. Techniques for training children to exhale through their upper airway include blowing whistles, bubbles, and feathers. Whether a child can tolerate the valve depends mainly on the patency of the upper airway around and above the tracheostomy tube. Measurement of the end-expiratory pressure (EEP) at the tracheostomy tube when the speaking valve is being put in place may be a useful noninvasive objective tool to assess the patency of the exhalation pathway. This measurement can aid the medical staff in decision making with regard to a change in tracheostomy tube size or further upper airway evaluation.[51-52] A speaking valve is contraindicated in patients who have severe tracheal stenosis, have excessive secretions, require continuously inflated cuffed tubes, or are unconscious or heavily sedated.

ACTIVITIES OF DAILY LIVING

Pediatric patients with a tracheostomy should be treated as normal children.[36] A child with a tracheostomy can take part in most play activities suitable for that age. With an infant or small child, all small toy parts or objects should be removed from the play area, because the child might put these into the tube. During outdoor play the caregivers must protect the child's tracheostomy from extreme temperatures and dirt in the air. Extremely cold or hot air may be irritating to the child's lungs. Heat and moisture exchangers are used to protect the airway from such irritants.

When bathing a child with a tracheostomy, the child may be placed in a tub, but care must be taken not to allow water into the tube. To wash a child's hair, the child is held on his or her back over a sink or tub. The hair is washed and rinsed with a cup of water and washcloth or sprayed carefully. The child can play in the water but should never be submerged in the water or left alone in the tub. An older child can take a shower as long as the tracheostomy tube and stoma are protected from water aspiration.

There is no need to buy special clothing for a child with a tracheostomy. However, parents are instructed to buy clothes that do not cover the tracheostomy. Items to avoid include turtlenecks, necklaces, scarves, or any type of material with fibers that could be released into the tracheostomy opening. The home environment should be kept as free of lint, dust, and animal hair as possible. It is imperative that no one smokes, uses powders, or sprays aerosols around or on the child. Particles and fumes can enter the lungs through the tube and cause breathing problems.

The primary caregiver may become ill and be unable to care for the child for an extended time. This is a major reason why more than one caregiver should be trained to care for the child. Qualified providers, or respite care, should be available to care for the child in the absence of the primary caregiver.

Transporting the child may require extra precautions and planning (Box 35-14). It is recommended that another individual besides the driver be in the vehicle with the child. Standard car seat restraints may not work for a child with a tracheostomy. A survey on the methods of transporting technology-dependent children found that the children were restrained appropriately; however, in 66% of the cases the heavy medical equipment was not secured.[37]

MECHANICAL VENTILATION IN THE HOME

As neonatal and pediatric respiratory care continues to evolve, the number of children with chronic respiratory failure who are medically stable has increased. Many of these children require some level of ventilatory assistance, ranging from noninvasive nighttime ventilation to 24-hour ventilatory support. The clinical conditions resulting in respiratory failure and chronic ventilatory support are varied and include chronic lung disease, acquired or congenital neuromuscular impairment, airway abnormalities, and ventilatory control disorders. Although the number of ventilator-assisted children is relatively small compared with other groups, the cost of care is substantial when specialized equipment and education are required and especially when hospital stays are prolonged. There is no argument that the hospital is an unsuitable environment for a ventilator-assisted child who is medically stable. There are many benefits of having the child at home, including an enhanced quality of life. Yet the discharge process for a ventilator-assisted child can be long and complicated. In few other situations does it require a more coordinated multidisciplinary team approach.

FAMILY PREPARATION

The decision to provide care at home must be family centered, not staff generated. Successful home management of a ventilator-assisted child depends largely

Box 35-14 Equipment Needed for Travel

- Trach-to-go bag
- Portable suction machine
- Extra suction canister and tubing
- Prescriptions (medicine, oxygen, and respiratory equipment)
- Pulse oximeter, extra probes
- Oxygen
- List of phone numbers (physician, HME provider, pharmacy)

HME, Home medical equipment.

on the parents' willingness and capacity to meet the needs of their child.[32] Care at home is time consuming, labor intensive, and expensive. Parents should be told that care at home will require more than normal parenting skills. It will impact every aspect of each family member's lifestyle and quality of life. Siblings often feel neglected, and marriages are challenged. An even heavier burden is imposed on single-parent families. However, families regularly agree that overcoming the challenges and finally arriving home is justified and worthwhile.

Before the discharge process begins for a ventilator-assisted child, the following criteria must be met:

- At least two adult caregivers must be willing to commit to participate in the necessary training and the child's ongoing care.
- Parents must be in agreement on taking the child home.
- Caregivers must be physically and mentally capable of providing home care for the child.

Once a family makes the decision to commit to caring for their ventilator-assisted child at home, a formal discharge process begins. One of the first steps to be done is to meet with all of the members of the discharge planning team. Parents should be informed that the discharge process may take several weeks or even months, depending on the individual child's needs. Identification of the two primary caregivers is essential at this point. Because transition to home for a ventilator-assisted child involves such an extensive commitment from the caregivers, they may be asked to sign contracts agreeing to the education and training, hospital rooming-in period, and the steps involved in discharge home. The caregivers should be given an overview of the discharge process with projected dates and timelines for certain steps in the process.

Moving the child from the intensive care unit to an area where the caregivers can be more involved in their child's care is an enormous step in beginning the discharge process. Even though formal teaching by the DME provider may not have begun, the caregivers can learn a great deal about the care of their child from the respiratory therapists, nurses, physical therapists, speech therapists, and occupational therapists who care daily for the child. Once teaching begins, the caregivers have more time to begin practicing their skills in their child's room. Quite often the most successful transitions home are with those families who have spent the most time at their child's bedside, taking an active part in the daily care.

Parents with ventilator-assisted children have commented on how they initially feel shocked and crushed by the uncertainty of their child's illness and their family's future. It may be helpful for the caregivers to be in contact with other parents who have a similar experience. The parents' ability and commitment to be involved in their child's care may vary during the course of the hospitalization, especially when the hospital stay extends into months. Parents struggle with their own adjustment and coping abilities and other aspects of their life. Research has shown that families of ventilator-assisted children face profound burdens in household management, social relations, and financial issues.[38] Because many caregivers must work outside the home, it is common for employment issues to become complicated during the discharge process. This is especially true when caregivers live and work quite some distance from the hospital, yet they are being asked to be with their child to receive training and to become more familiar with the bedside care.

SELECTION OF THE VENTILATOR AND DURABLE MEDICAL EQUIPMENT PROVIDER

There is no standard approach for selecting a ventilator for a pediatric patient. The ventilator and the settings chosen must be tailored to meet the needs of each child. The overall goal is to choose a ventilator capable of maintaining clinical stability with predetermined physiologic values. Ideally, ventilators chosen for home care should be user friendly, compact, and portable and operate on a variety of power sources.[4,39] The device should incorporate a reliable alarm system and should be trouble free for extended periods of time. Home care ventilators should have hidden controls or a locked panel to prevent pediatric patients or siblings from inadvertently altering the settings.

Practitioners must always consider the child's needs when selecting a suitable ventilator. Factors to be considered include, but are not limited to, home versus public school, distance to the health care provider, and how well it will meet the growing needs of the child. If the ventilator selected for home mechanical ventilation is not available in the hospital, the DME provider may be asked to supply the appropriate machine for a trial period before discharge.

A major advantage of a portable ventilator is the ability to use a variety of power sources, including house current, an internal battery for short periods, and an external battery for extended periods. Some portable ventilators can operate from a car battery by connecting to the cigarette lighter. A 12-V battery should be available for use during trips away from home and as an extended backup during an electrical power failure. A 12-V 74-A/hour, deep-cycle battery can power a ventilator for about 20 hours without recharging. A 12-V 34-A/hour, gel-cell battery can power a ventilator for about 10 hours before recharging is required. It is important to note how heavy the battery is and whether the combined weight of the battery and ventilator still allows portability. In rural areas where power outages frequently occur, or where it may take extensive time for electricity to be restored, it is often advisable to purchase a backup electricity generator. Another alternative is to have portable backup batteries or power packs.

The DME provider should be selected as soon as it is determined that the child will go home. Caregivers

should be given the option of selecting the provider; however, there may be few choices, because many may not provide ventilators for children. To obtain one that is an in-network provider with the child's insurance carrier or one that will accept Medicaid reimbursement may narrow the field even more. It is essential, though, that the chosen DME provider has home care personnel who are familiar with the care of infants and children with tracheostomies and who are also familiar with pediatric mechanical ventilation. If the provider agrees to accept the patient, then the home assessment can be scheduled and a list of needed supplies provided. The supply list should be given to the provider as soon as possible so that equipment can be ordered (Box 35-15).

A second ventilator, or backup ventilator, should be provided in the home for a child who meets the following conditions[40]:

- Cannot maintain spontaneous ventilation for 4 or more consecutive hours
- Lives in an area where a replacement ventilator cannot be provided within 2 hours
- Requires mechanical ventilation during mobility

An emergency backup or transport ventilator must be available in the event of a ventilator malfunction. Without a backup or transport ventilator in the home, the home care company must assume the responsibility for providing immediate service. It is also best to have extra ventilator circuits and a spare temperature probe in the home. Although it is not practical to duplicate all equipment, it may be reasonable to have a second suction machine and oxygen source to use at the school or at daycare.

User and clinician manuals should be available from the manufacturer, along with training materials. The user information manual should be left in the home for parents to use as a reference. All educational materials should be well organized and easy to understand. Various factors must be considered to achieve the goals of pediatric ventilatory support in the home environment (Box 35-16).

Box 35-15 Home Medical Equipment and Supplies for Ventilator-Assisted Children

- Mechanical ventilator
  - Primary ventilator
  - Backup ventilator
  - 12-volt battery and connecting cable
  - Ventilator circuits
- Humidification supplies
  - Humidifier and heater
  - Heat and moisture exchangers
- Tracheostomy supplies
- Suctioning supplies
- Self-inflating manual resuscitation bag
- Oxygen
  - Oxygen concentrator
  - Stationary oxygen system with regulator able to support resuscitation (½-15 L/minute regulator)
  - Portable oxygen system with regulator able to support resuscitation (½-15 L/minute regulator)
- Monitoring systems
  - Pulse oximeter (optional)
  - Apnea monitor (optional)

Box 35-16 Goals of Pediatric Home Mechanical Ventilation

- Enhance quality of life
- Extend life
- Provide an environment that promotes individual growth
- Improve psychological function
- Improve physical function
- Reduce morbidity
- Be cost beneficial

COMMON DELAYS TO DISCHARGE HOME

Despite the most valorous attempts at organization, communication, and planning within the discharge process, obstacles to discharge will still occur. The major barriers for chronically ventilated children include failure to obtain qualified nursing staff, delays in approval for home care funding, an unsuitable home environment, complex family issues, and arrangements for out-of-home placement.[41,42]

Recruitment of qualified nursing is a problem no matter where the child's home is. Some areas are better staffed than others, but there always tends to be a shortage of nurses who can care for a ventilator-assisted child. In some cases, the discharge date is set, the caregivers have completed all training and assessments, and the parents have roomed-in, and then, for various reasons, nursing staff is no longer available and the child cannot go home. When nursing shortage is an issue, some families have resorted to advertising for their nurses. Although it is not an option for most families, some have just opted to go home without nursing care.

Funding delays are often the greatest hurdle to getting the child home. Without reimbursement, home equipment cannot be obtained. The greatest difficulty arises when there is little or no reimbursement for the ventilator. Community resources, such as nursing, speech therapy, physical therapy, and occupational therapy, are also unattainable without funding. Without reimbursement, discharge is delayed indefinitely.

The sooner it is known that housing is unsuitable, the more likely solutions can be made. That is why it is so important that the DME provider obtain the home assessment as soon as it is determined that the child intends to be sent home. Many times the problems are simply that electrical outlets are not in compliance, or a ramp needs to be built to accommodate the wheelchair or adaptive stroller. There are situations in which the home is in an area that the nurses or DME provider refuses to travel to, because it is too far away or it is unsafe. Other situations include not having electricity or air conditioning, not enough space for the child's equipment, or even extreme situations in

which the caregivers have been evicted. The social worker is an invaluable member of the discharge planning team when these issues arise.

Family issues are all too often the most difficult barriers to overcome. The longer the hospital stay, the more likely that family dynamics will change. Strained finances, guilt, fatigue, worry, and emotional distress are all issues faced by most families of ventilator-assisted children. However, issues such as divorce, which often results in loss of one of the primary caregivers, and drug abuse and mental illness are the types of issues that tend to result in the longest delays.

Although it is not a commonly faced obstacle, making arrangements to discharge a ventilator-assisted child to an alternative site often leads to extensive delays. It may take weeks if not months to find a medical foster home for the child, which in turn requires home assessment and education of the foster parents. Locating an institution that accepts ventilator-assisted children may be difficult if the child resides in a state that does not have such a facility. It is often difficult for parents to agree to send their child to a facility that is hours away, much less in another state. It may be even more difficult to find a facility that has an opening available for the child.

HOME AT LAST

Before a ventilator-dependent child can be discharged home, the following criteria must be met. Ventilator settings must be stable for at least 1 week. The oxygen concentration must be less than 40%, and blood gas analysis must be stable and within normal limits for the individual child.[32] The home environment must be acceptable and the home equipment available either at the hospital or at the child's home. It is also essential that there be adequate home care available. This includes two primary caregivers who have successfully completed all of the training and the rooming-in period, as well as adequate home nursing staff. On the day of discharge, transportation home or to the alternative site of care may be provided by the caregiver's vehicle or by an ambulance. It is recommended that the respiratory therapist from the DME provider either follow the child home in a separate vehicle or meet the child when he or she arrives home and assist the family with "settling in" at home.

Children requiring mechanical ventilation have not only complex medical problems but home medical equipment that requires frequent evaluation (Box 35-17). Although equipment malfunction may be minimal, there can be no delay in troubleshooting when problems arise. For this reason it is imperative that these children be provided with appropriate medical expertise. This includes 24-hour availability of the DME provider's staff as well as nurses and respiratory therapists from a physician group managing the ventilator at home.

Ventilator-assisted children should be evaluated by a pulmonologist every 3 to 6 months. During the visits, the child's ventilatory status and oxygenation requirements are evaluated to determine optimal ventilator settings and the potential for weaning. Because children often have large leaks associated with uncuffed tubes, the child's tracheostomy is assessed for correct size and placement. In fact, studies have shown that 9 of 11 children with uncuffed tubes are inadequately ventilated, resulting in chronic hypercapnia and fatigue.[43-48] Problems with equipment are addressed, and continuing education of the caregivers is provided if necessary.

Box 35-17 Problems Associated With Home Mechanical Ventilation

- Disconnected ventilator circuit
- Leaks in ventilator circuit
- Obstructions in ventilator circuit
- Water in ventilator circuit
- Water in exhalation valve
- Water in external PEEP valve
- Dirty filter
- Leak around tracheostomy tube
- Ventilator autocycling
- Power surge
- Increased suctioning requirement
- Increased oxygen requirement
- Change in child's pulmonary status
- Change in child's nutritional status
- Change in child's activity level
- Development of infection
- Extensive time required to adjustment to home or environment

PEEP, Positive end-expiratory pressure.

A SUCCESSFUL TRANSITION HOME

Caring for technology-dependent children in the home often presents challenges for their families, their community, and the health care system. Every caregiver of a technology-dependent child is at risk of physical burnout, financial and emotional stress, depression, and social isolation, especially when support and resources are insufficient or inaccessible.[49,50] Many of these challenges can be resolved by interdisciplinary discharge planning, the use of discharge protocols, case management approaches, respite care, psychological counseling, and adequate financial provisions for sustaining home care.[51] A successful transition home often depends on when the discharge process begins. Waiting until the last minute often ends in failure. The advances in care and equipment that make a child's survival possible in the first place are many times the greatest challenges in the transition home. The family's central role in the discharge planning process must be recognized and supported, because in the end, successful transitions may have less to do with the child's medical condition than with the family's commitment to the child and their ability to adapt, work as a team, and persevere.

Clinical Highlight

Home Care Ventilator for a Premature Patient With Chronic Lung Disease

MEDICAL HISTORY

Your patient is a baby boy born at 23 weeks of gestation with chronic lung disease (CLD) complicated by supraglottic airway obstruction. The history summary includes tracheostomy placement with ventilator dependency on control-mode ventilation (CMV) and converted to high-frequency oscillatory ventilation (HFOV) because of worsening ventilation and oxygenation. The patient was able to be weaned to CMV and then weaned further to synchronized intermittent mandatory ventilation (SIMV). After 3 months of endotracheal intubation, the tracheostomy was placed. The patient was stabilized on ventilator settings for 4 weeks.

DISCHARGE PLANNING

The discharge planning referral to a durable medical equipment (DME) company and private duty nursing (PDN) was initiated to begin planning for home. The DME provided a home ventilator for the patient to be placed on and be evaluated for tolerance of changeover while the patient remained in the neonatal intensive care unit (NICU). Tracheostomy cardiopulmonary resuscitation (CPR) training was completed by the parents and additional caregivers who will be in the home (grandparents). The primary bedside nurse continues working with the caregivers for tracheotomy tube changes, suctioning, and bagging metered-dose inhaler (MDI) treatments to the tracheotomy. A social worker is involved to assist with the financial resources because the family has limited access to funds. Commercial insurance is not available at either parent's work; therefore the patient will be eligible for the state Medicaid program.

Nutritional support is stable, because the patient is able to take all feedings orally. No gastrostomy tube has been placed at this time. The home therapy referral was made and will be established once discharge is complete with the patient stable at home. A discharge planning meeting is scheduled with the ventilator discharging team. This was initiated to bring all parties together and discuss the plan of care and discharge.

HOME ASSESSMENT

The DME provider performed the home assessment at the current address and found electrical limitations in the bedroom where the patient will reside. The minimum width of doorways was found to be in an acceptable range, and accessibility to bath, kitchen, and laundry were all acceptable. Telephone service is not available in the home, but caregivers do have cellular phones available. An emergency escape route is planned, with an alternate route established. The parents are asked to inform all possible caregivers about the escape route to ensure the plan is understood and enforced if necessary. The fuse box is labeled for ease in accessing in an emergency. The number of individuals in the home beside the patient includes the mother of the baby, father of the baby, two sisters, and one brother. General cleanliness and condition of the home met needed criteria. The family recently moved into the home and is still unpacking. The home is kept clean, but organization of personal effects is needed. This should be completed before the medical equipment or supply is brought into the home. Once this is complete, it will reduce the possibility of misplacing medical supplies. The DME provider has the following recommendations for the family before patient discharge:

- Two power strips to be used only for medical equipment
- Two flashlights for emergency lighting and charging of the backup or transport ventilator with additional batteries in a room other than where the patient resides

The DME provider reported back to the discharge team that assessment passed with some minor limitations.

DURABLE MEDICAL EQUIPMENT TRAINING

A meeting was set with the parents for training on the medical equipment. Caregivers, including both parents, were present for the orientation. Training material presented to caregivers include training manuals, cleaning instructions, and necessary reference sheets. Basic anatomy and physiology were discussed in relation to the patient's current medical condition. Monthly supplies were provided; caregivers were educated on the use of each item and were given an explanation of the quantity of supply to expect per month as dictated by covered benefits from the insurance provider. When education was completed a competency-training summary was documented, signed, and dated by the respiratory therapist and caregivers. An update of progress was reported back to the ventilator discharge team. They were informed that orientation has been completed.

PARENT CARE UNIT

The parents checked in and attended the parent care unit (PCU) for 48 hours. This task was able to be successfully completed, and all care was delivered to the patient by the parents without the assistance of nursing staff. The DME provider was contacted by the parents during PCU with questions regarding the suction machine. Troubleshooting was done over the phone with the parents and the issue was able to be resolved; it was discovered that the charger was not completely engaged with the unit to provide a charge. The parents were able to complete PCU without incident. Information regarding the fact that the parents successfully completed PCU was sent to all providers involved, and a plan was set to discharge the following morning.

DAY OF DISCHARGE

Time of discharge was set for 11:00 AM. A full assessment of the patient was completed by the rounding physician team, discharging ventilator team, and pulmonary team. The PDN and respiratory therapist from the DME provider were present for the discharge. The parents worked with the respiratory therapist to get all equipment on the adaptive stroller, including placing the patient on the transport ventilator and placing a heat and moisture exchanger (HME) inline to the ventilator circuit; other supplies for the bedside were loaded for travel home. Discharge orders were signed by the discharging physician and instructions provided to caregivers. The parents loaded the patient into the car, and the DME provider followed the caregivers to their home. Upon arrival to the home, the parents and the DME provider carried the patient in while the patient remained on the ventilator circuit. Upon arrival to the patient's room, the patient was placed on the home ventilator. The PDN completed an assessment of the patient while the DME provider completed the transfer to

home. This included plugging in all equipment, assessing saturations, verifying ventilator settings, and confirming the comfort level of the parents and other caregivers. Reinforcement of on-call phone numbers to the caregivers was done. A follow-up call was placed to the parents once the patient was home for a few hours.

FOLLOW UP

The DME provider did an in-home follow-up daily for the remainder of the week. At the end of the week, the parents were reinstructed on how to reach the DME provider on call as well as the home ventilator team physicians. When the DME provider returned to work the following week, an additional trip to the home was completed to ensure that the parents were comfortable and confident in the use of the equipment and supplies and to discuss with the parents any questions that may have arisen since the last time the DME provider had been in the home. A complete ventilator check was documented, ensuring that the orders correlated with the present settings. The DME provider continued to communicate with the family throughout the first month to verify the parents had what was needed to care for their child as well as answer all questions. Per the policy of the DME provider, the therapist evaluated the need to continue returning to the home on a daily basis. The parents were doing well, and DME provider opted to make a weekly call to the parents. Upon completion of the first month at home, the DME provider assisted the parents with ordering of the first month's supplies. This entailed a full inventory done with one of the parents. Reinstruction of monthly supply quantities was discussed, and a date and time were set with the parents for delivery of the monthly order. The DME provider continued to do ventilator checks per policy and assisted the parents with questions and concerns that arose. The patient remained on continuous ventilation for approximately 7 months. The weaning process then began, allowing the patient to come off the ventilator for 5 to 10 minutes at a time, as tolerated. This time increased until the patient was off the ventilator all waking hours and then on to being off the ventilator at all times. After 21 months of being at home with a ventilator, the patient was able to be decannulated with minimal medical needs from the DME provider.

Key Points

- Critical components of discharging a child to home with technology dependency are excellent communication by all parties involved, timely planning to have all necessary roles and expectations established, overcoming possible barriers that may cause delay in discharge, and awareness to the needs of not only the child but the parents or caregivers as well.
- Recognizing, understanding, and addressing the possible barriers that may be present, either in the home, with the parents or caregivers, or related to finances will assist the entire team ensure a successful discharge.
- With multiple oxygen systems available on the market, finding the one best suited for the child's needs is extremely important. Liquid oxygen, oxygen concentrators, and compressed gas sources are most commonly used in a home environment. The patient's oxygen liter flow should be the determining factor for selecting a modality source.
- To ensure the child has all the key components needed when traveling outside the home, a list is generated for a designated trach-to-go bag. This is an essential part of caring for a child with technology needs.
- Understanding when a child needs his or her tracheotomy tube changed is key for caring for a child with a trach. The child will have clinical signs to be aware when the need is present for a tube change.
- Preparing a parent or caregiver for attending to a child with a ventilator takes a great deal of time, understanding, and patience, as well as preparation. Parent and caregiver training never ceases; it is done daily from the time the child is still an inpatient and continues even after discharge to home.
- Things to consider when selecting a home ventilator include the portability of the unit, weight and battery capabilities of the unit, and how the unit will be used for the child. Determining which DME provider is best suited for the child is always important as well. In considering providers, the family should consider what insurance companies are in network with the provider, the distance of the provider to where the child will reside, and whether the provider is capable of managing the pediatric population.

Assessment Questions

See Evolve Resources for answers.

1. After a home assessment, what is the most common barrier that may delay a patient's discharge?
   - **A.** Electrical issues
   - **B.** Not owning a home
   - **C.** Need for flashlights
   - **D.** Width of the doorway too large
2. "A medical staff member designated to transition a patient from hospital facility to home or other level of care" is the definition for which of the following?
   - **A.** Social worker
   - **B.** Discharge planner
   - **C.** Speech pathologist
   - **D.** Durable medical equipment (DME) provider
3. What is an indication for changing a tracheostomy tube?
   - **A.** Respiratory distress
   - **B.** Weekly tracheostomy change
   - **C.** Suction catheter does not pass freely
   - **D.** All of the above
4. In a home care setting, how often should a routine tracheostomy change be performed?
   - **A.** Monthly
   - **B.** Daily
   - **C.** Weekly
   - **D.** Biweekly

5. In the home, what equipment is needed for a ventilator-dependent child?
   - **A.** Heater/humidifier unit
   - **B.** Wall flow meter
   - **C.** Sterile gloves
   - **D.** Microwave
6. The goal of having caregivers stay for an in-hospital trial is to:
   - **A.** Give an opportunity for backup assistance from hospital staff
   - **B.** Give caregivers a chance to relax
   - **C.** Allow caregivers to assist with finances
   - **D.** Take patients away from the bedside nurse so they can admit new patients
7. Prolonged hospital stays can cause emotional stress on families. Which would be a stressor for a family with a premature child that has required a prolonged stay?
   - **A.** Strained finances
   - **B.** Feeling of guilt
   - **C.** Exhaustion
   - **D.** All of the above
8. A 12-year-old boy with Duchenne muscular dystrophy is admitted to the hospital for a planned tracheotomy and preparation for home mechanical ventilation. Discharge planning should begin for this child and his family:
   - **A.** Immediately after placement of the tracheostomy tube
   - **B.** On admission to the hospital
   - **C.** After transition to the home mechanical ventilator
   - **D.** Once the child is medically stable
9. The parents of an infant who is ventilator dependent have missed several educational sessions that are required before discharge home. They have also been sporadic in visiting their child and practicing bedside skills. What action should the discharge planning team take next?
   - **A.** Submit a report to the local child neglect hotline.
   - **B.** Ask the infant's physician to counsel with the parents.
   - **C.** Provide the parents with a discharge contract or agreement.
   - **D.** Suggest that the parents attend a parenting class together.
10. Which of the following is usually the major obstacle to providing quality care in the home of a technology-dependent child?
    - **A.** High cost and inadequate funding of home care services
    - **B.** DME providers that do not employ respiratory therapists
    - **C.** Inability to provide home nursing
    - **D.** Lack of two committed in-home caregivers
11. The need for home oxygen therapy for infants is most often established by:
    - **A.** Arterial blood gas analysis
    - **B.** Oxygen saturation measured by pulse oximetry
    - **C.** Sleep scoring from polysomnography studies
    - **D.** Capillary blood gas analysis
12. An infant requires oxygen with a nasal cannula at 0.5 L/minute. The mother states that because of financial difficulties they have moved to a one-bedroom house. Which of the following oxygen systems would be most appropriate to provide in this home?
    - **A.** Liquid oxygen with a base unit reservoir
    - **B.** An oxygen concentrator
    - **C.** A compressed gas H cylinder of oxygen
    - **D.** Multiple compressed gas E cylinders of oxygen
13. An infant will be discharged home with an apnea–bradycardia monitor. Which of the following instructions should the parents be given?
    - **A.** "Your baby only needs the monitor during naps and when sleeping at night."
    - **B.** "The belt is tight enough if you can fit two fingers between it and your baby's chest."
    - **C.** "When the monitor alarms, immediately check for correct electrode placement."
    - **D.** "Do not place lotion on your baby's chest."
14. During use of a home apnea–bradycardia monitor, which of the following is the most common cause of a false alarm?
    - **A.** The baby is crying.
    - **B.** The lead wires are loose.
    - **C.** The baby is breathing shallowly.
    - **D.** The baby is burping.
15. How often should a cuffless tracheostomy tube in a child be changed when at home?
    - **A.** Once a day
    - **B.** Once a week
    - **C.** Once each month
    - **D.** Only when it becomes obstructed
16. After placing a speaking valve on a child with a 4.5 cuffless pediatric tracheostomy tube, the child exhibits signs of difficulty in exhaling. Which of the following changes should be made?
    - **A.** Change to a 4.5 cuffed tracheostomy tube.
    - **B.** Replace the tracheostomy tube with a fenestrated tube.
    - **C.** Change to a 4.0 cuffed tracheostomy tube.
    - **D.** Downsize to a 4.0 cuffless tracheostomy tube.
17. In which of the following situations should a second (backup or transport) ventilator be placed in a child's home?
    - **A.** The child requires the ventilator only at night while sleeping.
    - **B.** The child's home is within a 1-hour drive of the DME provider.
    - **C.** The child is sprinting from the ventilator for 2 hours twice each day.
    - **D.** The home nursing agency can provide nurses only at night.

REFERENCES

1. Allen J, Zwerdling R, Ehrenkranz R, Gaultier C, Geggel R, American Thoracic Society, et al. Statement on the care of the child with chronic lung disease of infancy and childhood. *Am J Respir Crit Care Med*. 2003;168:356.
2. Social Security Administration. Supplemental security income for the aged, blind, and disabled; deeming of income and resources–SSA. Interim rules with comment period. *Fed Regist*. 1982;47:24274.
3. Gracey K, Talbot D, Lankford R, Dodge P. The changing face of bronchopulmonary dysplasia: Part 2. Discharging an infant home on oxygen. *Adv Neonatal Care*. 2003;3:88.
4. AARC (American Association for Respiratory Care) clinical practice guidelines: discharge planning for the respiratory care patient. *Respir Care*. 1995;40(12):1308-1312.
5. DeWitt PK, Jansen MT, Ward SL, Keens TG. Obstacles to discharge of ventilator-assisted children from the hospital to home. *Chest*. 1993;103:1560.
6. Hospital discharge of the high-risk neonate–proposed guidelines. American Academy of Pediatrics. Committee on Fetus and Newborn. *Pediatrics*. 1998;102:411.
7. Gilmartin M. Transition from the intensive care unit to home: patient selection and discharge planning. *Respir Care*. 1994;39:456.
8. Guidelines for home care of infants, children, and adolescents with chronic disease. American Academy of Pediatrics Committee on Children with Disabilities. *Pediatrics*. 1995; 96:161.
9. Czervinske MP. Ensuring quality care for infant tracheostomy patients: part 1. *AARC Times*. 1999;23:31.
10. Fiske E. Effective strategies to prepare infants and families for home tracheostomy care. *Adv Neonatal Care*. 2004;4:42.
11. American Association for Respiratory Care. AARC Clinical practice guidelines: providing patient and caregiver training. *Respir Care*. 1996;41(7):658-663.
12. Glenn KA, Make BJ. *Learning Objective for Positive Pressure Ventilation in the Home*. Denver: National Center for Home Mechanical Ventilation and National Jewish Center for Immunology and Respiratory Medicine; 1993.
13. American Medical Association Home Care Advisory Panel. Physicians and Home Care: Guidelines for the Medical Management of the Home Care Patient. Chicago: American Medical Association; 1992.
14. Managed care and children with special health care needs: a subject review. American Academy of Pediatrics, Committee on Children with Disabilities. *Pediatrics*. 1998;102:657.
15. Hill LV, Thompson MK. Case management of technology-dependent children: a family-centered approach. *J Home Care Pract*. 1994;6:37.
16. McCarthy MF. A home discharge program for ventilator-assisted children. *Pediatr Nurs*. 1986;12:331.
17. Medical Home Initiatives for Children with Special Needs Project Advisory Committee. American Academy of Pediatrics. The medical home. *Pediatrics*. 2002;110:184.
18. American Academy of Pediatrics. Committee on Child Health Financing. Guiding principles for managed care arrangements for the health care of newborns, infants, children, adolescents, and young adults. *Pediatrics*. 2000;105:132.
19. Managed care and children with special health care needs: a subject review. American Academy of Pediatrics Committee on Children with Disabilities. *Pediatrics*. 1998;102:657.
20. Balfour-Lynn IM, Primhak RA, Shaw BN. Home oxygen for children: who, how, and when? *Thorax*. 2005;60:76.
21. Harris ND, Stamp JM. Current developments in oxygen concentrator technology. *J Med Eng Technol*. 1987;11:103.
22. American Academy of Pediatrics, Committee on Fetus and Newborn. Apnea, sudden infant death syndrome, and home monitoring. *Pediatrics*. 2003;111:914.
23. AARC (American Association for Respiratory Care) clinical practice guidelines: pulse oximetry. *Respir Care*. 1991;36:1406.
24. Ghanayem NS, Hoffman GM, Mussatto KA, et al. Home surveillance program prevents interstage mortality after the Norwood procedure. *J Thorac Cardiovasc Surg*. 2003;126:1367.
25. Lewarski JS. Long-term care of the patient with a tracheostomy. *Respir Care*. 2005;50:534.
26. Fiske E. Effective strategies to prepare infants and families for home tracheostomy care. *Adv Neonatal Care*. 2004;4:42.
27. Sherman JM, Davis S, Albamonte-Petrick S, et al. Care of the child with a chronic tracheostomy. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med*. 2000;161:297.
28. Hodge D. Endotracheal suctioning and the infant: a nursing care protocol to decrease complications. *Neonatal Netw*. 1991;9:7.
29. Fitton CM. Nursing management of the child with a tracheotomy. *Pediatr Clin North Am*. 1994;41:513.
30. Miyasaka K, Suzuki Y, Sakai H, Kondo Y. Interactive communication in high-technology home care: videophones for pediatric ventilatory care. *Pediatrics*. 1997;99:E1.
31. AARC Clinical practice guidelines: humidification during mechanical ventilation. American Association for Respiratory Care. *Respir Care*. 1992;37:887.
32. Torres LY, Sirbegovic DJ. Problems caused by tracheostomy tube placement. *Neonatal Intensive Care*. 2004;1652.
33. Miyasaka K, Suzuki Y, Sakai H, Kondo Y. Interactive communication in high-technology home care: video phones for pediatric ventilatory care. *Pediatrics*. 1997;99:E1.
34. Dettelbach MA, Gross RD, Mahlmann J, Eibling DE. Effect of the Passy-Muir valve on aspiration in patients with tracheostomy. *Head Neck*. 1995;17:297.
35. Keen SE, et al. Effect of in-home nursing care on distress and coping resources in caregivers of ventilator- assisted children at home. *Am Rev Respir Dis*. 1991;143A:257.
36. Jansen MT, et al. Caregiver's safety restraint practices for technology-dependent children during motor vehicle transportation. *Am Rev Respir Dis*. 1993;147A:410.
37. Tsara V, Serasli E, Voutsas V, Lazarides V, Christaki P. Burden and coping strategies in families of patients under noninvasive home mechanical ventilation. *Respiration*. 2006; 73:61.
38. University of Illinois. *Conference Proceedings: Strategies for Success in Home for Medically Fragile Children*. Springfield, IL: University of Illinois, Division of Services for Crippled Children; 1989.
39. American Association for Respiratory Care. Clinical practice guidelines: long-term invasive mechanical ventilation in the home. *Respir Care*. 2007;52:1056.
40. DeWitt PK, Jansen MT, Ward SL, Keens TG. Obstacles to discharge of ventilator-assisted children from hospital to home. *Chest*. 1993;103:1560.
41. Edwards EA, O'Toole M, Wallis C. Sending children home on tracheostomy dependent ventilation: pitfalls and outcomes. *Arch Dis Child*. 2004;89:251.
42. Kacmarek RM, et al. Imposed work of breathing during synchronized intermittent mandatory ventilation (SIMV) provided by five home care ventilators. *Respir Care*. 1990;35:405.
43. Robert P, et al. Work of breathing imposed during spontaneous breathing in the SIMV mode of home care ventilators [abstract]. *Respir Care*. 1992;37:1358.
44. Gilgoff IS, Peng RC, Keens TG. Hypoventilation and apnea in children during mechanically assisted ventilation. *Chest*. 1992;101:1500.
45. Chatburn RL, Volsko TA, El-Khatib M. The effect of airway leak on tidal volume during pressure- or flow-controlled ventilation of the neonate: a model study. *Respir Care*. 1996; 41:728.

46. Bach JR, Alba AS. Tracheostomy ventilation: a study of efficacy with deflated cuffs and cuffless tubes. *Chest*. 1998; 97(3):679.
47. Keens TG, et al. Frequency, causes, and outcomes of home ventilatory failure. *Am Rev Respir Dis*. 1993;147A:408.
48. Leonard BJ, Brust JD, Nelson RP. Parental distress: caring for medically fragile children at home. *J Pediatr Nurs*. 1993;8:22.
49. Thyen U, Kuhlthau K, Perrin JM. Employment, child care, and mental health of mothers caring for children assisted by technology. *Pediatrics*. 1999;103:1235.
50. Capen CL, Dedlow ER. Discharging ventilator-dependent children: a continuing challenge. *J Pediatr Nurs*. 1998;13:175.
51. Johnson DC, Campbell SL, Rabkin JD. Tracheostomy tube manometry: evaluation of speaking valves, capping and need for downsizing. *Clin Respir J*. 2009;3(1):8-14.
52. Utrarachkij J, Pongsasnongkul J, Preutthipan A, Chantarojanasri T. Measurement of end-expiratory pressure as an indicator of airway patency above tracheostomy in children. *J Med Assoc Thai*. 2005;88(7):928-933.
53. Gannon BA. Theophylline or caffeine: which is best for apnea of prematurity? *Neonatal Netw*. 2000;19(8):33-36.
54. McCoy RW. Options for home oxygen therapy equipment: storage and metering of oxygen in the home. *Respir Care*. 2013;58(1):65-85.

Quality and Safety

36

Lisa Tyler, Linda Napoli

Outline

Learning Objectives

After reading this chapter, the reader will be able to:

1. Define *quality* and *patient safety.*
2. Describe the evolution of the quality movement and its importance to health care.
3. Discuss the elements of teamwork and the effects on quality outcomes.
4. Explain the impact of leadership support on quality and the use of a just culture to facilitate accountability.
5. Describe how quality outcomes are measured and compared both internally and externally.
6. Discuss the aspects of high-reliability organizations as related to key concepts, evidence-based practice, patient safety indicators, and the Agency for Healthcare Research and Quality (AHRQ).
7. Explain how information technology can have both positive and negative effects on health care organizations and quality outcomes.
8. Identify the various processes used to build safety practices and tools used to define problems.
9. Discuss James Reason's culture of safety theory and how it relates to errors.
10. Recognize different methods used to support safety behaviors to prevent errors.

Key Terms

Agency for Healthcare Research and Quality (AHRQ)
benchmarking
crew resource management (CRM)
department of Defense (DoD)
error
evidence-based practice
Failure Modes and Effects Analysis (FMEA)
Health Failure Modes and Effects Analysis (HFMEA)
high-reliability organizations (HRO)
Institute of Medicine (IOM)
just culture
Kaizen
Lean methodology
near miss
negligence
Plan-Do-Study-Act (PDSA)
precursor
quality
quality indicator
root cause analysis (RCA)
SBAR
sentinel event
serious safety event
Six Sigma
Team Strategies and Tools to Enhance Performance and Patient Safety (TeamSTEPPS)
ventilator-associated pneumonia (VAP)

Quality and safety in health care are two key factors facing health care providers today. Internally there is a focus on improving quality and safety, which starts at the CEO and board level and continues throughout the organization. Externally there is emphasis on how measures of quality and safety are reported and shared across health care systems. Children differ in many ways compared with adults in regard to health care delivery and the relationship to medical errors and harm. Primary contributing factors include children's characteristics and development stages, demographics, dependency on parents and other caregivers concerning care and legal status, and varying epidemiology of medical conditions.[1] In addition, many devices and drugs are used "off-label," which means they have not been tested or approved for use in pediatrics. This can create a burden for health care providers to render services and deliver medications as discrepancies arise between what the patient needs and what is approved to be used. For this reason, patient-safety problems and solutions for children are multifaceted with unique attributes. Therefore understanding the main safety strategies in the pediatric population is vital. They are (1) epidemiology of errors and identification of the source of the issue; (2) understanding the science and safety aspects behind the culture; and (3) having a core source of safety solutions that are incorporated into risk assessment and solutions for each unique characteristic.[2]

Pediatric errors in the inpatient setting have been researched and described in a variety of studies. It has been reported that approximately 13 adverse events per 1000 hospital discharges occur in patients newborn through 15 years old.[3] **Negligence** (described as a lack of skills and/or failure to follow or deviation from standard practices and procedures) was determined to be the cause in 27.6% of events. Adverse drug events were identified in 2.3% of hospitalizations, and 19% were deemed preventable. Serious errors occurred more often in the critical care setting, and adverse drug events occurred three times more often among pediatric patients than among adults. Neonatal intensive care unit (NICU) data revealed 47% of errors were medication related, 11% related to patient misidentification, 7% were from delay or errors in diagnosis, and 14% involved errors in the administration or methods of using a treatment.[4]

WHAT IS QUALITY IN HEALTH CARE?

A variety of theories of quality care have been discussed with continued development across different health care platforms. The **Institute of Medicine (IOM),** a nonprofit organization whose purpose is to provide advice on issues related to science, medicine, and health, defines health care **quality** as the "degree to which health services for individuals and populations increase the likelihood of desired health outcomes (quality principles) and are consistent with current professional knowledge (professional practitioner skill), and meet the expectations of the market place."[5] Patient safety is defined by the IOM as "the prevention of harm to patients." Emphasis is placed on a system of care delivery that prevents errors; learns from the errors that do occur; and is built on a culture of safety involving health care professionals, organizations, and patients.[6] For that reason, safety is the foundation upon which all other aspects of quality care are built.

Quality practices and processes must be embedded in the foundation of health care institutions for both patient care and financial well-being. The public's increasing awareness of quality care through the reporting of high-profile reports on safety failures has had a significant impact on the focus of quality outcomes. A commitment to total quality is a necessary part of an organization's journey toward improvement. The philosophy of total quality consists of an attitude that is infused into the entire organization, both internally and externally. Those who work in organizations dedicated to the concept of total quality constantly strive for excellence and continuous improvement in everything they do.

HEALTH CARE QUALITY EVOLUTION

The awareness and subsequent scrutiny of quality care evolved through massive reporting processes and evaluation of landmark events. In 2000 the IOM issued *To Err Is Human: Building a Safer Health System.* This report estimated up to a million patients experienced some type of preventable error, with 44,000 (120 patients per day) to 98,000 (268 patients per day) Americans dying as a result of preventable medical errors.[7] To put this into perspective, it is equivalent to one Boeing 737 or 747 crashing and killing everyone on board every day.[8] The typical consumers would never tolerate such odds. It further reported that adverse events occur in 2.9% to 3.7% of hospitalizations, with 7000 deaths per year from medication errors alone.[7]

Error is an act producing a preventable adverse outcome compared with the natural progression of disease leading to injury or death. More people die in a given year as a result of medical errors than from motor vehicle accidents (43,458), breast cancer (42,297), and acquired immune deficiency syndrome (AIDS; 16,516).

The report made several suggestions to improve patient safety:

- Improve leadership and knowledge.
- Identify and learn from errors.
- Set performance standards and expectations for safety.
- Implement safety systems in health care organizations.[7]

The second major report from the IOM committee, *Crossing the Quality Chasm: A New Health System for the 21st Century* (2003), expanded the work outlined in *To Err Is Human* to an industry-wide process redesign,

targeting a culture of improving the quality of care. The report focused on the quality of care currently present in the US health care system. *Crossing the Quality Chasm* included a call for action to improve the American health care delivery system as a whole, in all its quality dimensions, and found too often health care failed to deliver its potential benefits. Other problem areas include gaps or chasms (wide differences) in patient care, performance variability, and the inability to use resources effectively (fragmented delivery systems and waste and overuse of services) because of system structures.

The committee defined six concrete components of high quality care:

- Safe—The patient is not harmed or injured by any care or procedure.
- Effective—The patient receives the desired or expected result from the care or procedure administered.
- Patient-centered—Care is provided to a patient with respect and awareness of his or her preferences, needs, and values, with the patient involved in clinical decisions.
- Timely—Care is provided at the right time, avoiding harmful delays.
- Efficient—Care is performed in an organized and capable way, achieving desired results, with minimal waste in time, effort, or supplies.
- Equitable—Patient receives care characterized by justice and fairness with impartiality toward all.[6]

Even with hospitals focusing on quality and attempting to integrate these guidelines into care, 3 years later an estimated 380,000 to 450,000 preventable adverse drug events occurred in hospitals each year.[9] In a more recent report, the Centers for Disease Control and Prevention noted that another 100,000 deaths could be attributed to infections. New studies were presented in the April 2011 issue of *Health Affairs* suggesting the rate of preventable harm may be up to 10 times higher than the IOM estimate.

In 2008 medical errors cost the United States $19.5 billion, with $17 billion directly associated with additional medical cost. This cost is attributable to increased hospital cost (length of stay), malpractice, and lost income for households.[11]

Errors are also costly by creating a loss of trust in the medical system. In October 2011 Health Grades reported that patients being treated in a 5-star rated hospital, as compared with a 1-star rated hospital, had a 73% lower mortality rate and 54% lower risk of dying. Distinction among type of hospital, patient, or procedure is not always available for further analysis.

TEAMWORK

Developing teams of caregivers for multidisciplinary communication was described early on by IOM as a necessary component of change that needed to occur to improve patient safety. The traditional health care model is hierarchical, with physicians giving orders and others doing what they say. The airline industry had this same problem; pilots were given the ultimate authority. When the airline industry embarked on a campaign to improve safety, they promoted a concept known as **crew resource management (CRM).** It is reminiscent of a "stop the line" philosophy used in many factory operations to decrease defects in manufacturing. With CRM, crews were taught to function as a team, with each member having equally important roles and responsibilities regarding safety.[12] The expectation is for every member to appropriately assert concerns for safety. The culture of health care organizations must shift to emulate the importance of teamwork. This can be especially difficult because many units, departments, or locations of a given organization may have very different cultures. Every member of the team has to be valued and be able to contribute. This will result in better coordination of care, early recognition of errors, and more rapid interventions.[12]

One program used by healthcare professionals to improve teamwork within and across health care systems is called **TeamSTEPPS (Team Strategies and Tools to Enhance Performance and Patient Safety).** This three-phase program was developed by the **Agency for Healthcare Research and Quality (AHRQ)** and the **Department of Defense (DoD)** to improve team collaboration and communication in health care institutions.[37] Health care workers (physicians, nurses, respiratory therapists, etc.) perform interdependent tasks while functioning in explicit roles while sharing the common goals of quality and safety in care. They must coordinate their actions to make patient care safe and efficient; however, most often team members do not train together.[37] TeamSTEPPS is designed to provide hospitals a systematic approach to integrating teamwork into everyday practices of health care workers to improve quality, safety, and efficiency of care.

TeamSTEPPS represents a major advancement in addressing team performance issues in health care. Its framework is founded on four core competencies: leadership, situation monitoring, mutual support, and communication.[38] Leadership is defined as an ability to direct and coordinate, assign tasks, motivate team members, resource, and facilitate optimal team performance. Situation monitoring is the ability to develop common understandings of the team environment and apply appropriate strategies to accurately monitor teammate performance and maintain a shared mental model. Mutual support describes the ability to anticipate other team members' needs through accurate knowledge and shift workload to achieve balance during high periods of workload or pressure. Communication is the ability to effectively exchange information among team members, regardless of the medium.[39] These core competencies are surrounded by

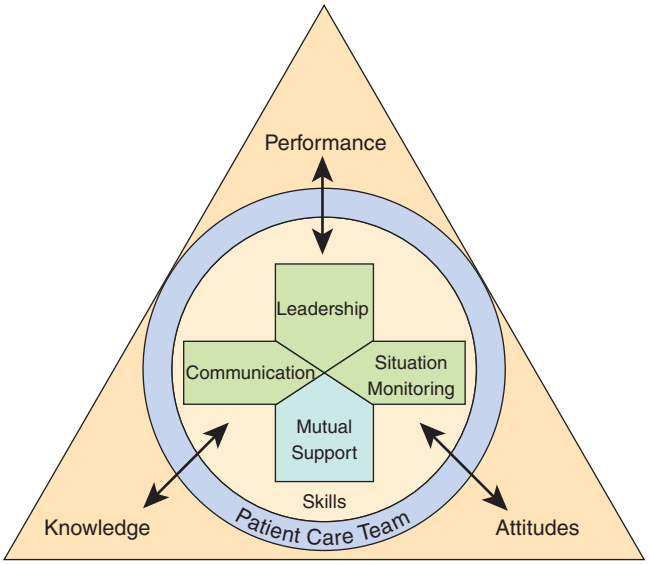


FIGURE 36-1 TeamSTEPPS instructional framework. (Henriksen K, Battles JB, Keyes MA, et al., editors. *Advances in Patient Safety: New Directions and Alternative Approaches (Vol. 3: Performance and Tools)*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008 Aug. http://www.ahrq.gov/.

the patient care team inclusive of the patients and patients' experiences. Performance, knowledge, and attitudinal outcomes are described in the corners, resulting from proficiency on the central skills or core competencies (Figure 36-1).

Emphasis is placed on delineating team skills, establishing the tools and strategies team members can use to gain proficiency of those skills, and identification of tools and strategies that can be used to overcome common barriers to achieve desired outcomes. Box 36-1 lists common barriers found in the hospital environment and tools and strategies used it mitigate the barriers to achieve the desired outcomes.[38]

LEADERSHIP

Willingness to admit everyday errors is important in designing the work environment to be able to permit errors to improve on processes. Before the IOM report *To Err Is Human,* individual personal blame had been attributed to errors. This made people unwilling to come forward and admit errors, because disciplinary action would be applied. In an attempt to counteract this concern, there was a move toward a "blame-free" environment. The reality is no one can offer a blame-free system in which any conduct can be reported without acceptance of responsibility at some level. There is a balance between the need to learn from mistakes and the need for accountability.

JUST CULTURE

The concept of a just culture in lieu of no blame has been introduced to address the concept of accountability and unsafe behavior. A **just culture** focuses on identifying and addressing systems issues leading individuals to engage in unsafe behaviors while maintaining individual accountability by establishing a zero tolerance for reckless behavior. It distinguishes between human error, at-risk behavior, and reckless behavior (ignoring a safety step). As stated by the AHRQ, "in a just culture, the response to an error or near miss is predicated on the type of behavior associated with the error, not the severity of the event."[13]

An example is the process of confirming patient identification before performing procedures. A therapist neglects to do this and performs the treatment on

Box 36-1 TeamSTEPP Barriers and Tools and Strategies to Achieve Outcomes

BARRIERS	TOOLS AND STRATEGIES	OUTCOMES
• Inconsistency in team membership • Conventional thinking • Complacency • Lack of time • Lack of information sharing • Hierarchy • Defensiveness • Conflict • Lack of coordination and follow-up with co-workers • Fatigue • Workload	• Brief • Huddle • Debrief • STEP • Cross monitoring • Feedback • Advocacy and assertion • Two-challenge rule • CUS • DESC script • Collaboration • SBAR • Call-out • Check-back • Handoff • IPASS the BATON	• Shared mental model • Adaptability • Team orientation • Mutual trust • Team performance • Patient safety

From Barriers, Tools & Strategies, and Outcomes in TeamSTEPPS® Pocket Guide. AHRQ Publication No. 14-0001-2. Rockville, MD: Agency for Healthcare Research and Quality; December 2013. Available at https://www.ahrq.gov/teamstepps/instructor/essentials/pocketguide.html.
BATON, Background Actions Timing Ownership Next; *CUS,* Concerned Uncomfortable Safety Issue; *DESC,* Describe Express Suggest Consequence; *IPASS,* Introduction Patient Assessment Situation Safety Concerns; *SBAR,* Situation Background Assessment Recommendation; *STEP,* Status Team Environment Progress.

the wrong patient. If the organizational system allows for inconsistency of providing identification bands for patients, it needs to be addressed as a system issue. Focus would be placed on the improvements in the system and not the individual. If, on the other hand, the therapist neglected to perform patient identification when the system sufficiently supports the placement of identification bands, and gave a treatment to the wrong patient, then the therapist has been reckless and has to be held accountable for the error.

MEASURING QUALITY IMPROVEMENT

Various systems for classifying errors are used today. According to Health Performance Improvement (HPI),[14] safety events can be classified in three ways: near misses, precursor events, and serious safety events.

Near misses are errors that do not reach the patient because they are detected before they do. An example would be morphine being ordered at a higher dose than should be given; the pharmacist checks the order before preparing the drug, recognizes it is outside normal dosing guidelines, and informs the physician.

The second classification is a **precursor** safety event, an event that reaches the patient but results in minimal to no detectable harm. If that same morphine dose error is not detected by the pharmacist or nurse and gets delivered to the patient but the patient does not have any adverse response, then it is a precursor safety event.

A **serious safety event** is an event that reaches the patient and results in moderate to severe harm or death. If the overdose of morphine is given and the patient experiences a depression in respiratory effort resulting in apnea or death, this becomes a serious safety event. Serious safety events must be reviewed through a **root cause analysis (RCA)** to determine whether a gap in care or a deviation from normally accepted practice has occurred. This is an important determination, because harm can even occur when normally accepted practices have been followed. Such events would not be classified as serious safety events.

It has been suggested that for every serious safety event, there are hundreds of precursor safety events and thousands of near misses. It is important for health care organizations to not only analyze serious safety events but also review and report near misses and precursor events. Thorough reporting and analysis of near misses, precursor safety events, and serious safety events will identify systems needing improvement.

The Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) also reviews errors that are classified as **sentinel events.** The Joint Commission defines a sentinel event as "an unexpected occurrence involving death or serious physical or psychological injury, or the risk thereof."[15] Organizations voluntarily report events after having completed an RCA. They then track categories for what has been submitted and reviewed. This allows recognition of trends in patient safety. They also will report sentinel events on their website and encourage organizations to apply learning techniques to prevent similar events from occurring. As an example, in their Sentinel Alert 38, tubing misconnections were highlighted.[16] Tubing misconnections are a potentially common area of concern for respiratory therapists. There have been reports of feeding tubes being connected to cuff pilot balloons of artificial airways and suction ports on inline suction catheters. After this report, organizations should have internally identified all possible tubing misconnections that could occur and implemented processes to eliminate the potential for this error.

Through reviewing sentinel events, The Joint Commission sets national safety patient goals annually with the purpose of improving patient safety. The 2016 goals are listed in Table 36-1.

Demonstrating improvements in quality outcomes encompasses measuring whether efforts made lead to

Table 36-1 Joint Commission 2016 National Patient Safety Goals

GOAL	SPECIFICS
Identify patients correctly	Use at least two ways to identify patients. Make sure the correct patient gets the correct blood.
Improve staff communication	Get important test results to the right staff on time.
Use medications safely	Label medications before a procedure. Take extra care with patients who take medicines to thin blood. Record and pass along correct information about a patient's medicines.
Use alarms safely	Ensure that alarms on medical equipment are heard and responded to on time.
Prevent infections	Use hand cleaning guidelines from the CDC. Use proven guidelines to prevent infections that are difficult to treat. Use guidelines to prevent infection of the blood from central lines. Use proven guidelines to prevent infection after surgery. Use proven guidelines to prevent infections of the urinary tract caused by catheters.
Identify patients at risk	Identify patients at risk for suicide.
Prevent mistakes in surgery	Make sure the correct surgery is done on the correct patient and at the correct place on the patient's body. Pause before surgery to make sure that a mistake is not being made.

CDC, Centers for Disease Control and Prevention.

change toward the primary goal or at least moving in the desired direction. Further analysis must define whether efforts could contribute to unintended results in different parts of the system and require additional resources to bring a process back into acceptable range.[17] Quality measure reporting should reflect quality practices, encourage better performance, and identify areas of improvements compared with other similar organizations. Reporting of quality measures may be mandatory or voluntarily reported. State-to-state mandated reporting varies. In addition, other regulatory organizations may direct certain reporting obligations. Voluntary reporting is used to help the consumer search for high-quality health care. *U.S. News and World Report* magazine uses voluntary reporting to identify its best hospitals.

BENCHMARKING—INTERNAL/EXTERNAL

Measures of quality and safety can track progress of improvement initiatives using reporting benchmarks. **Benchmarking** in health care is defined as the continual and collaborative discipline of measuring and comparing the results of key work processes with those who have what are considered best practices.[18] This process enables organizations to continuously measure services, practices, costs, and products using best practices to improve care. There are two types of comparative benchmark models, internal and external.

Internal benchmarks are used to identify best practices within the organization over time. It is important to understand that what is considered best practice within the organization over time may not be reflected in other institutions.[7] To be effective at internal benchmarking, implementing a process designed to promote idea sharing is required. Steps for the process include the following:

1. Identify processes to benchmark.
2. Organize efforts by conducting audits of current processes, determining what tools are most appropriate for the analyzing processes.
3. Identify a similar internal process for comparison.
4. Prioritize ideas from the team and turn them into projects with timelines for adopting best practices.
5. Evaluate outcomes of the two processes to determine what causes the significant differences between them.
6. Evaluate transferability of those aspects leading to improved performance.
7. Transfer the aspects and monitor results.[19]

External benchmarking requires a comparison of work with other organizations with the intent to find new ideas, methods, products, or services. The objective is to continuously improve one's own performance by measuring how it performs by comparing it with others.[20] External benchmarking involves using comparative data between organizations to scale performance and to identify processes that have been proven successful in other organizations. External benchmarking is usually performed through some type of intermediary, such as National Association of Children's Hospitals and Related Institutions (NACHRI) or Children's Hospital Association (CHA). Organizations must be able to define who to benchmark against. Most reporting is general and does not account for differences across the health care continuum. For example, evaluating results for community hospitals and tertiary care facilities may not provide a reasonable comparison.

Some experts believe internal benchmarking is the most important type of comparison. Internal benchmarking may provide several advantages over its external counterpart, because access to information is more readily available. One drawback of external benchmarking is that target companies may be reluctant to share information for fear of losing competitive distinctions.[20] This is typically not the case with internal functions. Another advantage is the transferability of practices. Although there may be geographic and process differences within an organization, a cohesive infrastructure provides a common basis for benchmarking standards. External benchmarking can be difficult with cultural diversity of organizations, practices that may work for one but not another because of varying organizational operations. Finally, internal benchmarking can provide a seemingly safe training environment in which skills and processes can be developed. This process prepares organizations for external benchmarking processes.[20] A disadvantage of internal benchmarking is that set targets may fall short of actual best practice in the industry.

There are known discrepancies in the way in which organizations confirm the existence of **ventilator-associated pneumonia (VAP),** a subtype of hospital-acquired pneumonia that can occur when a person is receiving mechanical ventilation via an artificial airway. This makes it difficult to use external benchmarking data in setting goals for rate reduction. Most organizations are currently using internal VAP rate to set goals for improvement.

RELIABILITY

HIGH-RELIABILITY ORGANIZATIONS

High-reliability organizations (HRO) consistently minimize adverse events despite complex and hazardous work by maintaining a commitment to safety at all levels, from the frontline clinician to upper executives. To improve the ability to provide the highest quality care, health care must apply these concepts, which are described in Table 36-2.

Because many of these concepts are very different from the way providers have practiced in the past, health care workers have to conceptualize ways to apply them. If tasks are too complex, it becomes impossible to distinguish doing the work right from doing it wrong. If there are no opportunities to talk about issues with other staff, there is little chance people will

Table 36-2 High-Reliability Organization Attributes

Sensitivity to operations	There has to be constant awareness of the state of the systems and processes that affect patient care. If errors occur, quickly identify and fix them. People should be familiar with operations beyond their own job. People communicate clearly so there is a clear picture of any given situation. Implementing patient care rounds and safety huddles is a strategy for accomplishing this.
Preoccupation with failure	Systematically study potential problems instead of only reacting to actual problems. Analyze near misses and precursor safety events as failures that reveal potential danger rather than as evidence of success and ability to avoid danger.
Reluctance to simplify	Accept that the work is complex and do not expect simplistic solutions to work. Take nothing for granted. Listen to different points of view. Develop clinical guidelines, protocols, and rapid response teams.
Deference to expertise	To provide quality health service to increase the likelihood of desired health care outcomes, recognize available knowledge and defer to most relevant expertise. Listen to all team members, physicians, nurses, respiratory therapists, parents, patients, etc.
Commitment to resilience	Cultivate the ability to detect, contain, and respond to system failures.

be exposed to other views or information and little opportunity to discuss near misses. If leaders aren't routinely observing and talking with staff providing direct patient care, they will not understand the operations for which they are responsible. Some approaches that have been tried successfully are covered in the following sections.

Simplifying Work Processes

To be successful in making a system more reliable, organizations can reduce what staff are expected to do into a limited set of clearly defined behaviors. Leaders can encourage staff to incorporate error prevention techniques into their work.

Daily Check-Ins

Daily check-ins are short and focused meetings between the unit leadership and staff. This supports the importance of any effort that leadership is involved in and allows staff to raise questions.

Executive Rounds

Leadership within an organization is the driving force behind the culture that exists within it. For quality and safety to be a priority, the message must come from the CEO and board. Having executives around in the clinical environment will create an opportunity for leaders to model the behavior that they want staff to perform. During rounding, hospital leaders are able to retain an awareness of operations that will assist them in good decision making. Rounds allow staff to raise issues with leaders and solidify the importance of quality and safety behaviors. Leaders must follow up on any issues that are raised so continual feedback can occur.

Safety Huddles

Safety huddles are used as a way to gather the clinical team together throughout the day. An example is to have huddles on units every 12 hours to raise safety issues with the entire team. The huddles are usually very short but allow anyone to raise concerns about safety.

Performance Management

Performance management is extremely important to reward staff for desired behavior and identify and resolve any unwanted behaviors.[21]

Implementation of these concepts will result in patient safety being an intrinsic part of how organizations operate all the time. This is proven based on results from other industries similar to health care, in that they are complex, high-risk systems that have accomplished great safety improvements by doing so. They have driven themselves to become HROs. As a definition, "reliability depends on the lack of unwanted, unanticipated and unexplainable variance in performance."[22] What can be learned from other similar industries? In the United States in 1980 there were 7.3 unplanned nuclear reactor shutdowns per 7000 hours. In 2000 there were none (Figure 36-2).

The nuclear power industry worked hard on safety culture and error prevention and was able to achieve this dramatic improvement in safety statistics. The airline industry was able to reduce their accident rate over 30 years from about 25 accidents per year to near zero. This was accomplished using the same principles applied to nuclear power. Despite being complex and high-risk industries, they have successfully developed processes to remain safe.

EVIDENCE-BASED PRACTICE

Health care organizations consist of diverse levels of experience pertaining to clinical process innovations, and staff tolerance for change involving incorporation of evidence into practice differs. **Evidence-based practice (EBP)** can facilitate quality improvement efforts as on ongoing process. Primarily EBP is the multidisciplinary approach to decision making in which the practitioner systematically finds, appraises, and uses the most current and valid research findings as the basis for clinical decisions. These theories can be

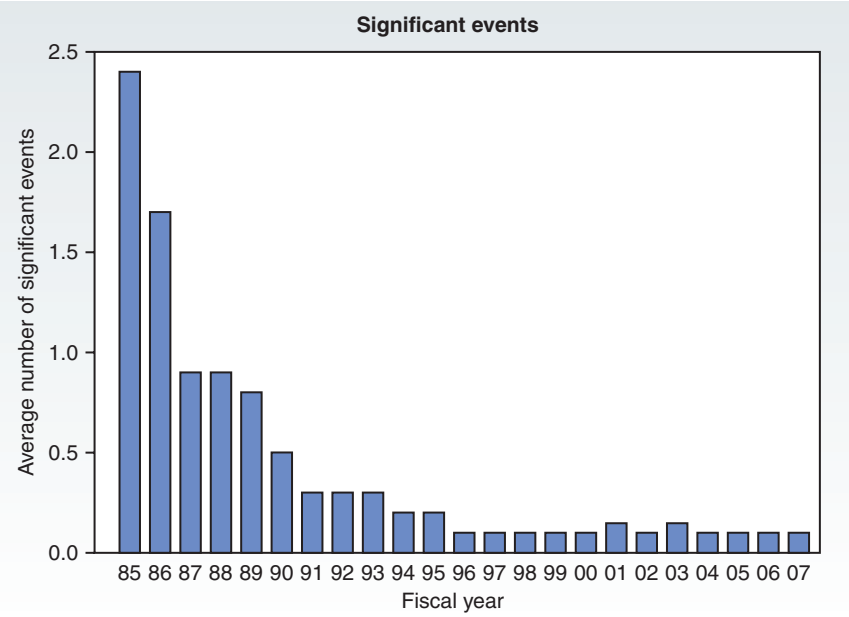


FIGURE 36-2 Nuclear reactor significant events (1985-2007). (Data from U.S. Nuclear Regulatory Commission New Release No. 09-033, February 2009.)

applied to the health care organizational structure and processes. A generalized approach for constructing quality improvement processes should include the following:

- Identification of a problem and executive visibility
- Designation of clinical champion and team
- Process flow chart prepared before and after implementation of the intervention or change, to identify responsibility and ensure resource needs are transparent
- Mapping out of necessary tools to support changes that are developed and used to track outcomes built into decision support and information systems and education training materials
- Monitoring with feedback if provided to involved staff on a regular basis
- Continual detailing of the intervention, which is reviewed for ongoing improvement and maintenance

Figure 36-3 conceptualizes what is required when incorporating evidence into practice.

Clinical care guidelines should be established using evidence to improve clinical outcomes. Challenges in pediatric evidence-based practice are present because of limited accessibility and readiness of applicable data.

PRACTITIONER SKILLS

Achieving high-quality care on a consistent basis in a reliable way requires all health care team providers to make the right decisions about the appropriateness of services as well as the skills, judgment, expertise, and timely execution of care provided.[5] The decision-making process should include focus on utilization of resources, quantity and necessity of treatments and tests ordered, and appropriateness of therapy with a thorough evaluation of risk–benefit analysis. Once the treatment plan is in place, duty falls on the

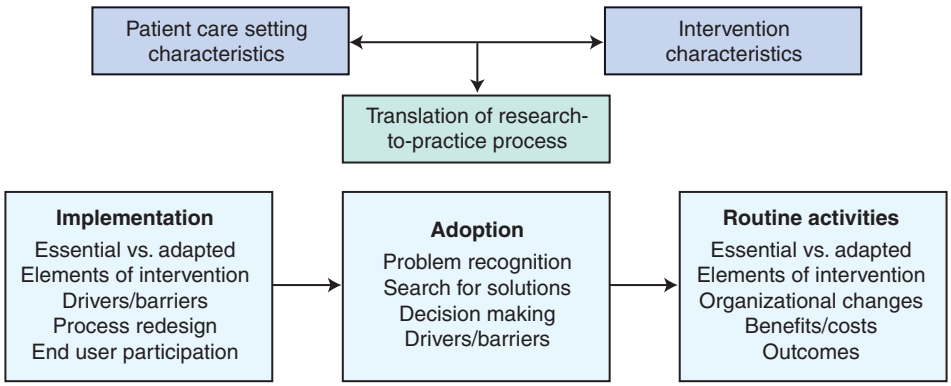


FIGURE 36-3 Transferring evidence into practice.

performance or skill—that is, how well actions were carried out—of the individual to provide care in the manner that fits the policies and standards in place to reduce errors and optimize patient safety.

AGENCY FOR HEALTHCARE RESEARCH AND QUALITY

The AHRQ is a federal authority for patient safety and quality care. The AHRQ is a leader, particularly in pediatrics, funding safety and quality improvement efforts, formulating information, and distributing those findings to health care practitioners and the public to optimize awareness.[23] The reports and assessments provide organizations with comprehensive, evidence-based information on typical medical conditions and new health care technology. More recent reviews of potential pediatric safety issues reveal that a hospitalized child who experiences a safety event, as compared with those who do not, have a length of stay 2 to 6 times longer, hospital mortality 2 to 18 times greater, and hospital charges 2 to 20 times higher. In addition, the severity of illness and type of hospital, outside of birth trauma, are directly associated with patient safety incidents. After extensive review, 18 **quality indicators** for both provider level and diagnostic area were recommended as measurable components. Because these indicators have the most potential to cause an adverse event in hospitalized children, safety systems targeting these areas should reduce length of stay and any additional events in this patient population[23] (Box 36-2).

Box 36-2 Pediatric Quality Indicator Set

PROVIDER-LEVEL INDICATORS	AREA-LEVEL INDICATIONS
Accidental puncture or laceration	Asthma admission rate
Decubitus ulcer	Diabetes short-term complication rate
Foreign body left during procedure	Gastroenteritis admission rate
Iatrogenic pneumothorax in neonates at risk	Perforated appendix admission rate
Iatrogenic pneumothorax in nonneonates	Urinary tract infection admission rate
Pediatric heart surgery mortality	
Pediatric heart surgery volume	
Postoperative hemorrhage or hematoma	
Postoperative respiratory failure	
Postoperative sepsis	
Postoperative wound dehiscence	
Selected infections due to medical care	
Transfusion reaction	

From AHRQ Quality Indicators™: Pediatric Quality Indicators (https://qualityindicators.ahrq.gov/Downloads/Modules/PDI/V50/Pediatric_Ind.pdf).

As part of AHRQ's safety mission and initiatives, this federal agency actively provides information, tools, and grants to improve the statistics for health care–associated infections (HAIs). Action alerts are posted monthly, keeping the health care community up to date with the latest research. The goal is to identify and prevent infections at the point of care.

Health care–associated infections are infections patients acquire while receiving treatment for another condition in some type of health care facility. Millions of infections and thousands of deaths occur annually, making HAIs the most common complication of hospital care. Financially, HAIs add $28 to $33 billion to health care costs. AHRQ researches barriers and challenges in preventing the most common and therefore most costly HAIs. These infections cause extended hospital stays and increased cost and risk of mortality. Types of infections include bloodstream infections (BSIs), catheter-associated urinary tract infections (CATIs), surgical site infections (SSIs), and VAP, which together account for more than 80% of all HAIs.[24]

In an AHRQ Evidence Report/Technology Assessment, *Prevention of Healthcare Associated Infections,* researchers identified proper handwashing hygiene as a major intervention for all HAIs. The report suggests printed or electronic reminders and staff education as successful methods for improving patient outcomes.[24]

According to the US Department of Health and Human Services (HHS), AHRQ is a leader in collaborating and aligning its efforts with cross agencies in developing comprehensive short- and long-term goals to reduce and eliminate HAIs nationwide. The Partnership for Patients is one of those agencies. Their shared goal is to "improve the quality, safety, and affordability of health care for all Americans."[24] This will result in more than 1.8 million fewer injuries with more than 60,000 lives saved over a 3-year period. Working with Partnership for Patients, the AHRQ-prioritized safety measures include those in the following sections.

Reduction of Health Care–Associated Infections

Appropriate timing of antibiotics for surgical patients will help reduce wound infections after surgery, a common occurrence. If successful, postoperative sepsis, a severe bloodstream infection occurring after surgery, will decrease. Receiving the right antibiotic at the right time on the day of surgery is most effective in preventing HAIs postoperatively. Additionally, "ensuring good glycemic control, using appropriate hair removal methods, continuing beta blocker therapy when appropriate, and administering appropriate thromboembolism prophylaxis can reduce morbidity and mortality."[24]

Central Line–Associated Bloodstream Infections

Because children who require central lines are often already in critical condition because of their medical condition, which can include trauma or premature

birth, any new infections can negatively affect their chances of recovery. Great emphasis needs to be placed on the proper insertion and management of central lines, which will result in a significant lowering of infection rates.[24]

Reduction of Serious Adverse Events

Serious adverse events (SAEs) are situations arising from medical and surgical procedures or adverse drug reactions, which are commonly treated in outpatient settings—physician offices, hospital outpatient departments, and hospital emergency departments. If successfully prevented, ambulatory care visits as a result of adverse effects of medical care will diminish.

Mechanical adverse events are SAEs for the homebound patient caused by the placement or use of catheters. Bleeding, hematomas, or knotting of the catheter are examples of these events. Patients often visit an ambulatory care center for assistance.

Respiratory Failure

Respiratory issues are not uncommon after surgery. Reintubation or prolonged mechanical ventilation may be necessary. "Causes include: over-sedation, exacerbation of underlying cardiovascular or respiratory conditions, and ventilator-associated pneumonia."[24] Close attention should be paid to these risk factors.

Preventable and Premature Mortality Rates

Rapid identification and aggressive treatment of complications may prevent deaths after hospital care. Death may occur from "pneumonia, thromboembolic events, sepsis, acute renal failure, gastrointestinal bleeding or acute ulcer, shock, or cardiac arrest."[24]

Thirty-Day Mortality Rates

Reducing deaths within 30 days of admission, especially from pneumonia and acute myocardial infarction, is another safety initiative.

INFORMATION TECHNOLOGY

The role of information technology (IT) is crucial to the quality and patient safety movement. Pediatric-specific technology is evolving but is challenged because of the fact that most computerized systems are designed for adults. Limited effectiveness in preventing medication errors without significant additional improvement processes make for specific localized institutional needs. Health IT systems enable more reliable, effective communication within and across health care settings. Accessibility to patient information at the point of care assists clinicians with decisions and can reduce error potential.[25] A variety of IT health systems are currently available that perform checks in real time, assisting with calculations and alerting providers of potential adverse events. Additional system benefits may include recommended treatment decisions based on evidence-based medicine, prescription systems in which orders are checked for accuracy, and patient records that can be accessible to both health care practitioners and patients.

Technology can be an efficient solution for facilitating prescription orders, whereas the paper-based process often leads to errors resulting from illegible handwriting, incorrect dosing, or missed drug–drug interactions and allergy alerts. As meaningful use stages are defined and increased focus is placed on the ability to exchange health information across health care settings, improved coordination of care is enabled. Health IT systems are tools that have been recognized to prevent medication errors and provide solutions to communication and accountability gaps. IT solutions provide the ability to assist clinical decision making. Although effective IT systems within a health care setting are important in realizing better quality of care, expanding these practices beyond the primary and acute care setting increases the opportunity to detect potential adverse events through access to current, accurate, and complete patient health information.

There are potential drawbacks to IT implementation. If it is not optimally integrated into the workflow of the organization, it can generate extra work for the clinical team. Another barrier to the adoption of IT is the extreme cost of implementation and maintenance of the system. In addition, the cultural adjustment associated with the adoption of a new system such as electronic health records can be challenging if people resist practice change.

DESIGNING SAFE PROCESS

SIX SIGMA

Six Sigma was developed by Motorola as a quality improvement (QI) strategy. The term itself is derived from the Greek letter *sigma*, which statisticians use to measure standard deviations or known variance and the degree to which almost perfect production can occur.[26] Six Sigma is based on the scientific method and involves improving, designing, and monitoring processes to minimize or eliminate waste while optimizing satisfaction and increasing financial stability. There are two main methods Six Sigma uses to measure processes. One inspects process outcomes by counting defects and uses a statistical conversion rate. The second method predicts process performance by estimating process variation.[27]

Six Sigma employs a five-step strategic process: define, measure, analyze, improve, and control.[28] Goals, stakeholders, and process owners of an improvement activity are identified in the define stage of the Six Sigma strategic process. A task is identified, historical data are reviewed, and a scope of expectations is defined. Various tools such as focus groups, mapping, and cause–effect diagrams are used to define improvement process.[29] Next, standards are selected and performance

objectives and sources of variability are defined. During the measure step, quantitative measurements of current practices are compiled. Collected data are analyzed and validated to determine the capability of the new process. In addition, objective data are used to identify ways to eliminate gaps between the current state and the desired state, and statistical tools are used to guide improvement plans. In the improve stage, planned changes are implemented and evaluated. Quantitative data are collected again and used to evaluate the outcome of the implemented change. The final step of the process is the control step. This step is considered the most important in the process: requirement identification and construction of formal plans and processes for maintaining control of the new system.[26]

Although created for the manufacturing industry, Six Sigma is successfully used to decrease defects and variations, decrease operating costs, and improve outcomes in a variety of health care settings and processes.[27] Standardizing processes to improve efficiency and outcomes should be a focus of patient safety efforts in health care organizations.

LEAN PRODUCTION

The **Lean methodology**, derived for the Toyota production system, targets customer needs and aims to improve processes by removing activities that are considered no-value-added. The basic principles of Lean are to minimize waste in all aspects of production. The critical components of Lean include identifying exactly what defines "value" to the customer and then creating a value map, similar to a process map but with the addition of a value-added or no-value-added step from the customer's perspective.

Successful application of the Lean methodology in the health care system includes eliminating unnecessary activities associated with overcomplicated processes and workarounds with frontline staff.[27] The goal of the methodology is to maximize value added, activated in the best possible sequence, to enable continuous operations. In essence this will improve quality and prevent errors.[27] In addition, Lean methodology can be used to develop applications for evidence-based practice processes and needs.[26]

ROOT CAUSE ANALYSIS

Another extensively used technique to identify and understand the underlying causes of an event as well as potential associated events is RCA. The RCA technique is a retrospective, systematic process using information from an unplanned event to identify and understand the underlying causes of the event.[26] It is used to identify trends and assess risk when human error is suspected, with the understanding that the system issues, not individual factors, are likely the root cause of most problems.[6] It is important to understand in health care that a problem often has more than one cause and that errors as a result of those causes can be interrelated.

A multidisciplinary team completely examines the event, aims to uncover underlying causes, and identifies causal, situational, enabling, and contributing factors, both active and latent, of the incident. The final step of the RCA is developing recommendations for system and process improvement based on the findings of the investigation.[27] RCA has been shown to be a useful technique to report errors and differentiate between active and latent errors, identifying the need for change to policies and procedures and serving as a basis to suggest system changes, including improving the communication of risks.[27]

The Joint Commission now requires an RCA be performed in response to all sentinel events (significant harm to a patient) and expects the organization to develop an action plan aimed at reducing future risks based on the findings, as well as to monitor the effectiveness of the action plan.[26]

FAILURE MODES AND EFFECTS ANALYSIS

Failure Modes and Effects Analysis (FMEA) is a prospective risks assessment tool used to identify and eliminate known and potential failures, problems, and errors for a system, design, process, or service before they actually occur. This technique was developed by the US military and is used by the National Aeronautics and Space Administration (NASA) to predict and evaluate potential failures and unrecognized hazards and to proactively identify steps in a process to reduce or eliminate future failures. It was adapted for health care by the Department of Veteran Affairs and the National Center for Patient Safety.[26]

In health care the goal is to use a multidisciplinary team to evaluate a process from the quality improvement perspective.[27] The estimated effect of each process failure is determined by how likely it is to occur, how visible the failure is, and how catastrophic the failure would be if it happened. Information learned from the FMEA process can be used to provide data for prioritizing improvement strategies, serve as a benchmark for improvement efforts, educate and provide a rationale for practice change, and increase the ability of the team to facilitate change across all services and departments within a hospital.[27] This tool is most effective when new processes are being designed.[26]

Health Failure Modes and Effects Analysis (HFMEA) is used to provide detailed hazard analysis of smaller processes and develop specific recommendations. It is important to list all possible and potential failure modes of each process and determine whether they warrant further action.[27]

How are these quality improvement strategies similar? Can they work together in synergy or should they be done in isolation? Although these QI systems were developed from outside the medical field, they have

successfully been adapted to health care processes. Lean and Six Sigma are often used together; though different in approach, their complementary processes can be used simultaneously. Six Sigma can be used to identify variation of practice, then measure the scope of the problem. Lean can identify the voice of the customer and the defined value to formulate the clinical question to ask. A part of Lean is **Kaizen,** which means continuous quality improvement, emphasizing the philosophy that poor quality arises from bad systems rather than bad people, which is part of the Lean principles.[30]

PLAN-DO-STUDY-ACT

The **Plan-Do-Study-Act (PDSA;** Figure 36-4) method is aggressively used to make constructive changes in the health care industry as a rapid-cycle improvement process.[31] It is one of the most commonly used methodologies in health care. Introduced by Shewart and Deming as a continuous quality improvement business practice, PDSA moved into health care when the Institute for Healthcare Improvement (IHI) recommended it for implementing a process for quick change.[26] This method uniquely implements small and frequent changes that are analyzed for effectiveness before they are implemented on a large-scale basis.[31] The PDSA quality improvement efforts aim to establish a functional relationship between changes in behavior and capability and outcomes. To establish targeted constructive changes, three questions are posed before implementing a PSDA cycle:

1. What is the goal of the project?
2. How will one know whether the goal was reached?
3. What will be done to reach the goal?

The PDSA method aims to determine the nature and scope of the problem, the necessary changes, a plan to implement those changes, who should be involved, and what should be measured to determine the impact of the change. Once data and information are collected, key measures are reviewed to indicate the success or failure of the implementation.[27] In the *Planning* phase, current situations and root causes are evaluated. The hypothesis is developed about what will occur with the change. The *Do* phase includes small-scale testing or pilots being carried out. The *Study* or check phase examines the results. It is in this phase where the assessment of the change is based on quantitative or qualitative data. In the *Act* phase, the decision to enact or abandon the planned change is made from the analysis of data in the previous stage. This includes whether the change will be moved to larger scale implementation. Ideally multiple PDSA cycles are used in succession, starting with the easiest and then moving to more difficult.[26] Most PDSA quality improvement efforts find greater success using a series of small and rapid cycles to achieve the goals of intervention.[27]

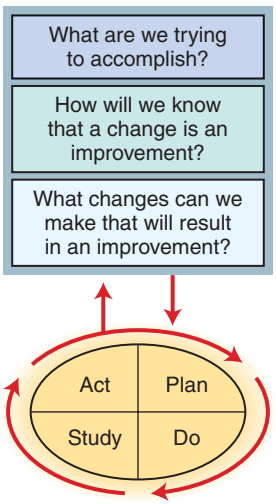


FIGURE 36-4 Plan-Do-Study-Act cycle.

TOOLS FOR PROCESS EVALUATION

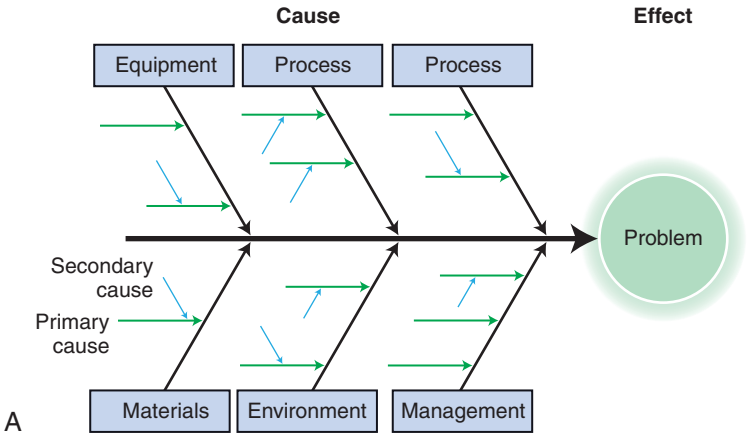
A variety of tools ranging from basic to complex are used to define and analyze distinct processes that typically produce quantitative data. This section provides a few examples of quality tools used by organizations to facilitate improvement processes.

Flowcharts are used to map each step of a process showing logical sequencing for completion of an operation. A flowchart is a good starting point for a team seeking to improve an existing process or planning a new process or system. Check sheets are simple tools to measure the frequency of events or defects over a time interval. This process is used for information gathering and can be used easily while providing immediate data to help understand processes.

In cause-and-effect diagrams, commonly known as fish-bone diagrams, the problem (effect) is stated in a box and the likely causes (bones) are listed around the heading that leads to the effect. This is often used to identify contributing factors of a complex problem. The spaghetti diagram is a visual way to depict the material or information flow through a process in a diagrammatic form (Figure 36-5). The spaghetti diagram helps identify waste that is often not even recognized as such—for example, walking to and from a medication dispensing machine that is located too far away for staff using it. This diagram helps determine the physical flow and distance that information and people travel to process work (see Figure 36-5).

Tree diagrams help to identify the tasks and methods needed to solve a problem and reach a goal. These diagrams entail creating a detailed list of tasks that need to be accomplished to achieve a goal. One example of a tree diagram is a driver diagram. Figure 36-6 is an example of the driver diagram process used to outline reducing HAI through the reduction of VAP.

Quality tools are different than the improvement process. Multiple tools might be needed for any given process improvement project.



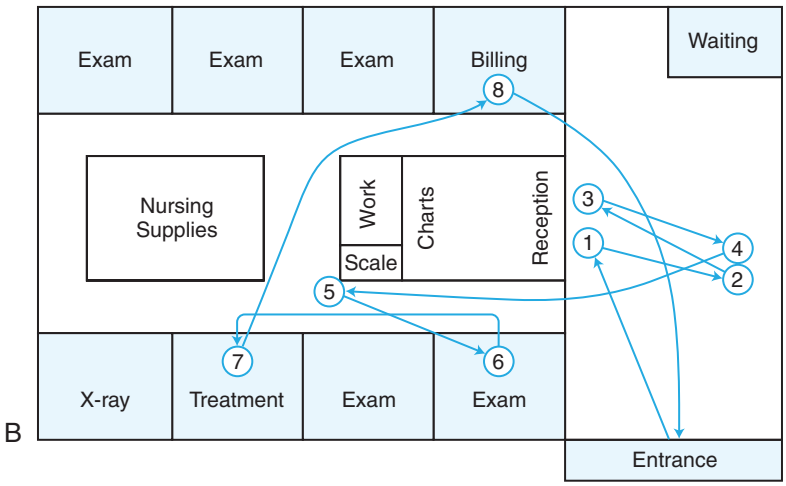


FIGURE 36-5 A, Fishbone diagram. B, Spaghetti diagram.

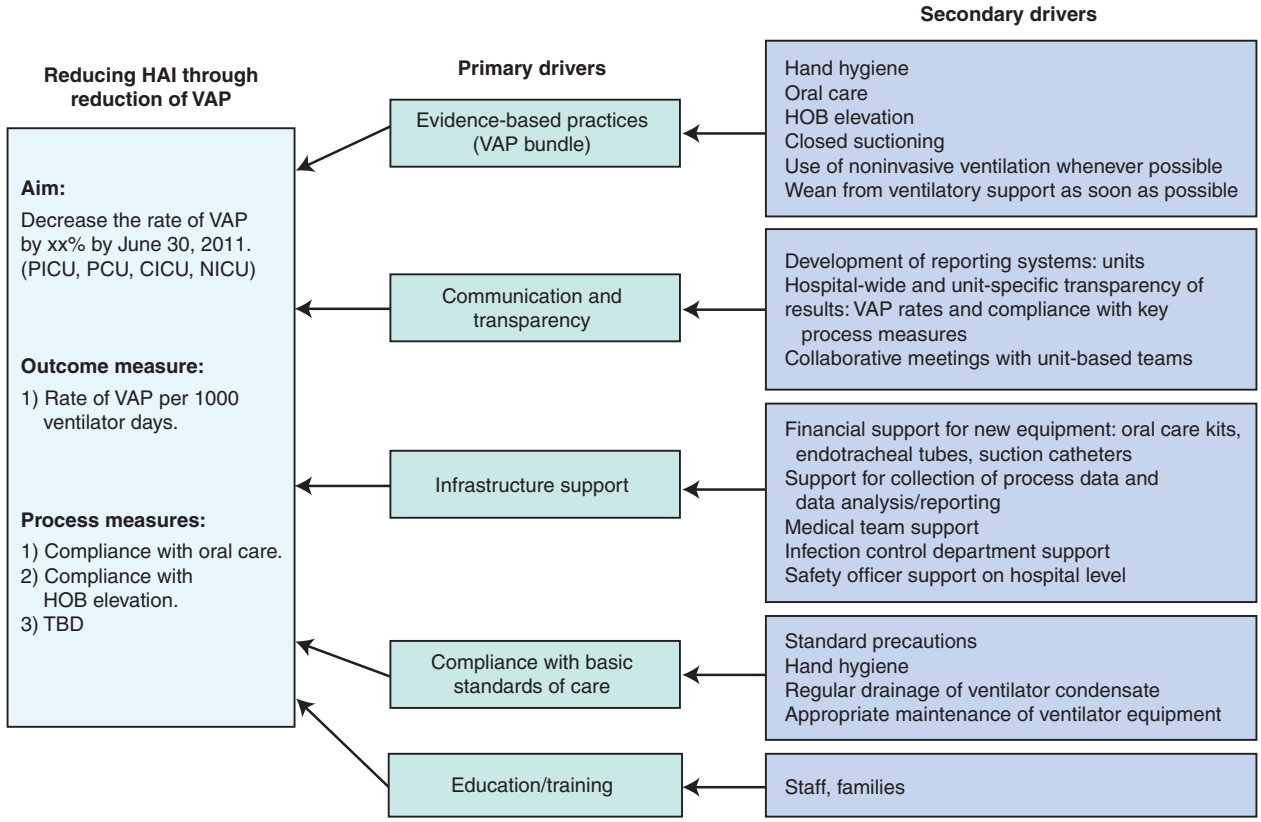


FIGURE 36-6 Driver diagram. *CICU,* Cardiac Intensive Care Unit; *HAI,* health care–associated infections; *HOB,* Head of Bed; *NICU,* neonatal intensive care unit; *PCU,* Progressive Care Unit; *PICU,* pediatric intensive care unit; *TBD,* To Be Determined; *VAP,* ventilator-associated pneumonia.

HANDOFF COMMUNICATION

Handoff communication is a high-risk process causing errors that lead to ineffective care and patient safety breaches. It is estimated that 80% of serious medical errors involve miscommunication among caregivers when a patient is transferred or handed off to another area. Improving the accuracy, completeness, and accessibility of patient information can reduce ineffective handoff communication. In 2006 the Joint Commission added a handoff-related goal to its expanding set of national patient safety goals and made specific expectations that health care organizations implement a standardized approach to handoff communication. One way to improve communication processes is the use of a standardized method of handoff.

CULTURE OF SAFETY

A study by Taylor et al. showed the incident report system used in children's hospitals does not always support quality care. Their study showed that incidents of actual harm to the child were reported, but not "near misses." Quality improvement comes from the "near misses" as well as the harmful events. Improving education of staff concerning what should be reported and how to report an incident is a priority. They summarized that a reporting system should be "easily accessible, require a small amount of time and be in electronic format, where possible."[32] As Taylor's team states, ultimately, reporting medical errors should be seen not as a punitive exercise but as an essential ingredient in providing optimal patient care.[32]

James Reason, a well-known professor and expert on the practice and theory of safety, describes safety cultures as shared values and beliefs that interact with an organization's structures and control system to produce behavioral norms. An ideal safety culture is the necessary driver in sustaining efforts to reduce operational hazards. Two kinds of fallibility are present: individual and systems. Individual accidents are ones in which specific persons or groups are both the agent and the victim.[33]

There are many layers of defense, barriers, and safeguards that are a part of a systems approach to prevent errors. They include alarms, physical barriers, and alerts, as well as procedural and administrative controls. Their function is to protect patients from hazards or harm. Most often they work effectively, but many systems have weaknesses or gaps. These gaps are created by active failures and latent conditions. Nearly all adverse events involve a combination of these two factors. Active failures are unsafe acts committed by people who are in direct contact with the patient or system. Latent conditions are the inevitable flaws within the system caused by failures in design or process and management's inability to anticipate all possible scenarios. The Swiss cheese models shown in Figure 36-7 illustrate both how layers work to prevent errors from reaching patients and how at times the holes line up in sequence to allow harm to patients and produce what can be a serious adverse event.[34]

SAFETY BEHAVIORS FOR ERROR PREVENTION

A key area for improving safety is to promote behaviors that prevent errors. Most organizations have implemented methods to do this based on an analysis of their own needs and what will work best within their internal culture to obtain the best improvement results. Techniques for preventing errors may include coaching and cross-checking, speaking up for safety by incorporating

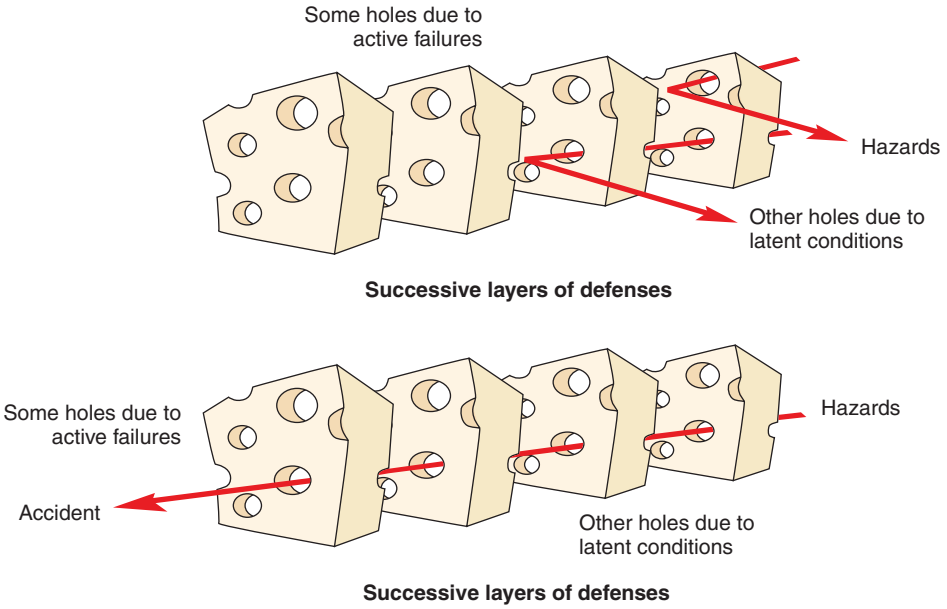


FIGURE 36-7 Swiss cheese models.

an organizational phrase that should make everyone stop and listen, critical thinking development, effective communication techniques, and paying attention to details. Everyone must incorporate coaching and cross-checking into the way an organization functions. It must be viewed as a positive intervention. It is important to look out for one another to catch possible mistakes and build a greater sense of accountability of the team. This helps everyone perform at their best and promotes team performance. It involves encouraging safe and productive behaviors and discouraging behaviors that are not a part of the peer coaching process. Often a 5:1 positive feedback ratio is used to reinforce good habits and eliminate bad ones.

Speaking up for safety normally encompasses using smart words to guide practices and avoid resistance; verbiage typically includes phrases like "I have a concern," "I need clarification," and "Help me to understand." It will also provide a means for going up the chain of command if necessary.

Thinking critically about observations made during the course of the workday, asking questions, and listening to your "gut" enable practitioners to practice with a questioning attitude. It is important to reflect on practices and processes that one may have issues with and resolve any questions that one may have with source verification, content expert substantiation, and other confirmation processes.

Paying attention to detail can be very effective in avoiding slips during patient care. Self-checking by stopping and thinking before acting can reduce the probability of making an error. This process should only take a few seconds and is especially critical when asked to perform a task that one has not done in a while.

Communicating effectively entails a variety of safety practices to ensure accurate communication and understanding. Phonetic clarification is a tool to ensure that correct information is being transmitted. When communication involves a letter, the letter is followed by a word that begins with the letter—for example, "C Charlie, A Alpha, T Tango." In addition, numerical clarification is used to ensure that accurate numbers are being communicated. For 50, one would say, "50, that's five-zero." Implementation of leading zero placement and following zero elimination when using decimals is another effort in place to improve communication.

Handoff communication using **SBAR** (Situation/Background/Assessment/Recommendation) has become a widely accepted sign-out strategy because of the support of the Joint Commission and the IHI. It uses a structured method for all communication practices between providers.[24]

Situation: Who or what you are calling about and the immediate problem

Background: A brief description of the relevant history related to the condition

Assessment: Your view of the situation and your perception of the urgency of action

Recommendation: Your suggestion about the action that should be taken or your request for guidance on what action to take

SBAR originated at Kaiser Healthcare but can also be credited to the nuclear US Navy. The Joint Commission then expanded the strategy to include interactive communication that allowed for questions between givers and receivers of information, a process for verification of the information exchanged, and an opportunity to review historical data and finally a process that limited interruptions.[35]

A three-way repeat back is another method to ensure that important information is transferred in a clear, complete, and accurate manner. This involves the sender providing an order, request, or information in a clear and concise format; the receiver acknowledges by repeating back the order, request, or information, and then the sender acknowledges the accuracy of the repeat back. If the information is incorrect, the process is repeated.

Patient safety has to become second nature and an intrinsic part of how respiratory therapists practice. As part of the multidisciplinary team, respiratory therapists have a responsibility to perform the techniques mentioned in this chapter to reduce errors and improve practice. As public awareness has increased and continues to do so, all health care organizations will need to be able to provide evidence of improvements in safety. To accomplish this, there will be many exciting changes in the future. Respiratory therapists need to be involved in and lead such changes in areas related to practice. In 1859 Florence Nightingale said, "It may seem a strange principle to enunciate as the very first requirement in a Hospital that it should do the sick no harm."[36] Although this concept was never fully understood at the time, the time is now to do so. We have a long way to go, but by embracing proven quality and safety techniques, health care can be as safe as other high-risk, complex industries.

Case Study

As hospitals engage in creating a culture of safety within their organizations, elimination of health care–associated infections has been a focus. In Tyoli Hospital it was noted that there had been 5 ventilator-associated pneumonias (VAP) per 1000 ventilator days confirmed using Centers for Disease Control and Prevention criteria over the past month. The hospital realized an improvement effort must be initiated. A multidisciplinary team was assembled to consider how to move forward. The team consisted of respiratory therapists, nurses, physicians, and infection prevention specialists. When the team convened, they realized they needed data and information to move forward. They performed a literature review of VAP, did external

Continued

benchmarking, and reviewed practices across all intensive care units to look for best practices. Specific care elements for patients on ventilators were clustered into a bundle. A bundle is a group of independent steps that when implemented collectively and reliably result in significantly better patient outcomes than when individually applied. An example of a bundle to reduce VAP is provided in the following list:

- Elevation of head of bed
- Daily assessment of readiness to extubate
- Comprehensive oral care
- Daily assessment of readiness to wean/extubate
- Keeping ventilator circuit free from condensate
- Inline suction catheters
- Peptic ulcer disease prophylaxis
- Deep venous thrombosis prophylaxis

When all these things were completed, the team developed a driver diagram (see Figure 37-5). The diagram identified factors that would affect accomplishing the goal of reducing VAP, along with the specific reduction goal and the process measures used to monitor compliance with implemented changes.

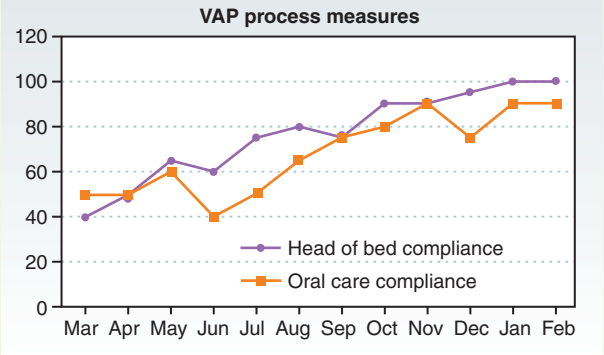
The next phase was educating all staff involved in care of patients on ventilators, with the expectation that everyone would follow the same care bundle, and included all disciplines. Clinical champions were identified for each area and discipline to lead the process change. The implementation process can be launched successfully if the health care system is effectively designed, with champions from administration, leadership, and frontline staff maintaining the initiative's momentum. Before implementing the standardized care delivery process, staff members were introduced to evidence-based information about VAP. They also were oriented to the ventilator bundle and daily goal sheets at staff meetings and in-services, through poster presentations and one-to-one individual sessions. Ongoing education, reeducation, and reinforcement provided ample opportunity for staff to voice concerns, ask questions, and offer feedback about the initiative.

Case Study

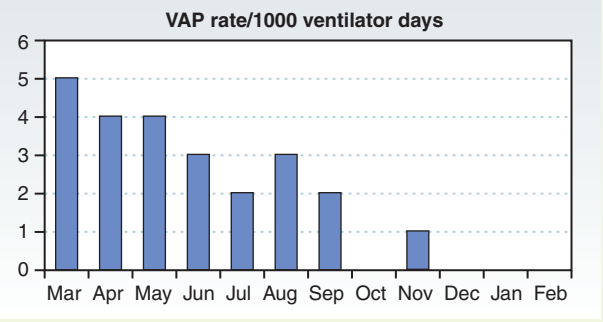
Ventilator-Associated Pneumonia

Compliance rate for identified process measures were used as an indicator of degree of bundle implementation. Compliance rate was calculated as the number of interventions delivered versus the number of possible interventions. Weekly audits were conducted to collect data and track compliance with the use of the daily goal sheet and the bundle interventions, reeducating and reinforcing, as necessary, to address any noncompliance issues. Once data were available, findings were analyzed and reported graphically to visually reinforce the staff's efforts. In addition, a weekly schedule for team meetings to allow for open communication occurred, which encouraged participation and gained buy-in from the frontline clinicians. Storyboards for emphasis of implementation and current VAP rate (as an example, "Days VAP free") were useful tools in making these changes to standard operating procedure.

The following figure displays the process measure compliance over the next year.



Tyoli hospital continued its focus on VAP prevention and monitored VAP rates per 1000 ventilator days monthly. Their VAP rates are depicted in the following figure.



After review of these data, Tyoli hospital's efforts at VAP reduction would be best affected by implementing which of the following?

1. Reeducation of staff on head of bed to influence VAP rates.
2. Implementation of oral care kits to improve compliance.
3. Continuation of current activities while monitoring compliance.
4. Selection of other process measures to improve VAP rates.

See Evolve Resources for answers.

Key Points

- Health care quality is defined as the degree to which health services for individuals and populations increase the likelihood of desired health outcomes (quality principles), are consistent with current professional knowledge (professional practitioner skill), and meet the expectations of the marketplace. Patient safety is the foundation upon which all aspects of quality care are built.
- The awareness and subsequent scrutiny of quality care evolved through massive reporting processes and evaluation of landmark events. In 2000 the IOM issued *To Err Is Human: Building a Safer Health System.* The second major report from the IOM committee, *Crossing the Quality Chasm: A New Health System for the 21st Century* (2003), expanded the work, calling for action to improve the American health care delivery system as a whole.
- The culture of health care organizations must shift to emulate the importance of teamwork.
- The concept of a just culture in lieu of no blame has been introduced to address the concept of accountability and unsafe behavior. A just culture focuses on identifying and addressing systems issues leading individuals to engage in unsafe behaviors while maintaining individual accountability by establishing a zero tolerance for recklessness.
- Demonstrating improvements in quality outcomes encompasses measuring whether efforts made lead to change toward the primary goal or at least moving in the desired direction. Internal and external benchmarking are two methods used to calculate outcomes.
- HROs consistently minimize adverse events despite complex and hazardous work by maintaining a commitment to safety at all levels, from the frontline clinicians to upper executives. This is accomplished by sensitivity to operations, preoccupation with failure, reluctance to simplify, deference to expertise, and commitment to resilience.
- Information technology provides accessibility to patient information at the point of care, assists clinicians with decisions, and can reduce error potential. Drawbacks include the generation of extra work for the clinical care providers, the extreme cost of implementation, and a cultural adjustment associated with the adoption of a new system.
- Safety processes include Six Sigma, Lean methodology, RCA, FMEA, and PDSA. Tools include fishbone diagrams, spaghetti diagrams, and flowcharts.
- James Reason describes the many layers of defense, barriers, and safeguards that are part of a systems approach to prevent errors, but gaps or holes are present that may lead to patient harm. Nearly all adverse events involve a combination of these two factors. Active failures are unsafe acts committed by people who are in direct contact with the patient or system. Latent conditions are the inevitable flaws within the system caused by failures in design or process and management's inability to anticipate all possible scenarios.
- Methods health care practitioners can use to prevent errors include coaching and cross-checking, speaking up for safety, thinking critically about observations, paying attention to detail, and communicating.

Assessment Questions

See Evolve Resources for answers.

1. The Institute of Medicine defines what as the foundation upon which quality care is built?
   a. Safety
   b. Situational awareness
   c. Errors
   d. Research
2. *To Err is Human* said approximately how many patients were injured per year as a result of medical errors in the United States?
   a. 25,000
   b. 150,000
   c. 77,000
   d. 100,000
3. When using a crew resource management philosophy in health care, who would be considered able to ask questions to anyone on the team?
   a. Physician
   b. Nurse
   c. Respiratory therapist
   d. Anyone
4. Using the concept of a just culture, if a respiratory therapist fails to follow proper procedure when the system supports such procedures, the therapist would be dealt with in what way?
   a. System improvement
   b. Employee accountability and discipline
   c. Employee termination
   d. System interruption and reengineering
5. Benchmarking is a common practice in comparing results (quality) both internally and externally. Which of the following statements is true about benchmarking?
   a. External benchmarking is an easy way to compare organizations.
   b. Internal benchmarking provides more access to information.
   c. External benchmarking always specifies differences between types of hospitals.
   d. Internal benchmarking makes it difficult to effect change.
6. What types of work can evidence-based practice help support?
   a. Care protocols and guidelines
   b. Safety error resolution
   c. Staff callout procedures
   d. Management education
7. The use of electronic medical records can improve patient care by providing which of the following?
   a. Workflow between different areas of the hospital
   b. Making it less expensive to provide care
   c. Enhancing accuracy of prescriptions
   d. Giving the clinician less patient information
8. What attribute do Six Sigma and Lean methodology have in common?
   a. Process and efficiency improvement
   b. Fishbone diagram implementation
   c. Clinical outcome variation
   d. Employee and management development

9. The Swiss cheese model by James Reason is used to describe which of the following concepts?
   a. There are no defenses to prevent errors.
   b. Quality improvement can only be based on serious safety events.
   c. Employees do not fear punitive responses to errors.
   d. There are defenses against errors but errors still occur.

10. Which of the following is the most important thing health care providers can improve to enhance patient safety?
   a. Communication
   b. Detail orientation
   c. Staffing levels
   d. Orientation

REFERENCES

1. Steering Committee on Quality Improvement and Management and Committee on Hospital Care. Policy statement–principles of pediatric patient safety: reducing harm due to medical care. *Pediatrics*. 2011;127(6):1199-1210.
2. Woods DM, Holl JL, Shonkoff JP, Mehra M, Ogata ES, Weiss KB. Child-specific risk factors and patient safety. *J Patient Saf*. 2005;1(1):17-22.
3. Leape LL, Brennan, TA, Laird N, et al. The nature of adverse events in hospitalized patients: results of the Harvard Medical Practice Study II. *N Engl J Med*. 1991;324(6):377-384.
4. Suresh G, Horbar JD, Plsek P, et al. Voluntary anonymous reporting of medical errors for neonatal intensive care. *Pediatrics*. 2004;133(6):1609-1618.
5. Buttell P, Hendler R, Daley J. Quality in healthcare concepts in practice. In: Cohn KH, ed. The Business of Healthcare. Vol 1. Westport, CT: Preager; 2007:61-95.
6. America CO. Crossing the Quality Chasm: a New Health System for the 21st Century. Washington, DC: National Academy Press; 2001.
7. Kohn L, Corrigan J, eds. To Err is Human: Building a Safer Health System. Institue of Medicine, Committee on Quality of Health Care in America. Washington DC: National Academy Press; 2000.
8. Nance JJ. Why Hospitals Should Fly. Bozeman, MT: Second River Healthcare Press; 2008.
9. Institute of Medicine. Preventing Medication Errors. Available at: http://www.iom.edu. Accessed September 2012.
10. Andel C, Davidow SL, Hollander M, Moreno DA. The economics of health care quality and medical errors. *J Health Care Finance*. 2012;39(1):39-50.
11. Shreve J, ven Dan J. The Economic Measurement of Medical Errors. Schaumberg, IL: Society of Actuaries/Milliman; 2010.
12. Ransom ER, Joshi MS, Nash DB, Ransom SB. The Healthcare Quality Book. 2nd ed. Chicago: Health Administration Press; 2008.
13. Marx D. Patient Safety and the "Just Culture": A Primer for Health Care Executives. National Heart, Lung, and Blood Institute; National Institutes of Health: AHRQ; 2001:1-28.
14. Healthcare Performance Improvement. www.HPIresults.com: Available at: http://www.hpi.com. Accessed September 2012.
15. The Joint Commission. Sentinel Event. The Joint Com-mission; [Online] 2013. Available at: http://www.jointcommission.org/sentinel_event.aspx. Accessed October 2012.
16. Joint Commission on Accreditation of Healthcare Organizations, USA. Tubing misconnections–a persistent and potentially deadly occurrence. *Sentinel Event Alert*. 2006;(36):1-3.
17. Varkey P, Reller MK, Resar RK. Basics of quality improvement in health care. *Mayo Clin Proc*. 2007;82:735-739.
18. Gift RG. *Benchmarking in Health Care*. 5th ed. Chicago: American Hosptial Publishing; 1994.
19. Southard PB, Parente DH. A model for internal benchmarking: when and how? *Benchmarking Int J*. 2007;14(2):161-171.
20. Kay JF. Health care benchmarking. *H K Med Diary*. 2007;12(2).
21. Hines S, Luna, K, Lofthus J, et al. *Becoming a High Reliability Organization: Operational Advice for Hospital Leaders*. Contract No. 290-04-0011. The Lewin Group: Agency for Healthcare Research and Quality: 2008. http://www.ahrq.gov/professionals/quality-patient-safety/quality-resources/tools/hroadvice/hroadvice.pdf.
22. Hollnagel E. Simplification of complexity: the use of simulation to analyze the reliability of cognition. In: Aldemir S, MA, Cacciabue PA, eds. *Reliability and Safety Assessment of Dynamic Process Systems*. Berlin: Springer Verlag; 1993.
23. Lacey S, Smith JB, Cox K. Pediatric safety and quality. In: Hughes R, ed. *Patient Safety and Quality: An Evidence Based Handbook for Nurses*. Rockville, MD: Agency for Healthcare Research and Quality; 2008:1-30.
24. Agency for Healthcare Research and Quality. *Patient Safety Primers*. Safety Culture. U.S. Department of Health and Human Services; September 2012. http://psnet.ahrq.gov/primer.aspx?primerID55. Accessed January 2013.
25. Cortelyou-Ward K, Swain A, Yeung T. Mitigating error vulnerability at the transition of care through the use of health IT applications. *J Med Syst*. 2012;36:3825.
26. Seidl KL, Newhouse RP. The intersection of evidence-based practice with 5 quality improvement methodologies. *J Nurs Adm*. 2012;42(6):299-304.
27. Hughes RG. Tools and strategies for quality improvement and patient safety. In: Hughes RG, ed. *Patient Safety and Quality: An Evidence Based Handbook for Nurses*. Rockville, MD: Agency for Healthcare Research and Quality; 2008: 1-20.
28. Barry R, Murcko A. *The Six Sigma Book for Healthcare: Improving Outcomes by Reducing Errors*. 1st ed. Chicago, IL: Health Administration Press; 2003.
29. Lanham B, Maxson-Copper P. Is Six Sigma the answer for nursing to reduce medical errors and enhance patient safety? *Nurs Econ*. 2003;21(1):39-41.
30. Graban M, Swartz JE. Change for health. *Manage Serv*. 2012; 56(2):35-39.
31. Berwick DM. Developing and testing changes in delivery of care. *Ann Intern Med*. 1998;128(8):651-656.
32. Taylor JA, Brownstein D, Christakis DA, et al. Use of incident reports by physicians and nurses to document medical errors in pediatric patients. *Pediatrics*. 2004;114:729-735.
33. Reason J. Achieving a safe culture: theory and practice. In: *Work & Stress*. Vol 3. Abingdon, Oxford, UK: Taylor & Francis Ltd; 1998:293-306.
34. Reason J. Human error: models and management. *BMJ*. 2000;320:768-770.
35. Freitag M, Carroll VS. Handoff communication: using failure modes and effects analysis to improve the transition in care process. *Qual Manag Health Care*. 2011;20(2):103-109.
36. Nightingale F. *Notes on Hospitals*. London: Longman, Green, Longman, Roberts, and Green; 1863.

37. Agency for Healthcare Research and Quality. *TeamSTEPPS*. AHRQ; 2017. Available at: https://www.ahrq.gov/teamstepps/index.html. Accessed March 2017.
38. King HB, Battles J, Baker DP, et al. TeamSTEPPS™: Team Strategies and Tools to Enhance Performance and Patient Safety. In: Henriksen K, Battles JB, Keyes MA, et al., eds. *Advances in Patient Safety: New Directions and Alternative Approaches (Vol. 3: Performance and Tools)*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008 August. Available at: https://www.ncbi.nlm.nih.gov/books/NBK43686/.
39. Agency for Healthcare Research and Quality. TeamSTEPPS. AHRQ: 2017. Available at: https://www.ahrq.gov/teamstepps/instructor/essentials/pocketguide.html#frame. Accessed March 2017.

Glossary

A

Abdominal compartment syndrome Intraabdominal pressure >20 mmHg with associated organ dysfunction. Symptoms include acute kidney injury due to pro-inflammatory cytokines, venous compression, and local renal compression, as well as competition with diaphragmatic excursion.

Acrocyanosis Blue hands and feet with decreased perfusion.

Acute life-threatening event An episode characterized by some combination of apnea (central or obstructive), color change (cyanotic, pallid, erythematous or plethoric) change in muscle tone (usually diminished), and choking or gagging.

Acute lung injury Acute respiratory failure with substantial morbidity and mortality. See *ARDS*.

Acute respiratory distress syndrome (ARDS) A severe form of acute lung injury characterized by pulmonary edema and alveolar collapse secondary to the disruption of the alveolar-capillary membrane and surfactant dysfunction. Subsequently, hypoxemia and widespread infiltrates on chest radiographs can occur after a variety of predisposing pulmonary and nonpulmonary insults.

Adaptive control ventilation Uses a pressure setting as the main determinate of lung inflation; however, it adjusts the pressure to maintain a desired tidal volume based on a preset algorithm.

Adaptive pressure ventilation A mode of ventilation that can provide either support or control modes of ventilation and adjust to lung physiology based on measured parameters determined by a preset closed-loop algorithm.

Aerosol A suspension of solid or liquid particles suspended in a gas.

Aerosol therapy Delivery of medical or bland aerosols generated by an aerosol device such as the nebulizer, the pressurized metered-dose inhaler or the dry-powder inhaler for the treatment of patients with pulmonary or systemic diseases.

Agency for Health Care Research and Quality (AHRQ) A federal authority for patient safety and quality care.

Air bronchogram The radiographic appearance of the air-filled bronchus against surrounding opacified alveoli.

Airway clearance technique (ACT) Sometimes called *airway clearance therapy.* A therapy or technique designed to improve secretion or mucus management.

Airway obstruction Obstruction of the upper or lower airway.

Airway resistance The pressure difference per unit flow as gas flows into or out of the lungs (flow/pressure).

All-age reference equations Published in 2012 by the European Respiratory Society Global Lung Initiative taskforce, these equations define normal values for common spirometry indices down to 3 years of age.

Allograft rejection The rejection of tissue transplanted between two genetically different individuals of the same species.

Alveolar volume The tidal volume that interacts with the alveolar-capillary membrane and is involved in gas exchange.

Amnioinfusion Injection of normal saline into the amniotic sac.

Anaphylaxis Systemic immunoglobulin E–mediated hypersensitivity response resulting from exposure to foreign antigen.

Anencephaly Congenital absence of the cranial vault, with the cerebral hemispheres completely missing or reduced to small masses.

Anesthetic gas mixtures Volatile gases designed to provide inhalational anesthesia. Anesthetics such as isoflurance, halothane, desflurance, enflurance, and sevoflurane.

Angiogenic clusters Small cellular pools that supply nutrition to the growing embryo. Also called *blood islands.*

Angioembolization A treatment that clogs small blood vessels and blocks the flow of blood.

Aorticopulmonary septum Formed by ridges between the bulbus cordis and truncus ultimately developing into separate aortic and pulmonary arteries.

Apgar Score Evaluation of newborns based on five factors heart rate, respiratory effort, muscle tone, reflex irritability, and skin color.

Apnea Pathological condition in which breathing ceases for longer than 20 seconds.

Apnea of prematurity (AOP) Sudden cessation of breathing that lasts for at least 20 seconds or is accompanied by bradycardia or oxygen desaturation (cyanosis) in an infant younger than 37 weeks of gestation.

Arterial blood gas Blood gas analysis of an arterial sample obtained via arterial puncture or directly from an arterial catheter.

Aspiration To draw in or out using a sucking motion.

Assist control ventilation Similar to control; however, it attempts to support patient efforts with fully control breaths. Frequency is then driven by the patient's effort.

Asthma Asthma is a reversible obstructive lung disease created by chronic inflammation of the airways. These inflamed airways often hyper-react (bronchospasm) to various triggers.

Asthma action plan A written management plan with information that a patient or family can refer should the patient become symptomatic.

Asthma education Disease-specific education designed to improve self-management.

Asthma triggers Exposure to allergen or aggravating agents that worsen asthma symptoms.

Atelectasis An absence of air in the lung parenchyma.

Atelectrauma Ventilator-associated lung injury that is also associated with the opening and closing of alveoli.

Atrial bulge One of three identifiable structures in the primitive heart.

Atrioventricular septal defect Also known as *AV canal* or *endocardial cushion defect*, refers to an anomaly in which there is absence of the septa between the atria and ventricles.

Autosomal recessive A genetic condition appearing only in individuals who have received two copies of an autosomal gene, one copy from each parent.

B

B_2 agonist Otherwise known as *bronchodilators* or *airway smooth muscle relaxants.*

Ballard Score Postnatal examination score for determining gestational age based on external physical findings.

Barium swallow A fluoroscopic evaluation of the esophagus using a barium sulfate contrast agent; same as esophogram

Barotrauma Ventilator-associated lung injury that is associated with inappropriate use of pressure that does not recruit or improve ventilation or oxygenation.

Benchmarking Continual and collaborative discipline of measuring and comparing the results of key work processes with those who have what are considered best practices.

Betamimetic Stimulating, mimicking, or referring to β-adrenergic receptors of the sympathetic nervous systems.

Bilateral choanal atresia Incomplete opening into the nasopharynx caused by membranous or bony structures

Biophysical profile (BPP) Technique for evaluating fetal status using fetal heart rate monitoring and ultrasound assessment of amniotic fluid volume, fetal muscle tone, gross fetal movement, and fetal breathing motion.

Blastocyst The ball of cells that results from repeated cellular shortly after fertilization.

Brain-lung crosstalk Complex interaction from the brain to the lung and from the lung to the brain.

Brief resolved unexplained event (BRUE) A sudden, brief, resolved episode characterized by some combination of cyanosis or pallor; absent, decreased, or irregular breathing; marked change in muscle tone (usually marked limpness); and/or an altered level of responsiveness. BRUE is a recent term intended to characterize many events previously described under the broader term of **Acute Life-Threatening Event (ALTE).**

Bronchial fremitus Vibrations of the chest resulting from movement of air through airways partially obstructed by mucus.

Bronchial provocation Also known as *challenge testing*. Used in documenting bronchial hyperreactivity.

Bronchiectasis A chronic condition resulting in the abnormal dilation of the bronchial airways.

Bronchiolitis obliterans An inflammatory lung disease of the small airways, or bronchioles.

Bronchoaveolar lavage (BAL) A medical procedure in which a bronchoscope is passed through the mouth or nose into the lungs and fluid is squirted into a small part of the lung and then collected for examination.

Bronchogenic cyst The most common foregut duplication cyst and can occur throughout the trachea and bronchi.

Bronchomalacia Increased flaccidity of the bronchial cartilage that leads to airway narrowing and collapse during respiration.

Bronchopulmonary dysplasia (BPD) A form of chronic lung disease that develops in preterm neonates treated with oxygen and positive-pressure ventilation (PPV).

Bronchopulmonary sequestration A focus of nonfunctioning lung tissue that lacks a bronchial connection to the normal tracheobronchial tree.

Bulbar muscles A muscle group that controls the epiglottis and other glottis structures, tongue, mouth, larynx, and throat and is important for airway protection and secretion clearance.

Bulboventricular loop Formed during early fetal development when the bulbus cordis and ventricular bulge merge, it is a one-ventricular structure that is the precursor of the ventricles.

Bulbus cordis One of three identifiable structures in the primitive heart eventually merges with the ventricular bulge to form the bulboventricular loop.

C

Calorimetry Clinically, the quantification of energy expenditure of a patient.

Capillary blood gas Blood gas analysis obtained via capillary puncture.

Capnography Refers to the measurement and display of carbon dioxide values during the respiratory cycle over time.

Carbon dioxide production The sum volume of carbon dioxide produced by cells in the body as a result of metabolism per unit of time.

Carboxyhemoglobin Hemoglobin that has carbon monoxide instead of the normal oxygen bound to it.

Cardiac output The amount of blood ejected from the heart over the course of 1 minute.

Cardiac index The ratio of the cardiac output to the body surface area.

Cardiomyopathy A chronic disease of the heart muscle (myocardium) in which the muscle is abnormally enlarged, thickened, and/or stiffened.

Cardiopulmonary exercise testing (CPET) performed in the pediatric age group to evaluate symptoms that only occur during exercise or as a more general assessment of the subject's exercise tolerance in specific disease states.

Carrier A person who carries the causative agent systemically but is asymptomatic or immune to it.

Cellulitis A spreading bacterial infection underneath the skin surface characterized by redness, warmth, swelling, and pain. Cellulitis commonly appears in areas where there is a break in the skin.

Central sleep apnea (CSA) Occurs when there is a cessation of airflow and no discernible respiratory effort.

Central venous catheter A catheter inserted in the central venous system.

Central venous oxygen saturation The percentage of oxygenated hemoglobin in central venous blood. This can be measured via blood sample or by fiberoptic catheters in vivo.

Central venous pressure The blood pressure of the central venous system, typically measured in the superior vena cava.

Centrifugal pump A type of pump used in ECMO—blood is propelled forward by a constrained vortex.

Cerebral perfusion pressure The difference between the systemic mean arterial pressure (MAP) and the intracranial pressure (ICP).

Cervical cerclage A procedure to suture close a cervix that has painlessly dilated in the second trimester of pregnancy. The most common method is a purse string suture placed transvaginally at the level of the internal cervical os.

Cervical dilation Opening of the cervix as a result of painful uterine contractions in labor. It is assessed by vaginal examination and expressed in centimeters or finger breadths; one finger breadth is approximately 2 cm. At full dilation, the diameter of the cervical opening is 10 cm.

Cervical effacement Thinning of the cervix associated with dilation of the cervix in labor.

Cervical insufficiency Painless dilation of the cervix early in the pregnancy. Depending on what point in pregnancy this occurs, cervical insufficiency can lead to miscarriage, stillbirth, or preterm delivery. Cervical insufficiency tends to be a recurring problem.

CHARGE A syndrome of defects including *c*olobomas, congenital *h*eart defects, choanal *a*tresia, *r*etarded development, *g*enital hyperplasia, and *e*ar anomalies.

Chest tube A flexible plastic tube inserted through the chest wall and into the pleural space.

Chest wall hematoma A hematoma is an abnormal collection of blood outside of a blood vessel. It occurs because the wall of a blood vessel wall, artery, vein, or capillary, has been damaged and blood has leaked into tissues where it does not belong.

Chief complaint Reason the child is presenting for treatment.

Choanal atresia Unilateral or bilateral obstruction of the posterior nasal apertures.

Chorion Structural part of the placenta facing the fetus serving as the vascular connection to the fetus through the umbilical cord.

Chorionic membrane Sac-like structure that surrounds the growing fetus.

Chorionic villi Capillary network within the chorion that allows gas and nutrient exchange between the mom and the fetus.

Chronic lung disease The initial diagnostic criteria mandated continuing oxygen dependency during the first 28 days of life with compatible clinical and radiographic findings to label an infant as having BPD. Later, it was proposed to use the need for supplemental oxygen at 36 weeks postmenstrual age (PMA) as the diagnostic criterion especially in preterm very low birth weight (VLBW) infants.

Chylothorax Abnormal collection of lymph in the pleural space.

co_2 elimination The sum volume of exhaled carbon dioxide.

Coarctation of the aorta Severe narrowing of the thoracic aorta in the proximity of the ductus arteriosus.

Compliance Ability of lungs and thorax to expand; expressed as the volume change per unit of pressure change.

Computed tomography A medical imaging procedure that creates sectional images that can be viewed in multiple imaging planes.

Concussion An injury to the brain that results in characteristic neurologic impairment.

Congenital diaphragmatic hernia A birth defect in which there is an abnormal opening in the diaphragm.

Congenital heart disease A malformation of the heart, aorta, or other large blood vessels that is the most common form of major birth defect in newborns.

Congenital lobar emphysema Defined by over-distention of one or more lobes of the lung, most frequently the left upper lobe.

Congenital pulmonary airway malformation An anomaly of the lower respiratory tract that results in a cystic mass of abnormal lung tissue.

Conscious sedation An induced state of sedation characterized by a minimally depressed consciousness in which the patient is able to continuously and independently maintain a patent airway, retain protective reflexes, and remain responsive to verbal commands and physical stimulation.

Continuous positive airway pressure (CPAP) Refers to application of continuous pressure during both inspiration and expiration in a spontaneously breathing neonate.

Contraction stress test (CST) Assessment of changes in the fetal heart rate (FHR) Especially decelerations in the face of uterine contractions induced by administration of intravenous dilute oxytocin solution. Repetitive decelerations in the FHR are called a *positive CST* and suggest that the fetus will not experience repetitive hypoxemic stress during labor.

Control ventilation Likely the oldest mode of ventilation designed to control ventilation with either pressure or volume targeting; however, does not determine patient interaction.

Conventional mechanical ventilation Ventilation mode that provides breaths per minute of 150 or less.

Corticosteroids An anti-inflammatory agent that is used to block late phase reaction to allergens, reduce airway hyperreactivity, and inhibit anti-inflammatory cell migration and activation.

Costal cartilaginous deformities Deformities of the cartilages that connect the sternum and the ends of the ribs.

Cough The process of expelling air forcefully to clear the airway.

Crew resource management (CRM) CRM was first developed in the airline industry to improve safety. CRM training encompasses a wide range of knowledge, skills, and attitudes including communications, situational awareness, problem solving, decision making, and teamwork.

Cricothyroidotomy An incision through the skin and cricothyroid membrane especially as an emergency procedure for relief of an obstructed airway.

Croup A common cause of upper airway obstruction resulting from inflammation of the larynx, trachea, and bronchi.

Cutdown method Placement of a catheter via surgical stoma that allows direct visualization and cannulation of the target vessel.

Cystic fibrosis A hereditary chronic disease of the exocrine glands, characterized by the production of viscid mucus that obstructs the pancreatic ducts and bronchi, leading to infection and fibrosis.

Cystic fibrosis transmembrane conductance regulator A membrane protein and chloride channel that is encoded by the CFTR gene.

D

Damage control surgery A technique of surgery used to care for critically ill patients.

Deadspace volume The portion of tidal volume that is not involved in gas exchange.

Decannulation Permanent removal of a trach tube.

Dedicated transport teams A transport team whose primary responsibility is to the transport of patients. These are usually higher volume transport programs, but these staff may assist in the intensive care units when normal transport duties are completed.

Deoxyhemoglobin Hemoglobin that does not have oxygen bound to its structure.

Department of Defense (DoD) A department of the federal government tasked with establishing military policies and maintaining American military forces.

Dextral looping A process that occurs between days 23 and 28 of gestation whereby the ventricular bulge balloons into a C-shaped loop that pushes the atrial bulge in a superior direction.

Diaphragmatic motion The diaphragm normally moves downward during inspiration and upward during expiration.

Diffusing capacity A test performed to determine the overall ability of the lung to transport gas into and out of the blood.

Direct calorimeter Refers the measurement of heat produced by a subject, usually to calculate energy expenditure.

Discharge planner Medical staff member designated to transition a patient from hospital facility to home or other level of care.

Disorders of the motor nerves Disorders that affect the motor neurons of the spinal cord and brainstem.

Disorders of the neuromuscular junction A disorder that occurs at the neuromuscular junction affecting neurotransmitting capabilities.

Diurnal ventilation Daytime use of ventilator assistance.

Doppler ultrasonography The detection of moving objects, such as intravascular blood exploiting shifts in frequency between emitted ultrasonic waves and their echoes.

Dry powder inhaler (DPI) An aerosol device designed to deliver drug in a powder form.

Durable medical equipment (DME) Medical equipment used in the home to aid in a better quality of living.

Dysphasia Any impairment in the ability to speak.

E

Ectoderm One of the three germ layers. Responsible for the development of the central and peripheral nervous systems, sensory epithelia, skin and special components of the skin, and teeth.

EEG arousal Disruption of the quality and duration of the sleep stages but no arousal to wakefulness. Disruption of the sleep architecture by EEG arousals causes inefficient and nonrestorative sleep.

Electrocardiography The measurement and interpretation of the electrical activity of the heart over time.

Electroencephalogram (EEG) A test used to evaluate the electrical activity in the brain.

Embryonic disk Structure making up the three germ layers the ectoderm, the endoderm, and the mesoderm.

Emergency department thoracotomy A procedure used to gain immediate control of life threatening cardiac injuries or control massive hemorrhage after trauma.

Empyema (pleural) Pleural effusion that has evidence of bacterial infection by evidence of pus, high white blood cell count (e.g., $>$ 15,000 per mm^3), or a positive Gram's stain.

Encephaloceles Defect resulting from failure of the embryonic neural tube to form correctly around the brain.

End tidal CO_2 The partial pressure of carbon dioxide at end exhalation.

Endobronchial ultrasound A technique that uses ultrasound along with bronchoscope to visualize the airway wall and the structures adjacent to it.

Endocardial cushions The structure that separates the atria from the ventricles in the developing heart.

Endoderm One of the three germ layers. Responsible for the development of the digestive system, respiratory system, urinary system, liver, pancreas, tonsils, thymus, thyroid, parathyroid, and epithelial lining of the auditory tube and tympanic cavity.

Endomyometritis Bacterial infection of the lining of the uterus and the underlying muscle after delivery of the newborn and placenta. Before the advent of affective antibiotics, a common cause of maternal morbidity and mortality.

Energy expenditure The quantity of energy, typically measured in kilocalories per day (kcal/day) resulting from metabolic processes.

Epiglottitis A life-threatening condition in which the epiglottis is inflamed.

Error An act of producing a preventable adverse outcome compared with the natural progression of disease leading to injury or death.

Escharotomy Surgical incision of the eschar and superficial fascia of the chest or a circumferentially burned limb to permit the cut edges to separate and restore blood flow to unburned tissue.

Esophageal atresia A serious birth defect in which the esophagus, which connects the mouth to the stomach, is segmented and closed off at any point. This condition usually occurs with tracheoesophageal fistula, in which the esophagus is connected to the trachea. Esophageal atresia occurs in approximately 1 in 4000 live births.

Esophogram A fluoroscopic evaluation of the esophagus using a barium sulfate contrast agent; same as barium swallow.

Evidence-based practice The multidisciplinary approach to health care in which the practitioner systematically finds, appraises, and uses the most current and valid research findings as the basis for clinical decisions.

Exhaled nitric oxide A biomarker of airway inflammation.

Expiratory positive airway pressure (EPAP) Expiratory positive airway pressure setting raises end-expiratory lung volume and impedes upper airway collapse.

Extracorporeal carbon dioxide removal The removal of carbon dioxide from the bloodstream in people who have elevated levels of carbon dioxide because of respiratory failure.

Extracorporeal membrane oxygenation (EMCO) A medical-surgical technique in which blood is drained from the body— extracorporeal—and mechanically pumped through an artificial lung—membrane oxygenator.

Extremely low birth weight (ELBW) infant Infant born with birth weight less than 1000 g.

F

Failure Modes and Effects Analysis (FMEA) A prospective risks assessment tool used to identify and eliminate known and/or potential failures, problems, and errors for a system, design, process, and/or service before they actually occur.

Failure to thrive Failing to gain weight in spite of an appetite and meet developmental milestones.

FAST examination Focused Assessment with Sonography for Trauma

Fetal alcohol syndrome (FAS) The total damage done to the child before birth because of the mother drinking alcohol during pregnancy. FAS always involves brain damage, impaired growth, and head and face abnormalities.

Fetal fibronectin (fFN) A protein produced by fetal cells and a type of fibronectin. fFN is found at the interface of the chorion and the decidua (between the fetal sac and the uterine lining). It can be thought of as an adhesive or "biological glue" that binds the fetal sac to the uterine lining.

Fetal hemoglobin Accounts for approximately 85% of the hemoglobin in the full-term infant.

Fetal lung fluid An intraluminal lung fluid important for the proper growth and development of the fetal lung.

Flexible fiberoptic bronchoscopy Bronchoscopy allows examination of the lower airways by a trained bronchoscopist. The flexible fiberoptic bronchoscope contains fiberoptic light bundles that places a light source at the tip of the instrument and allows examination of the lower airways. The flexible fiberoptic bronchoscope comes in a variety of sizes that are appropriate to the pediatric airway.

Fontanel A "soft spot" of the skull. The cartilage has not yet hardened into bone between the skull bones.

Fontan procedure The third and final stage of surgical palliation for single-ventricle cardiac lesions. It involves connecting the superior vena cava and the inferior vena cava directly to the pulmonary artery.

Foramen ovale One of the fetal shunts allowing blood to flow from the right atrium to the left atrium without traversing the pulmonary circulation in the fetus.

Foreign body aspiration Breathing a foreign object into the bronchus, resulting in airway blockage.

Functional residual capacity The volume of air remaining in the lungs at the end of passive expiration.

G

Gastroschisis Defect in the abdominal wall lateral to the midline with protrusion of the intestines.

Genotype The genome of a cell, an individual, or an organism.

Gentle ventilation A descriptive term for respiratory support for preterm infants using a low-tidal-volume strategy to decrease lung injury, with the acceptance of higher values for $Paco_2$.

Germinal matrix The highly cellular and highly vascularized region in the brain from which cells migrate out during brain development. The germinal matrix is the source of both neurons and glial cells and is most active between 8 and 28 weeks of gestation.

Gestational diabetes mellitus (GDM) Abnormal glucose tolerance of variable degree that occurs during pregnancy.

Glasgow Coma Scale score An assessment tool used to communicate the severity and depth of coma in a patient who has suffered traumatic brain injury.

Glenn procedure Second stage of surgical palliation for single ventricle cardiac lesions. It involves connection of the superior vena cava directly to the pulmonary artery. Pulmonary blood flow is supplied by venous return from the upper body, while blood from the lower body returns to the single ventricle.

Group B *Streptococcus* (GBS) A common bacterium that often colonizes the intestines and secondarily the lower genital tract. GBS is usually harmless in adults. In newborns, however, it can cause a serious illness known as group B streptococcal disease.

Growth restriction See *intrauterine growth restriction (IUGR)*

Grunting Audible expiratory noise caused by closure of the glottis during expiration.

H

Head bobbing Occurs when the sternocleidomastoids contract during inspiration, pulling the head down and the clavicles and rib cage up.

Health Failure Modes and Effects Analysis (HFMEA) A tool used to provide detailed hazard analysis of smaller processes and develop specific recommendations.

Heart-lung transplantation Surgical procedure carried out to replace both heart and lungs in a single operation.

Heart transplantation Surgical procedure involving the replacement of a patient's diseased or injured heart with a healthy donor heart.

Helium-oxygen gas mixture Otherwise known as *heliox.* Heliox is a mixture of helium and oxygen offered in two tank concentrations, 80%/20%, = and 70%/30%. Heliox blenders approved by the Food and Drug Administration can be used to mix various concentrations.

Hemofiltration An adjunct device used to regulate fluid management during ECMO. Similar to a dialysis-type filter, a hemofilter can be used to remove large volumes of fluid to increase the volume of red blood cells—hemoconcentration—or small amounts of fluid to augment urine output.

Hepatitis B virus (HBV) One of many viruses that infect the liver (hepatitis). HBV is endemic in parts of the world and results from "sharing" body fluids. In North America and Europe, it is associated with unprotected intercourse and needle sharing. HBV is an acute disease in most cases, with as much as a 5% mortality; it can infrequently progress to a chronic disease. The chronic form of HBV results in continuous shedding of the virus and high risk of cirrhosis and cancer. HBV can be contracted by the newborn of the individual shedding the HBV.

Herpes simplex virus (HSV) A very common sexually transmitted infection; type 2 HSV causes genital herpes and type 1 HSV usually causes cold sores but also can cause genital herpes; congenital HSV can be transmitted to the fetus during birth if the mother has an active infection.

Heterozygote Containing two different alleles of a gene.

High-flow nasal cannulae There is no single universally accepted definition. A reasonable definition would be a flow rate between 2 and 8 L/min.

High-frequency jet ventilation A mode of ventilation that combined with a low frequency ventilator provided short pulsed jets using an endotracheal tube (ETT) adapter, peak end-expiratory pressure (PEEP), and sigh breaths.

High-frequency oscillatory ventilation A mode of ventilation that provides small tidal volumes at very fast rates of 5 to 15 Hz with a piston and provides continuous distending pressure. To maintain such high rates, expiratory gas flow is enhanced by an active exhalation phase.

High-frequency percussive ventilation Delivers short bursts of gas to a sliding Venturi valve. The burst may

entrain air to deliver high-frequency distending pressure at peak inspiratory pressure (PIP) and peak end-expiratory pressure (PEEP). High-frequency breaths are active at both levels of pressure.

High-frequency ventilation Pressure mode of ventilation at a frequency of 150 breaths per minute or higher.

High-level disinfection A cleaning method that inactivates all viruses, fungi, and vegetative microorganisms but not necessarily all bacterial spores.

High position A placement position for an umbilical artery catheter. This position overlies the sixth through eighth thoracic vertebrae.

High-reliability organization (HRO) An organization that has succeeded in avoiding catastrophes in an environment where normal accidents can be expected because of risk factors and complexity.

Hila The area adjacent to the heart where the pulmonary bronchi, arteries, and veins enter and exit the right and left lungs.

Home assessment An evaluation of the home environment in which a ventilator-dependent child is to reside, meeting electrical criteria and accessible for adaptive strollers.

Homozygote A person who has two identical forms of a particular gene, one inherited from each parent.

Horizontal fissure A fissure separating the middle lobe from the right upper lobe of the lung; same as *minor fissure*.

Hug technique A rapid thoracic compression or "hug" is delivered to the sleeping infant's chest and abdomen with an inflatable jacket to produce a forced expiration.

Human immunodeficiency virus (HIV) A lentivirus (a member of the retrovirus family) that causes acquired immuno-deficiency syndrome (AIDS), a condition in humans in which progressive failure of the immune system allows life-threatening opportunistic infections and cancers to thrive.

Humidified high-flow nasal oxygen Medical gas conditioned at or near body temperature, saturated with water vapor, and delivered at flows higher than traditionally acceptable flow rates via a nasal cannula interface. More specifically, flows should be adequate to provide for high fractions of oxygen and ventilatory support as per the mechanism of deadspace washout and exceeding the inspiratory flow requirements of the patient.

Hydrops fetalis Massive edema in the fetus or newborn, usually in association with severe erythroblastosis fetalis. Severe anemia and effusions of the pericardial, pleural, and peritoneal spaces also occur. The condition often leads to death, even with immediate exchange transfusions after delivery. Also called *fetal hydrops.*

Hygromas Sacs of fluid resulting from a blockage in the lymphatic system.

Hyperinflation therapy In general a group of supportive therapies that increases functional residual capacity (FRC) by encouraging the patient to take deep breaths or by assisting with positive pressure.

Hypoplastic left heart syndrome A spectrum of lesions involving abnormal development of left-sided cardiac structures including the mitral valve, left ventricle, aortic valve, and aortic arch.

Hypoxemia Medical condition that is characterized by a reduced level of oxygen determined by arterial blood gas.

Hypoxia The reduction of oxygen supply to the body or region of the body. The deprivation of adequate oxygen.

I

Immunoreactive trypsinogen An assay used as a screening test for cystic fibrosis.

Impulse oscillometry Measurement of resistance and reactance using a loudspeaker to produce pulsations within the airway during normal quiet breathing.

Indirect calorimeter Refers to the approximation of heat resulting from metabolism through the measurement of oxygen consumption and carbon dioxide production, with the clinical goal of determining a patient's energy expenditure.

Inflammatory mediators Contribute to the development of ARDS, whether primarily or secondarily.

Infrared spectrometry Study of the specific absorption in the infrared region of the electromagnetic spectrum. It is used in the study of the chemical bonds within molecules.

Inhalation injury Currently the most common cause of death in patients with severe burns.

Inhaled nitric oxide Nitric oxide delivered in parts per million mixed with nitrogen and added to a breathing circuit mixed with oxygen.

Inspiratory positive airway pressure (IPAP) Inspiratory positive airway pressure setting determines the tidal volume.

Institute of Medicine (IOM) American nonprofit, nongovernmental organization founded in 1970, under the congressional charter of the National Academy of Sciences. Its purpose is to provide national advice on issues relating to biomedical science, medicine, and health, and its mission to serve as adviser to the nation to improve health.

Intimal mounds Endothelial tissue within the lumen of the ductus arteriosus that assist in postgestational closure of the ductus.

Intrauterine growth restriction (IUGR) Occurs when the estimated weight of the fetus is at or below the tenth weight percentile for his or her age (in weeks).

Intraventricular hemorrhage (IVH) Bleeding into the fluid-filled areas (ventricles) inside the brain. The condition is most often seen in premature babies.

Isoflurane The most commonly used inhalation anesthetic.

J

Just culture Identifies and addresses system issues leading individuals to engage in unsafe behaviors while maintaining individual accountability by establishing a zero tolerance for reckless behavior.

K

Kaizen Continuous quality improvement, emphasizing the philosophy that poor quality arises from bad systems rather than bad people.

Kyphosis Abnormal lateral curvature of the spine; also called *hunchback.*

L

Lamellar bodies A storage apparatus for surfactant consisting of concentric layers of lipid and protein and contained within the cytoplasm of alveolar type II cells.

Laminaria tent Used to expand the cervix in pregnant women to "ripen" (expand) the cervix to make labor and delivery easier and to cause abortions during the first half of pregnancy.

Lanugo Fine hair that covers premature infants mostly over the shoulders, back, forehead, and cheeks.

Laryngeal web A common laryngeal malformation that consists of accessory tissue between the vocal cords at the anterior commissure.

Laryngomalacia The inward collapse of the soft cartilage of the upper airway during inspiration.

Laryngotracheobronchitis Inflammation of the larynx, trachea, and bronchi; an acute severe infection of these parts marked by swelling of the tissues and excessive secretion of mucus, leading to obstruction of the respiratory passages.

Lean method The concept of streamlining processes and eliminating waste to keep costs low while maintaining high-quality products or services.

Left-to-right shunt Type of shunt n which oxygenated blood mixes with deoxygenated blood.

Leukocytosis White blood cell (WBC) greater than $25{,}000/mm^3$.

Leukopenia White blood cell count (WBC) less than $3500/mm^3$.

Level I trauma center A level designation from the American College of Surgeons (ACS) Committee on Trauma. Level I is the highest and III the lowest. Level I trauma centers must demonstrate 24 hour-a-day availability of surgical specialists and the intensive resources necessary for the immediate treatment of severely injured patients.

Listeria monocyogenes A group of bacteria capable of causing illness, including potentially fatal infections in the elderly, newborns, pregnant women, and persons with a weakened immune system. *Listeria monocytogenes* is the form of *Listeria* most commonly responsible for infections.

Low-birth-weight (LBW) infant Infant born weighing less than 2500 g.

Lower airway The trachea and distal structures. The trachea divides into the mainstem bronchi, which divide into smaller divisions called subsegmental bronchi.

Lower inflection point The point on the pressure–volume loop where the shape changes from concave to exponential. This point represents the start of alveolar expansion during inspiration.

Low position A placement position for an umbilical artery catheter. This position overlies the third to fourth lumbar space.

Low tidal volume ventilation A strategy of mechanical ventilation in which tidal volumes are limited (often targeted to 6 ml/kg based on the available adult acute lung injury data) while also limiting the plateau pressure.

Lung transplantation A surgical procedure involving the removal of one or both diseased lungs from a patient and the replacement of the lungs with healthy organs from a donor.

M

Macrosomia Abnormally large size of the body.

Mainstream capnography A method of measuring carbon dioxide during the breathing cycle that uses a sensor placed directly in the breathing circuit to analyze carbon dioxide.

Major fissures A fissure separating the upper and lower lobes of the lungs; same as *oblique fissures.*

Mass effect A displacement of normal anatomy because of a pathological abnormality.

Mean arterial pressure An indicator of left ventricular afterload. Estimated using the equation.

Mechanical ventilation A technique through which gas is moved toward and from the lungs through an exogenous device connected directly to the patient.

Meconium The green-tinged bowel content of an infant, which is usually passed within 48 hours after delivery.

Meconium aspiration The inhalation of meconium by a fetus or newborn. It can block the air passages and cause failure of the lungs to expand or other pulmonary dysfunction, such as pneumonia or emphysema.

Meconium ileus Obstruction of the small bowel with meconium in neonates.

Medicaid U.S. health care plan for qualifying patients with low incomes and resources.

Meningitis Inflammation of the overlying membranes of the brain and spinal cord, known as the meninges.

Mesoderm One of the three germ layers. Responsible for the development of the cardiovascular system, lymphatic system, connective tissues, muscle tissue, skins, kidneys, and reproductive tissues, among other areas.

Methemoglobin Forms when hemoglobin is oxidized to the ferric state. It causes the oxyhemoglobin dissociation curve to shift to the left, resulting in a decrease in hemoglobin's ability to combine with oxygen.

Micrognathia Small lower jaw.

Microstomia Small mouth.

Modified Allen's test A test used to verify the presence of collateral circulation to the hand and/or foot via selective manual occlusion of the arteries feeding the extremity.

Mottling Irregular areas of dusky skin alternating with areas of pale skin.

Myelomeningoceles Defect resulting from failure of the embryonic neural tube to form correctly around the spine.

Myopathy A disease of the skeletal musculature causing muscle weakness.

N

Nasal cannula A variable performance medical gas delivery interface that is designed with one or two prongs that inject gas into one or both nares.

Nasal flaring Contraction of muscles in the nasal passages during inspiration causes a widening of the nostrils.

Near-infrared spectrometry A non-invasive method of assessing oxygen supply and consumption balance in a tissue (such as the brain) and can be used to estimate blood flow.

Near miss An unplanned event or events that had potential to cause injury, illness, or harm but did not because it was detected before reaching the patient.

Nebulizer An aerosol device producing aerosolized suspension of liquid drug particles used for aerosol therapy.

Necrotizing enterocolitis (NEC) A serious bacterial infection in the intestine, primarily of sick or premature newborn infants. It can cause the death (necrosis) of intestinal tissue and progress to blood poisoning (septicemia).

Negative pressure assisted ventilation (NPAV) A method of respiratory assistance based on intermittent application

of subatmospheric pressure external to the chest wall through a tank or mold.

Negligence Lack of skills, failure, or deviation from standard practices/procedures.

Neuromuscular control of respiration The central and reflex neurological control system of breathing driven largely by chemical respiratory control (*neuro*) that interacts with the muscles of respiration (*muscular*).

Neuromuscular disease Broad term used to describe a disease that directly or indirectly affects the muscle function via nerve pathology.

Newborn screening Testing of newborns for serious treatable diseases, most of which are genetic.

Nonaccidental trauma A euphemism for child abuse; the injury or maltreatment of a child.

Noninvasive positive-pressure ventilation (NPPV) A method of respiratory assistance that involves an external interface and cyclical positive pressure device.

Non-rapid eye movement (REM) sleep During NREM sleep (dreamless sleep), the brain waves on the EEG recording are typically slow, the breathing and heart rate are slow and regular, the blood pressure is low, and the sleeper is relatively still.

Nonstress test (NST) A screening test for fetal well-being used in the second half of pregnancy. The mother depresses an event marker when fetal movement is perceived. Acceleration of fetal heart rate with movement is a "reactive" test and is considered reassuring.

Norwood procedure The first stage of surgical palliation for single ventricle cardiac lesions. It consists of consists of reconstructing the aorta and adding a shunt to provide pulmonary blood flow.

O

Obstructive sleep apnea (OSA) A breathing disorder that occurs in sleep and is characterized by repeated complete or partial obstruction of the upper airway such that gas exchange and/or sleep integrity are compromised.

Oligohydramnios A reduced quantity of amniotic fluid for an extended period; associated with lung hypoplasia.

Omphalocele Protrusion of the membranous sac that encloses abdominal contents through an opening in the abdominal wall into the umbilical cord.

Open lung strategy The clinical application of recruitment maneuvers followed by maintenance with appropriate level of positive end-expiratory pressure (PEEP) to prevent alveolar collapse.

Oxygen consumption The sum volume of oxygen that is consumed by the body as a result of metabolism, per unit of time.

Oxygen delivery Delivery of oxygen to body tissues as a function of oxygen content and cardiac output.

Oxygen hood A fixed-performance oxygen delivery device designed to surround the entire head of a neonate or infant.

Oxygen therapy The therapeutic administration of oxygen.

Oxygenation index A calculation used in critical care medicine to aid in determining the severity of illness and probable mortality associated with severe respiratory failure. The equation is:

$$OI = (F_{IO_2})(mPaw)/Pa_{O_2} \times 100.$$

Oxyhemoglobin The structure that is formed when oxygen is bound to hemoglobin in red blood cells.

Oxytocin A hypothalamic hormone stored in the posterior pituitary that has uterine-contracting and milk-releasing actions; it may also be prepared synthetically or obtained from the posterior pituitary of domestic animals. Used to induce active labor, increase the force of contractions in labor, contract uterine muscle after delivery of the placenta, control postpartum hemorrhage, and stimulate milk ejection.

P

Pancreatic insufficiency A condition characterized by a deficiency of the digestive enzyme produced by the pancreas, leading to impaired digestion of food.

Papillomatosis A condition marked by the presence of numerous papillomas.

Partial pressure of carbon dioxide in arterial blood $Paco_2$ is a measurement of carbon dioxide in arterial blood.

Partial pressure of oxygen in arterial blood *Partial pressure* is a way of describing how much of a gas is present and refers to the pressure exerted by a specific gas in a mixture of other gases. Pao_2 is a measurement of oxygen in arterial blood.

Patent ductus arteriosus The failure of the connection between the aorta and the pulmonary artery (ductus arteriosus) to close at birth.

Pectus carinatum Protruding xiphisternum or xiphoid process; also called *pigeon chest*.

Pectus excavatum Sunken or funnel chest.

Percutaneous method Insertion of a catheter through the skin to a target vessel.

Periodic breathing Irregular pattern of intermittent respiratory pauses longer than 5 seconds.

Peripheral artery catheter An indwelling catheter placed in a peripherally located artery.

Permissive hypercapnia Ventilation that allows $Paco_2$ to rise slowly over time as the pH becomes normalized. The goal is to reduce tidal volume and rate while preventing volutrauma during mechanical ventilation.

Phenotype The observable properties of an organism that are produced by the interaction of the genotype and the environment.

Placenta Vascular interface between the mom and the fetus allowing gas and nutrient exchange through the chorionic villi and the umbilical cord.

Placenta previa The location of the placenta so that it covers the cervical os (complete previa) or is located adjacent to or partially covers the os (partial previa). One of the most common causes of life-threatening hemorrhage in pregnancy.

Placental abruption Separation of the placenta from the wall of the uterus before the birth of the baby. This can result in severe, uncontrollable bleeding (hemorrhage).

Plan-Do-Study-Act (PDSA) Method to determine nature and scope of a problem.

Plan of care A detailed plan implemented for the medical needs of an individual.

Plethysmography A device (body box) that measures the volume of gas in the lungs, including that which is trapped in poorly communicating air spaces.

Pleural effusion Abnormal collection of fluid in the pleural space.

Pneumomediastinum Abnormal air in the tissue of the mediastinum, often tracking up into the neck.

Pneumonia A lung infection that primarily affects the alveoli and distal airways.

Pneumopericardium The presence of air in the pericardial cavity.

Pneumoretroperitoneum and pneumoperitoneum Air tracks downward to the extraperitoneal fascial planes of the abdominal wall, mesentery, and retroperitoneum and eventually ruptures into the peritoneal cavity.

Pneumothorax An accumulation of free air within the pleural space that compresses the lungs.

Poliomyelitis Infection caused by the polio virus.

Polyhydramnios The presence of excess fluid in the amniotic sac. By definition, polyhydramnios is diagnosed if the deepest vertical pool is more than 8 cm or amniotic fluid index (AFI) is more than ninety-fifth percentile for the corresponding gestational age. With a deep pocket of 8 cm as criteria of polyhydramnios, the incidence is 1% to 3% of all pregnancies. About 20% are associated with fetal anomalies.

Positive expiratory pressure (PEP) therapy designed to restrict expiratory flow and thereby creating backpressure designed to increase functional residual capacity and dilate secretion-filled airways.

Postductal Relating to that part of the aorta distal to the aortic opening of the ductus arteriosus.

Postductal oxygen saturation Measurement of oxygen saturation (of an infant's blood) occurring before the ductus arteriosus.

Potter's syndrome/sequence Potter syndrome/sequence and Potter phenotype refer to a group of findings associated with a lack of amniotic fluid and kidney failure in a fetus or infant.

Precipitous delivery Delivery of infant anywhere unintended or without a provider.

Precursor Somebody or something that comes before, and is often considered lead to the development of, another person or thing.

Preductal Right radial artery.

Preductal oxygen saturation Measurement of oxygen saturation of the blood taken after the ductus arteriosus.

Preeclampsia Multiorgan dysfunction of late pregnancy, most often diagnosed by hypertension, proteinuria, and edema. The disorder is of uncertain origin but is most commonly associated with first pregnancies, multifetal pregnancies, and underlying vascular and rheumatological conditions.

Preterm delivery The birth of an infant after the period of viability but before 37 completed weeks of gestation.

Premature rupture of membranes (PROM) Premature rupture of membranes (PROM) is an event that occurs during pregnancy when the sac containing the developing baby (fetus) and the amniotic fluid bursts or develops a hole before the start of labor.

Pressure ventilation Uses a pressure setting as the main determinate of lung inflation.

Pressurized metered-dose inhaler An aerosol device with pressurized cartridge and valves that emits precise dosages of drugs (between 10 and 100 µg) in suspension or solution.

Primary germ layers The endoderm, mesoderm, and ectoderm. Individual layers of specialized embryonic cells responsible for production of all tissues within the developing fetus.

Primary survey The initial assessment of children presenting with a traumatic injury.

Prune belly syndrome Congenital lack of abdominal musculature.

Pseudoglandular Refers to a stage of fetal lung development identified by the appearance of multiple round structures resembling glands.

$P_{TC}CO_2$ Partial pressure of carbon dioxide as measured using a transcutaneous monitor.

$P_{TC}O_2$ Partial pressure of oxygen as measured using a transcutaneous monitor.

Pulmonary acinar units Formed during the canalicular period, each unit consists of a respiratory bronchiole, alveolar ducts, and alveolar sacs.

Pulmonary hypertension A rare lung disorder characterized by increased pressure in the pulmonary artery.

Pulmonary hypoplasia An incomplete development of the lungs characterized by an abnormally low number and/or size of bronchopulmonary segments and/or alveoli.

Pulmonary interstitial emphysema A lung anomaly characterized by an increase in the air spaces distal to the terminal bronchioles with destruction of the alveolar walls.

Pulmonary mechanics Study or measurement physiological parameters (e.g. resistance, compliance, etc.) that affect a subject's work of breathing.

Pulmonary surfactant Complex mixture of phospholipids and proteins produced by type II pneumatocytes whose function is to lower surface tension proportionally to alveolar size.

Pulmonary vasodilation Vasodilation of the pulmonary vasculature by smooth muscle relation.

Pulse oximetry Noninvasive measurement of the saturation of hemoglobin, usually referring to the proportion of hemoglobin bound with oxygen.

Pulse pressure The difference between systolic and diastolic blood pressure.

Q

Quality The extent to which health services provided to individuals and patient populations improve desired health outcomes.

Quality indicator Measurement that provide a quantitative basis for clinicians, organizations, and planners aiming to achieve improvement in care and the processes by which patient care is provided.

R

Rapid eye movement (REM) sleep REM sleep (during which dreams occur) is characterized by rapid, low-voltage brain waves, irregular breathing and heart rate, and involuntary muscle jerks.

Rapid shallow breathing index A value that integrates two variables to determine the efficiency of tidal breathing.

Reactance Represents the "out of phase imaginary part" of impedance and encompasses both the elastane and inertia, which along with resistance define the mechanical characteristics of the equation of motion model.

Reduced alveolar recruitment Known as *atelectasis.*

Regional oxygen saturation in the brain ($bRSO_2$) The most common indication of near-infrared spectrometry because

in infants brain injury is often related to cerebral oxygenation and cerebral blood flow disturbances.

Respiratory control system Control of the respiration divided into both voluntary and metabolic (involuntary) control systems.

Respiratory distress syndrome (RDS) A syndrome in premature infants caused by developmental insufficiency of surfactant production and structural immaturity in the lungs.

Resting energy expenditure The amount of energy required by the body during resting conditions (usually expressed in kilocalories per day, kcal/day).

Retinopathy of prematurity (ROP) A condition in which premature babies experience disorganized blood vessel growth in their eyes. Although milder cases of ROP may spontaneously correct themselves, in the worst cases, ocular scarring caused by retinopathy of prematurity can result in blindness.

Right atrial pressure The blood pressure in the right atrium of the heart. This pressure indicates the filling pressure of the right atrium; normally 2 to 7 mm Hg.

Right-to-left shunt Type of shunt in which desaturated systemic venous blood bypasses the lungs and enters the systemic circulation.

Rigid bronchoscopy Procedure using a rigid bronchoscope. It is particularly useful in removal of a foreign body or when laser therapy is required.

Roller pump A type of mechanical pump used in extracorporeal membrane oxygenation (ECMO). Blood is compressed and displaced by a roller heads through durable tubing.

Root cause analysis (RCA) A retrospective systematic process using information for an unplanned event to identify and understand the underlying causes or the event.

S

Saccules An anatomical description of the lung parenchyma at about 26 weeks of gestation; the terminal structures of the lung at this stage of development are relatively smooth-walled, cylindrical structures.

SCIWORA Spinal cord injuries without radiographic abnormality.

Scoliosis Abnormal "sideways" curvature of the spine.

Secondary crests Anatomical description of the ridges that subdivide saccules during the embryological development of the lung.

Sentinel event Another name for serious safety event.

Sepsis Systemic evidence of infection characterized by temperature change, increased heart rate, increased respiratory rate, and leukocytosis or leukopenia.

Septum primum The structure that divides the primitive atria into left and right chambers.

Septum secundum A structure between the atria in the developing heart, which together with a flap from the septum primum for the foramen ovale.

Serious safety event An event that reaches the patient and results in moderate to severe harm or death.

Serum lactate Measurement of lactate in a blood sample. This value is indicative of anaerobic metabolism. Normally 0.7 to 1.3 mmol/L.

Sevoflurane An inhaled anesthetic that is often used to put children asleep for surgery.

Shock Inadequate tissue oxygen delivery.

Sickle cell A disease of an autosomal recessively inherited disorder of the hemoglobin structure.

Sidestream capnography A method of measuring carbon dioxide during the breathing cycle that uses a small sample line that aspirates a sample of gas from a T-piece placed at the breathing tube to the main unit where the gas is analyzed.

Signal extraction technology A type of pulse oximetry.

Simple oxygen mask A variable-performance, low-flow oxygen delivery device designed to surround the nose and mouth.

Six Sigma A process improvement set of tools and strategies developed by Motorola.

Sleep architecture The distribution of time spent in each stage of sleep is quantified during a sleep study and is referred to as *sleep architecture*.

Sleep-disordered breathing (SDB) A condition characterized by repeated episodes of hypopnea (underbreathing) and apnea (not breathing) during sleep.

Solid organ injury Injury to the liver or spleen.

Spacer A valveless device used to collect emitted aerosol, typically from a pressurized metered-dose inhaler (pMDI), placed in a circuit between the aerosol generator and the patient airway.

Specific airway conductance The reciprocal of airway resistance; 1/Raw measured at a specific lung volume.

Spinal muscular atrophy Include different disorders that clinically manifest as muscle weakness because of progressive destruction of the motor neurons.

Spirometry Measurement of breath air.

Sternocleidomastoids Neck muscles that serve to flex and rotate the head.

Stretor A low-pitched, wet sound similar to snoring.

Stridor A high-pitched, monophonic, audible noise that may occur during inspiration or expiration or may be biphasic.

Subcutaneous emphysema Air in the fascial planes of the neck and skin.

Subgaleal hemorrhage Tearing of the emissary veins where edema from blood loss can extend from the eyes to the nape of the neck.

Sudden infant death syndrome (SIDS) SIDS is the sudden death of an infant under 1 year of age that remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history.

Surface tension Forces created by the attraction of water molecules at the alveolar air–fluid interface that tend to collapse the alveolus.

Surfactant A surface-active phospholipoprotein formed by alveolar type II cells important in reducing alveolar surface tension and ultimately the work of breathing in the newborn; critical to the extrauterine survival of the immature fetus.

Surfactant proteins Pulmonary surfactant-associated proteins produced by type II pneumatocytes.

Surfactant replacement therapy Intratracheal administration of exogenous (natural or synthetic) surfactant for the treatment of various respiratory conditions associated with surfactant deficiency and/or inactivation.

Sweat chloride test A test used to evaluate a patient suspected of having cystic fibrosis.

Sweep gas The fresh gas supplied to a membrane oxygenator, usually composed of a combination of oxygen and

carbon dioxide, and titrated to achieve clinically acceptable blood gases.

Syphilis A chronic infectious disease caused by a spirochete (*Treponema pallidum*), either transmitted by direct contact, usually in sexual intercourse, or passed from mother to child in utero, and progressing through three stages characterized respectively by local formation of chancres, ulcerous skin eruptions, and systemic infection leading to general paresis.

T

Tactile fremitus Vibrations of the chest produced by the spoken voice.

TeamSTEPPS Team Strategies and Tools to Enhance Performance and Patient Safety

Tension pneumothorax Abnormal collection of air in the pleural space with increasing pressure causing significant shift of the mediastinal structures.

Tension time index The product of the inspiratory time-to-cycle time ratio and the integrated area under the pressure curve throughout the respiratory cycle.

Teratogen Any agent or factor that induces or increases the incidence of abnormal prenatal development.

Tetralogy of Fallot Congenital heart defect that includes four components (1) pulmonary artery stenosis, (2) ventricular septal defect, (3) overriding aorta to the right, and (4) right ventricular hypertrophy.

Therapeutic gas mixtures Gas delivered by inhalation for a specific purpose such as pulmonary vasodilation, bronchodilation, drug delivery, or to reduce work of breathing.

Thoracic gas volume The volume of gas contained within the chest during body plethysmography when the mouth shutter is closed. This measurement is a rough estimate of the functional residual capacity of the lung.

Thoracotomy A surgical procedure performed to open the chest cavity.

Tocolytic Of or being an agent that arrests uterine contractions in labor.

Total body surface area burn The severity of a burn is dictated by the percent of total body surface area involvement.

Tracheoesophageal fistula An abnormal opening between the trachea and the esophagus.

Tracheomalacia A condition in which the thoracic trachea abnormally collapses during expiration, leading to an expiratory wheeze.

Transbronchial biopsy A procedure in which a bronchoscope is inserted through the nose or mouth to collect several pieces of lung tissue.

Transcutaneous monitor A device or method that measures carbon dioxide or oxygen in the tissues just beneath the skin.

Transillumination Placing a high-energy or fiberoptic device on an infant's chest wall in a darkened room.

Transposition of the great arteries One of the most common congenital heart defects. The positions of the aorta and the pulmonary artery are reversed, with the aorta arising from the right ventricle and the pulmonary artery arising from the left ventricle.

Transpulmonary pressure The difference between the alveolar pressure and the intrapleural pressure in the lungs.

Trauma resuscitation The process of correcting physiologic disorders (such as lack of breathing or heartbeat) in an acutely unwell patient, especially as the result of trauma.

Traumatic brain injury A brain injury from an external force, possibly leading to permanent or temporary impairment of cognitive, physical, and psychosocial functions, with an associated diminished or altered state of consciousness.

Trophoblast The outer layer of the blastocyst, which combines with the endometrium to for the chorionic membrane.

Truncus arteriosus Rare defect in which a single great artery arises from the ventricles of the heart, supplying the systemic, pulmonary, and coronary arteries.

Tuberculosis A chronic bacterial disease caused by infection with *Mycobaterium tuberculosis.*

U

UHF/AM transceiver An ultra high frequency/amplitude modulation (UHF/AM) transceiver is a device comprising both a transmitter and a receiver that are combined and share common circuitry or a single housing. This communication device can communicate over two different frequency ranges.

Umbilical artery catheter An indwelling catheter placed in one of the two arteries in an infant umbilicus.

Unit-based transport teams A transport team assigned to an intensive care unit that responds to transport requests when they are received.

Upper airway Consists of all the structures connecting the mouth and nose with the glottis.

V

VACTERL A syndrome of defects including *v*ertebral, *a*nal, *c*ardiac, *t*racheal, *e*sophageal, *r*enal, and *l*imb anomalies.

Valved-holding chamber A spacer with a system of one-way valves used to reduce oropharyngeal deposition and reduce the need for hand–breath coordination, most commonly used with pressurized metered-dose inhalers (pMDIs).

Velamentous cord insertion An abnormal condition during pregnancy. Normally the umbilical cord inserts into the middle of the placenta as it develops. In velamentous cord insertion, the umbilical cord inserts into the fetal membranes (choriamniotic membranes), then travels within the membranes to the placenta (between the amnion and the chorion).

Venoarterial A method of extracorporeal membrane oxygenation (ECMO) support in which blood is drained from the venous system and returned to the arterial system; both heart and lung function are supported.

Venous blood gas Blood gas analysis obtained from a venipuncture or directly from a venous catheter.

Venoarterial Relating to or involving an artery and vein.

Venovenous A method of extracorporeal membrane oxygenation (ECMO) support in which blood is drained and returned form and to the venous system; only lung function is supported.

Ventilator-associated pneumonia (VAP) A sub-type of hospital-acquired pneumonia (HAP) that occurs in people who are receiving mechanical ventilation via an artificial airway.

Ventricular assist devices Used routinely in the treatment of end-stage adult heart failure, and have become a progressively emerging technology in pediatrics.

Ventricular bulge One of three identifiable structures in the primitive heart eventually merges with the bulbus cordis to form the bulboventricular loop.

Venturi mask A fixed-performance, high-flow oxygen delivery device design to provide a specific amount of oxygen via a Venturi entrainment device.

Vernix caseosa Gray-white cheeselike substance present in the skin folds of a term infant and more abundant in a preterm infant.

Very low birth weight (VLBW) infant Infant born weighing less than 1500 g.

Video-assisted thoracoscopic surgery (VATS) Minimally invasive surgery in the thorax with a video camera inserted in one aspect of the chest wall and operating instrument(s) inserted though other aspects of the chest wall. The surgeon views the operative field on a monitor.

Vocal cord dysfunction A condition characterized by full or partial vocal fold closure that usually occurs during inhalation.

Volumetric capnography A method by which exhaled gas flow and carbon dioxide measurements are made to calculate and display relevant parameters and waveforms such as airway dead space volume, alveolar volume, and carbon dioxide elimination.

Volutrauma Ventilator-associated lung injury that is associated with large tidal volumes.

W

Wharton's jelly A gelatinous substance contained within the umbilical cord that serves to protect umbilical vasculature and prevent the cord from becoming kinked.

Work of breathing The effort required to inspire air into the lungs.

Z

Zygote Fertilized egg.

Index

B

D

E

F

G

H

I

J

K

L

M

N

O

P

Q

R

S

T

U

V

W

X

Y

Z